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ELECTRON MICROSCOPIC STUDY OF THE GRANULAR VESICLES IN THE HUMAN SYMPATHETIC NEURONS

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SUMMARY

1) Electron microscopic study was conducted on the GV of the human sympathetic neurons.

2) GV, approximately 1,000 Å in diameter, were present not only in the pre-synaptic nerve endings as well as in the post-synaptic neuron-soma especially around the Golgi apparatus of sympathetic ganglion cells, but also in the axons of myelinated and unmyelinated nerve fibers.

3) In several peripheral vascular diseases, no significant difference in the size of GV in the sympathetic ganglion cells was noted.

4) Following administration of nialamide an increase in the number and size of both the GV and their cores was observed.

5) On the other hand, following reserpine treatment a remarkable decrease in the number and size of GV was observed

6) The GV in the sympathetic ganglion cells were assumed to be formed in the Golgi apparatus and CA seems to be included within the cores of the GV.

7) GV are transported to synapses or nerve endings through the axons of sympathetic nerve fibers.

8) CA included within the GV probably acts as a chemical transmitter substance.

INTRODUCTION

The central nervous control of the blood vessels of the limbs is mediated by sympathetic nerve fibers and, therefore, is disrupted by interruption of these fibers.

In peripheral occlusive vascular diseases, sympathectomy is a valuable surgical procedure, not only as a definitive method of producing dilatation of a vascular bed in spasm, but as an ancillary measure to complement reconstructive arterial operations.

However, the ultrastructure and function of the sympathetic nervous system

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Abbreviations used;
1) GV: granular vesicle (s), 2) NA: noradrenaline,
3) CA: catecholamine (s), 4) MAO: monoamine oxidase,

remain to be clarified further.

The characteristic membranous vesicles found in synaptic terminals of nervous tissue were named synaptic vesicles by De Robertis and Bennett (1955)[1], and many previous reports have suggested that the synaptic vesicles are essentially related to the chemical transmission in neuromuscular junctions.

In the electron micrograph, two kinds of synaptic vesicles are noted.

One is classical synaptic vesicle having some material of extremely low density (mean diameter about 500 Å), and the other is so-called GV.

The shape of this GV is circular and an electron dense core is included in the interior. Between the limiting membrane and the dense core there is always a clear space.

GV have already been demonstrated with unexpected frequency in nerve endings or synapses of some vertebrates and invertebrates.

Yet there are only few observations on the GV in the nerve cell bodies as well as on the possible origin of the synaptic vesicles.

Further, clear-cut electron micrograph showing the GV in the nerve fiber has not yet demonstrated up to the present.

In general, the chemical composition as well as the origin and the role of the GV remains to be clarified.

In the human sympathetic neurons the author observed a number of GV not only in the pre-synaptic nerve endings, but also in the post-synaptic nerve cell bodies. In addition, GV were noted in the axons of both myelinated and unmyelinated nerve fibers.

The purpose of this electron microscopic study is principally to investigate the locarization, the possible origin and the chemical nature of the GV in the human sympathetic neurons.

In order to investigate the chemical nature of the GV in the ganglion cells, human sympathetic ganglions were surgically removed following nialamide or reserpine treatment and changes in the vesicles were studied.

MATERIALS AND METHODS

Human sympathetic ganglions were obtained from the following groups.

Nialamide group consists of three patients with Buerger's disease and daily dose of 150 to 500 mg of nialamide (MAO inhibitor: 1-[2-(benzyl-carbamyl) ethyl]-2-isonicotinoylhydrazine) were administered for 9 days in one patient and for 14 days in two patients prior to surgical manipulation.

Reserpine group consists of six patients and includes one pulseless disease, two Buerger's disease, two arteriosclerosis obliterans and one Raynaud's disease. These patients received daily dose of 1.5 to 3 mg of reserpine (3, 4, 5-trimethoxybenzoyl methyl reserpata) for 6 to 14 days prior to surgical manipulation.

As a control, the thoracic and lumbar sympathetic ganglions obtained from hyperhidrosis, Raynaud's disease, Buerger's disease and arteriosclerosis obliterans were studied.

These specimens were fixed by immersion in ice cold 1% osmium tetroxide solution, buffered with veronal acetate to pH 7.4, to which 45 mg sucrose was added for each 1 ml solution.

Some specimens were fixed in ice cold 2% glutaraldehyde solution adjusted to pH 7.4 with phosphate buffer, and thereafter they were post fixed in osmium tetroxide solution buffered with phosphate to pH 7.4.

After two hours in the fixing medium, the specimens were rapidly dehydrated by passing through a series of graded concentrations of ethanol and propylene oxide, and then embedded in Epon 812 according to Luft's method[2].

Ultrathin sections were obtained with the LKB Ultrotome using glass knives, and they were doubly stained with lead hydroxide and uranyl acetate. The stained sections were examined with a Hitachi HU-11 C electron microscope.

OBSERVATIONS

In the human sympathetic neurons a number of GV were observed not only in the pre-synaptic nerve endings, but also in the post-synaptic nerve cell bodies (Figs. 4, 6).

In addition, GV were noted in the axons of both myelinated and unmyelinated nerve fibers (Figs. 7, 8, 9).

The diagram illustrates the submicroscopic structure of the human sympathetic ganglion cell (Fig. 1).

1) Control group

The mean diameter of the GV in the perikarya of human sympathetic ganglion cells was 1,026 Å, while that of the core was 717 Å (Fig. 5).

Therefore the core represented 69.9% of the GV.

In the patients with hyperhidrosis, Raynaud's disease, Buerger's disease and arteriosclerosis obliterans, no significant difference in the size of GV was noted in the sympathetic ganglion cells.

2) Alterations following nialamide treatment

Following administration of nialamide, increased number of GV was observed in the sympathetic ganglion cells and they were noted especially around the Golgi apparatus (Fig. 10).

At the same time the diameter of both the GV and the core was increased. The measured range of the former was form 1,009 to 1,450 Å (mean 1,226 Å), that of the latter was from 688 to 1,275 Å (mean 905 Å) (Fig. 11). In addition, the percentage of the core to GV increased to 73.8%.

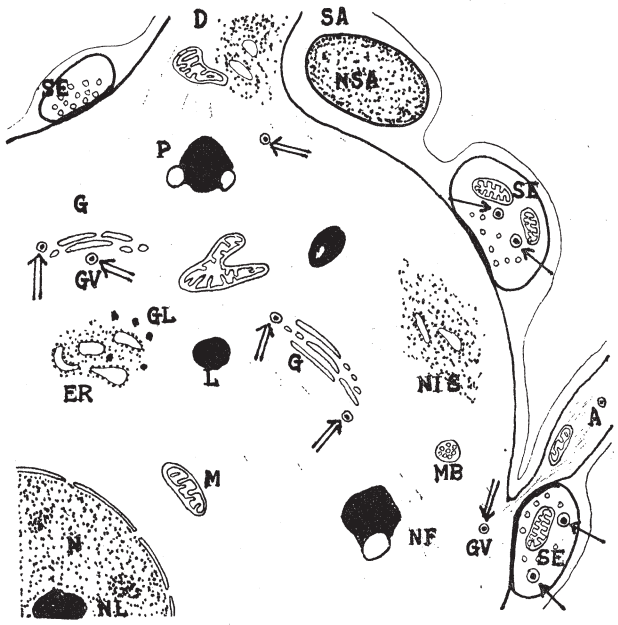

FIG. 1. Diagram showing the satellite envelope, the synaptic nerve endings, the neuronal processes and the components of the human sympathetic ganglion cell.

N: Nucleus, NL: Nucleolus, M: Mitochondrion, L: Lysosome, P: Pigment, G: Golgi apparatus, D: Dendrite, A: Axon, MB: Multivesicular body, NIS: Nissl substance, ER: Endoplasmic reticulum, GL: Glycogen, NF: Neurofilament, SA: Satellite cell, NSA: Nucleus of satellite cell, SE: Synaptic nerve ending, GV: Granular vesicle.

Single arrows indicate the GV in the synaptic nerve endings.

Double arrows indicate the GV in the perikaryon of sympathetic ganglion cell.

TABLE 1. Measurements of the sizes of thirty GV found in the human sympathetic ganglion cells from each group. SD: standard deviation

	Mean diameter of GV		Percentage of core to whole body (%)
	Whole body (Å)	Core (Å)	
	SD	SD	
Control group	1026±112.8	717± 95.7	69.9
Nialamide-treated group	1226±133.3	905±127.1	73.8
Reserpine-treated group	908±142.2	607±157.5	66.8

The statistical analysis

The differences of mean diameters of GV and their cores among three groups respectively were significant at 1 per cent level,

Pr. $\{F>7.09\}=1\%$

3) *Alterations following reserpine treatment*

A remarkable decrease in the number of GV in the sympathetic ganglion cells was observed following reserpine treatment (Fig. 12).

The diameters of the GV decreased and ranged from 690 to 1,150 Å (mean 908 Å). Also the cores became smaller and ranged from 328 to 950 Å (mean 607 Å). Furthermore, the percentage of the cores to the GV decreased to 66.8% (Fig. 13).

The above measurements of the sizes of GV and their cores in the sympathetic ganglion cells from each three groups can be listed as in Table 1.

From the statistical analysis, the differences of mean diameters of GV and their cores were significant at one per cent level.

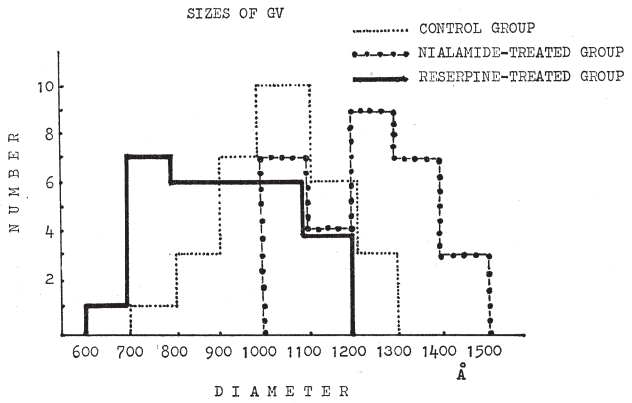

FIG. 2. Histogram showing the size distribution of each thirty GV found in the human sympathetic ganglion cells among three groups respectively.

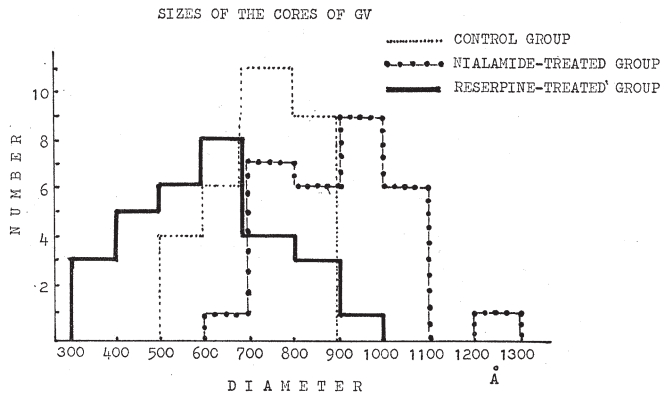

FIG. 3. Histogram showing the size distribution of each thirty cores of the GV found in the human sympathetic ganglion cells among three groups respectively.

Figures 1 and 2 show the size distribution histograms of GV and their cores found in the human sympathetic ganglion cells among three groups respectively (Figs. 2, 3).

DISCUSSION

A number of GV are recognized in the human sympathetic ganglion cells, in particular around the Golgi apparatus. The diameter of these GV is approximately 1,000 Å in Epon embedded tissue.

Up to date the GV have been observed by many investigators.

These investigators are listed in Table 2 with the size of GV observed, as well as the names of animals and nervous tissues they used[3)-11)].

"Neurosecretory granules" in the neurosecretory cells and "secretory granules" or "elementary granules" in the endocrine organs are very similar to the GV from morphological point of view.

However, up to date neurosecretory phenomena is, among the vertebrate, recognized only in the hypothalamo-hypophyseal system and caudal neurosecretory system in fishes (Sano, Tsuji and Iida 1965)[12)].

Since neurosecretory phenomena is not observed in the sympathetic nervous system, the GV is entirely different from these neurosecretory granules, secretory granules or elementory granules in nature.

Generally speaking, neurosecretory granules are larger than the GV in size, and the electron density of the core is higher than that of the GV (Gerschenfeld 1963)[8)].

TABLE 2. Previous reports on granular vesicles

Reporter	Name	Diameter (Å)	Tissue	Animal
Grillo (1962)	granule-containing vesicle	840 470	autonomic nervous system	rat
Pellegrino De Iraldi (1963)	granulated vesicle	425	adrenergic nerve ending in pineal gland	rat
Richardson (1962)	granular vesicle	300-900	nerve ending in vas deferens	rat
Shimizu (1964)	catecholamine-containing granule	1100	synaptic terminal	rabbit
Uchizono (1964)	cored or granulated synaptic vesicle	1000	synapse in ganglion	frog toad
Gerschenfeld (1963)	dense synaptic vesicle	600-1100	synapse	slug snail
Oosaki (1965)	dense vesicle	400-1200	nerve cell	planaria
Ross (1959)	dark-cored vesicle	600-800	chemoreceptor cell of carotid body	cat
Honjin (1965)	granular vesicle	830	nerve process in Auerbach's plexus	mice

There are two divergent hypotheses on the origin of synaptic vesicles which are essentially related to the chemical transmission.

One is that the synaptic vesicles are probably produced within the perikaryon of nerve cells and then they are transported proximo-distally as a result of axoplasmic flow (Van Breeman, Anderson and Reger 1958[13]; Mac Intosch 1959[14]; Palay 1960[15]; Horridge, Chapman and Mac Kay 1962[16]; Ochs, Dalrymple and Richards 1962[17]).

The other is that the synaptic vesicles might be produced in the synapses or nerve endings (De Robertis 1963[18]; Good 1963[19]).

According to Knowles (1964)[20], the assemblage and/or transformation of neurosecretory material might have taken place in the distal part of a neurosecretory system.

Chronic degenerative section of the cervical sympathetic nerves and superior cervical ganglia leads to the depletion of choline acetylase content at the distal part of the nerve, whereas at the proximal part of the nerve the content of this enzyme is increased (Hebb and Waites 1956)[21].

Moreover, after the ligation of nerve trunk, accumulation of vesicles is observed at the site of damming of sciatic nerve trunk or skin nerve (Uchizono 1966[22]).

The high content of NA in the sympathetic nerves and ganglia has been demonstrated by Euler and Hillarp (1956)[23].

And the nerve cell bodies show about the same rapid depletion of CA as the terminals following the administration of reserpine (Norberg 1965)[24].

According to Dahlström and Fuxe (1964)[25], the adrenergic nerve fibres running from the ganglia to the innervated tissues can be clearly visualized with the histochemical fluorescence method.

Therefore, it is accepted that CA exist in the sympathetic ganglia and nerves.

On the other hand, Euler and Swanbeck (1964)[26] reported that the appearance of the vesicles in chain-like structure in the sediment obtained by suspension of extracted particles of bovine splenic nerves suggested the existence of a system similar to that described in the occurrence and formation of granules in the Golgi apparatus.

With regard to pharmacological action of reserpine, many published studies demonstrated a pronounced loss of CA after administration of reserpine (Coupland 1959[27]; De Robertis and Vaz Ferrera 1957[28]; Eränkö and Hopsu 1958[29]; Holzbauer and Vogt 1956[30]).

Bertler, Hillarp and Rosengren (1961)[31] postulated that reserpine blocked the storage of CA in the granules and did not directly affect the synthesis.

Hillarp in 1960[32] suggested that reserpine acted as a secretory stimulus since there was a decrease in CA and adenosine triphosphate in both the normal and denervated adrenal medulla of the reserpinized rat without an in-

crease in adenosine mono or diphosphate in the cells. He implied that reserpine activated a release or inhibited a storage mechanism.

Fletcher (1964)[33] indicated a decrease in the number of dense granules in the medullary cells as well as a change in the internal structure of the granules after the administration of reserpine, and suggested that reserpine might be affecting the binding sites of CA within the granules.

In recent years a considerable number of reports have accumulated on MAO and MAO inhibitors.

In the majority of sympathetic ganglion cells MAO activity is observed histochemically in both cytoplasm and nuclei (Tanabe 1961)[34].

MAO inhibitors block the mechanism whereby monoamines are metabolized and their administration *in vivo* is associated with an increased content of intracellular amines (Zeller and Fouts 1963)[35].

According to Norberg (1965)[24], the increased NA content observed in the superior cervical ganglion following the administration of MAO inhibitors is found to be localized predominantly in the cell bodies of the adrenergic neuron.

As to the nature of the GV in the synapses or nerve endings several reports have been published.

Pellegrino De Iraldi and De Robertis (1963)[4] reported the possible mechanism of action of reserpine, iproniazid and pyrogallol on the submicroscopic structure of adrenergic nerve endings of the pineal gland.

They demonstrated a rapid depletion of the GV following the injection of reserpine, and conversely an increase in the number of the GV, and increase in the size and the density of their cores when treated with iproniazid.

Many previous investigators reported different values on the size of the GV. These difference probably is due to the speciality of species or due to the spherical shape of the GV in various nervous tissues. The specimen obtained from the edge of the GV shows smaller diameter and the specimen obtained from the largest circumference of the GV shows the largest diameter. On the other hand, the thickness of the specimen also plays some role in this regard.

However, in author's observation, mean diameters of each three groups obtained from statistical analysis and histograms showed significant difference.

Shimizu and Ishii (1964)[6] observed a marked decrease in the number of the GV in the synaptic terminals of rabbit hypothalamus following reserpine treatment. And the drug Win 18501-2 produced prominent decrease in the content of NA and the number of GV.

Furthermore, depletion or remarkable reduction in number of synaptic vesicles in sympathetic neurons was demonstrated by Uchizono (1965)[36] by applying an intense stimulation onto the preganglionic nerve trunk of sympathetic ganglion of the toad or the frog.

Wolf, Potter, Richardson and Axelrod (1962)[37] reported, using electron

microscopic autoradiography technique, the existence of NA in the electron-dense core of the GV in sympathetic axons.

The so-called elementary neurosecretory granules are found in the perikaryon of all neurosecretory cells. It is generally accepted that these electron-dense particles are produced in the Golgi apparatus as seen in the other protein-secreting cells (Scharrer and Brown 1961[38]; Bern, Nishioka and Hagadorn 1961[39]; Murakami 1962[40]; Afzelius and Fridberg 1963[41]; Bargmann and Lindner 1964[42]).

From the previous reports and the author's observations, there is a striking similarity of morphological appearance as well as pharmacological response between the GV in the synapses or in the nerve endings and the GV of the sympathetic ganglion cells.

The evidences that the GV are produced in the Golgi apparatus are as follows;

a) GV were observed especially around the Golgi apparatus in the perikarya of sympathetic ganglion cells.

b) An increase in the number of GV were observed especially around the Golgi apparatus following the administration of nialamide. On the other hand, a decrease in the number of GV was observed following the administration of reserpine.

c) At higher magnification the limiting membrane of GV was consisted with a unit membrane that was the similar structure to that of the Golgi membrane.

d) Electron dense materials were frequently observed in the Golgi apparatus, and the density was almost the same to that of the core of GV (Fig. 14).

e) Moreover, the figures suggesting that the GV might be produced as a result of vesiculation of the Golgi membrane was observed.

Therefore, the GV in the sympathetic ganglion cells are probably produced as a result of vesiculation of Golgi apparatus and then they seem to be transported proximo-distally to the synapses or the nerve endings as a result of axoplasmic flow.

And CA is probably included within the cores of the GV in the sympathetic ganglion cells.

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EXPLANATION OF FIGURES

FIG. 4. Electron micrograph showing a part of a control human thoracic sympathetic ganglion cell obtained from a 33 year old female with Raynaud's disease. Arrows indicate GV. N: Nucleus, M: Mitochondrion, G: Golgi apparatus, ER: Endoplasmic reticulum, NIS: Nissl substance, P: Pigment, GL: Glycogen, SA: Satellite cell, NSA: Nucleus of satellite cell. ×10,000

FIG. 5. GV (arrows) in the neighborhood of Golgi apparatus in the control thoracic sympathetic ganglion cell obtained from a 33 year old female with Raynaud's disease. ×30,000

FIG. 6. A pre-synaptic nerve ending (SE) filled with a number of both kinds of synaptic vesicles, mitochondria, and glyogen granules. SY: Sympathetic neuron-soma, M: Mitochondrion, GL: Glycogen granules. Single arrows indicate GV. Double arrows indicate classical synaptic vesicles (agranular synaptic vesicles). ×14,000

FIGS. 7 A, 7 B. Accumulation of pigment-or lysosome-like bodies, lamellar bodies, mitochondria, multivesicular bodies, two kinds of synaptic vesicles, glycogen granules, free ribosomes and et cetra is demonstrated in the axoplasm of the unmyelinated nerve fiber near the synapse. SY: Sympathetic perikaryon, M: Mitochondrion. Single arrows indicate GV. Double arrows indicate classical synaptic vesicles (agranular synaptic vesicles). Fig. 7 A ×14,000 Fig. 7 B ×12,000

FIG. 8. Electron micrograph showing the GV (arrow) in the axon of a myelinated nerve fiber. The axon (A) contains neurofilaments, mitochondria, glycogen granules and et cetra. ×20,000

FIGS. 9 A, 9 B. Electron micrographs showing the GV (arrows) in the axons of unmyelinated nerve fibers. Fig. 9 A ×20,000 Fig. 9 B ×20,000

FIGS. 10, 11. GV (arrows) in the lumbar sympathetic ganglion cells obtained from a 21 year old nialamide-treated male with Buerger's disease. Note the increase in number and size of GV and their cores around the Golgi apparatus. Fig. 10 ×15,000 Fig. 11 ×20,000

FIG. 12. GV (arrows) in the lumbar sympathetic ganglion cell obtained from a 57 year old reserpine-treated male with arteriosclerosis obliterans. The number and size of both the GV and their cores are apparently diminished. ×10,000

FIG. 13. GV (arrows) in the thoracic sympathetic ganglion cell obtained from a 36 year old reserpine-treated female with Raynaud's disease. Note the decrease in the size of GV and their cores. ×30,000

FIGS. 14 A, 14 B. Golgi apparatus of human sympathetic ganglion cells. Note the existence of electron-opaque materials (double arrows) within the Golgi vacuole and the GV (single arrows) in the neighborhood of Golgi apparatus. Fig. 14 A. ×20,000 Fig. 14 B ×20,000

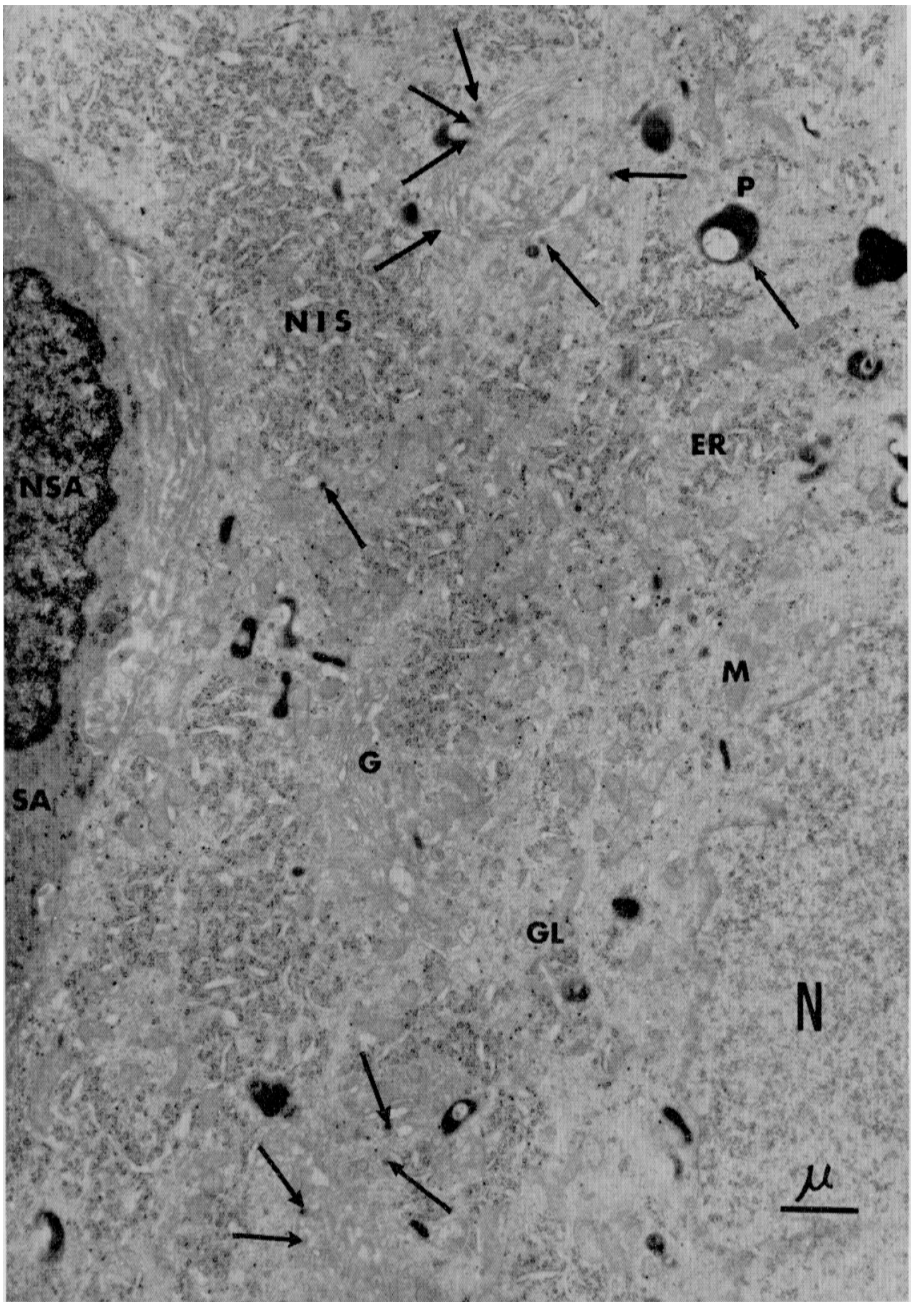

FIG. 4

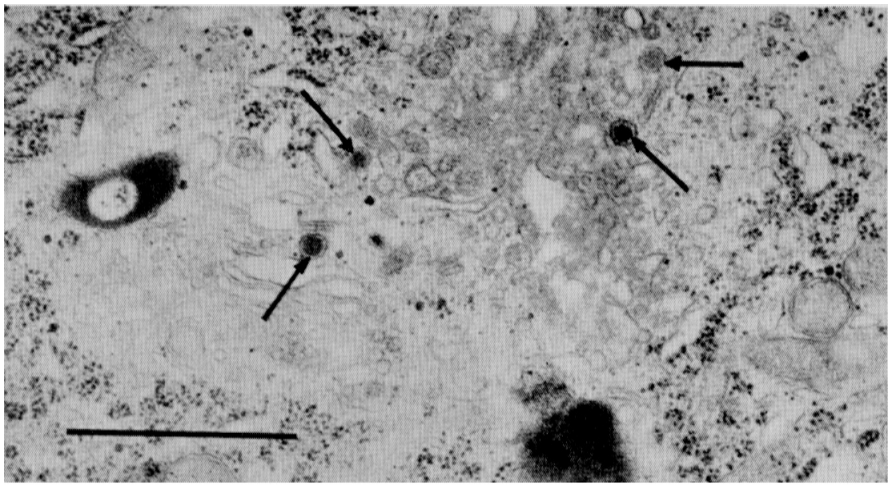

FIG. 5

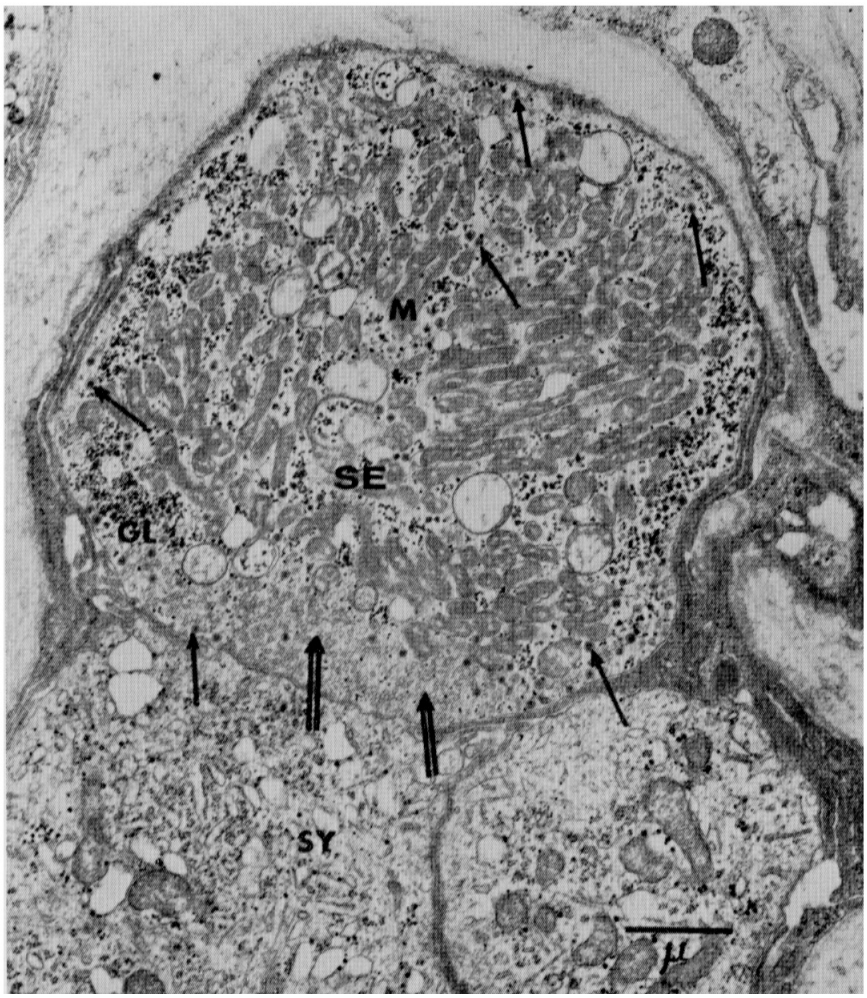

FIG. 6

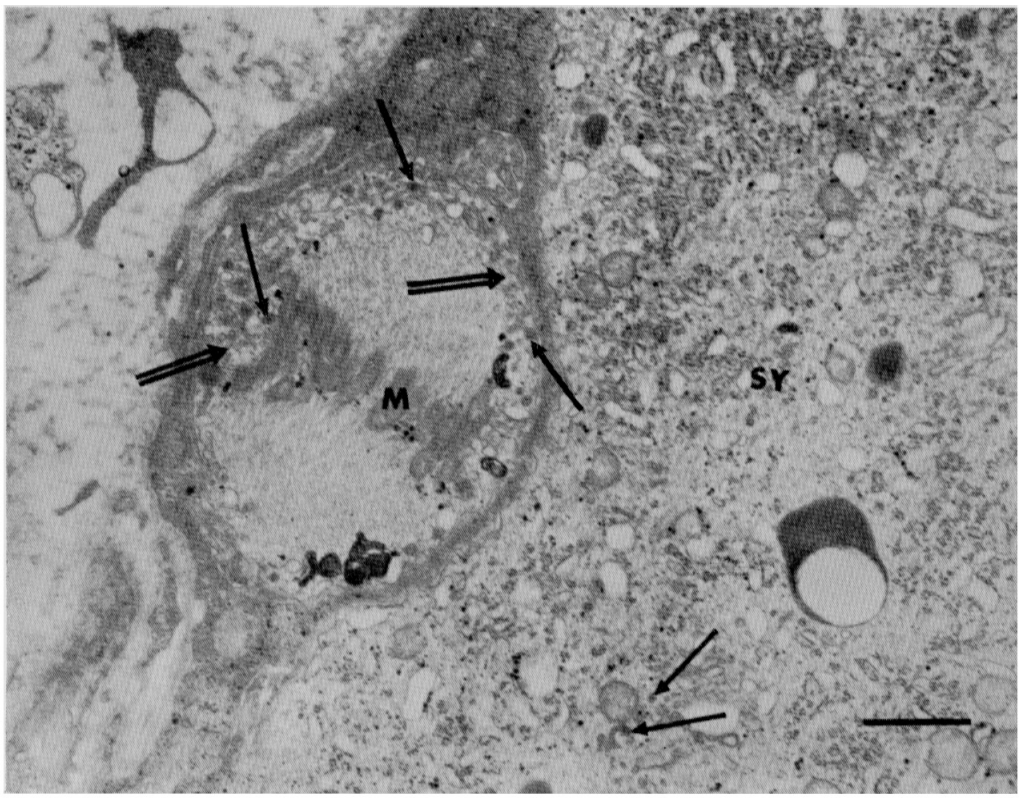

FIG. 7 A

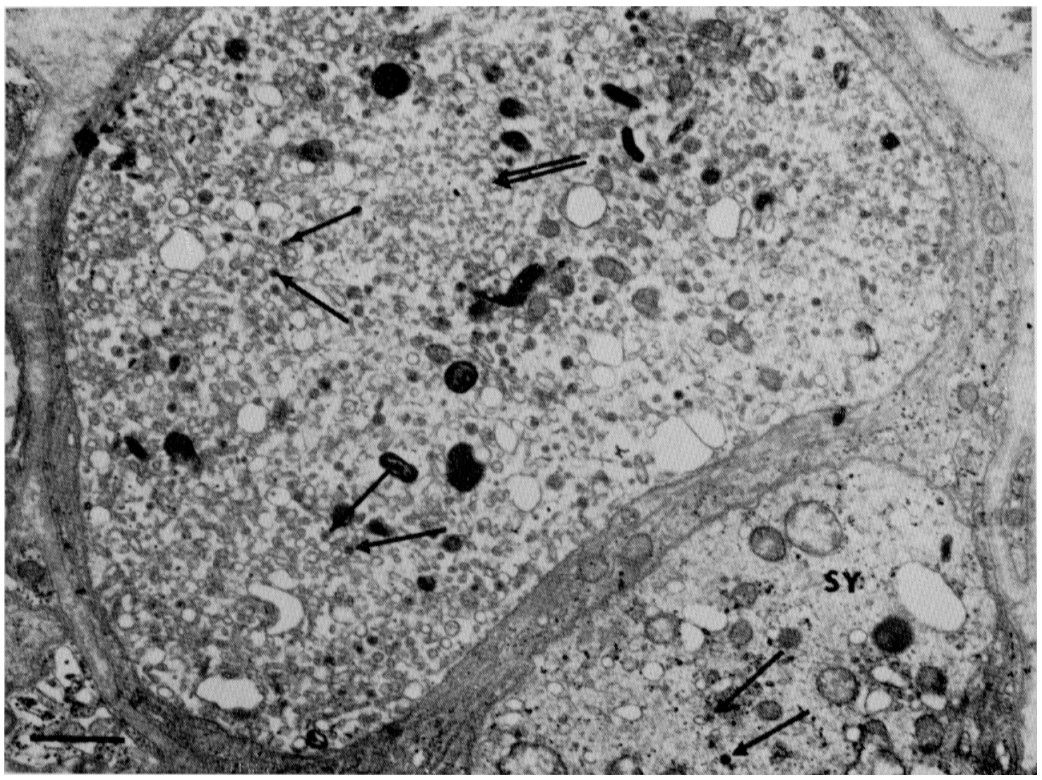

FIG. 7 B

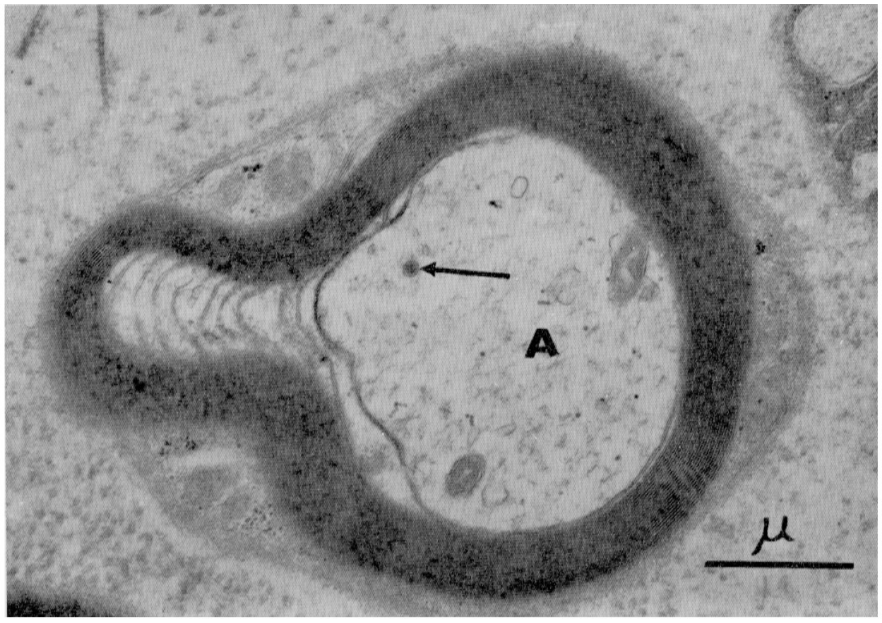

FIG. 8

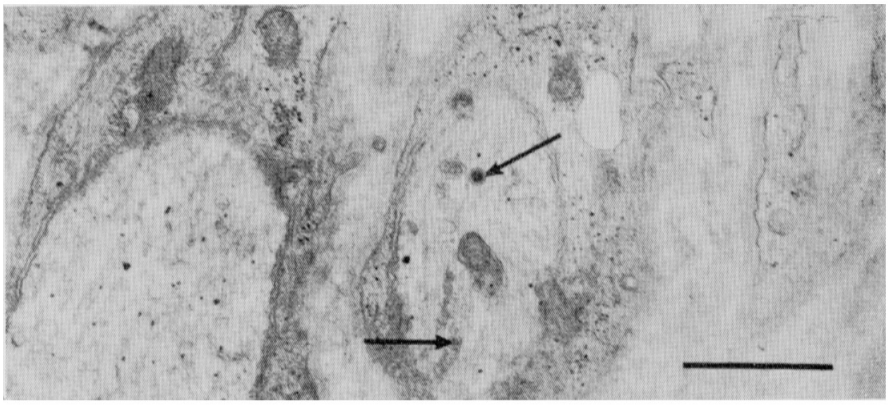

FIG. 9 A

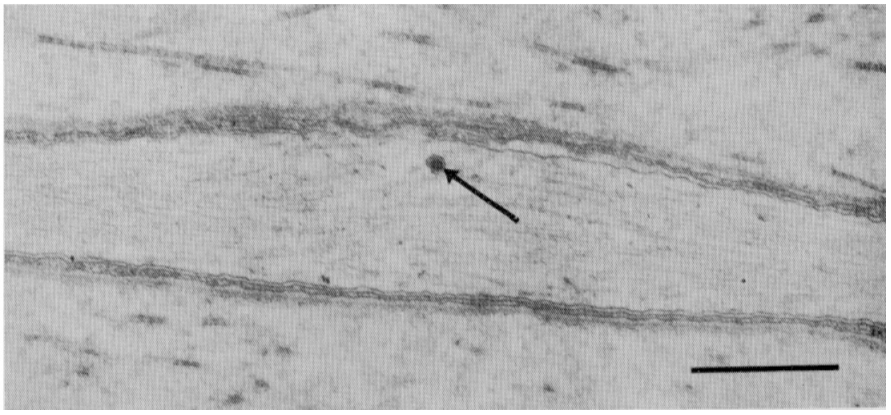

FIG. 9 B

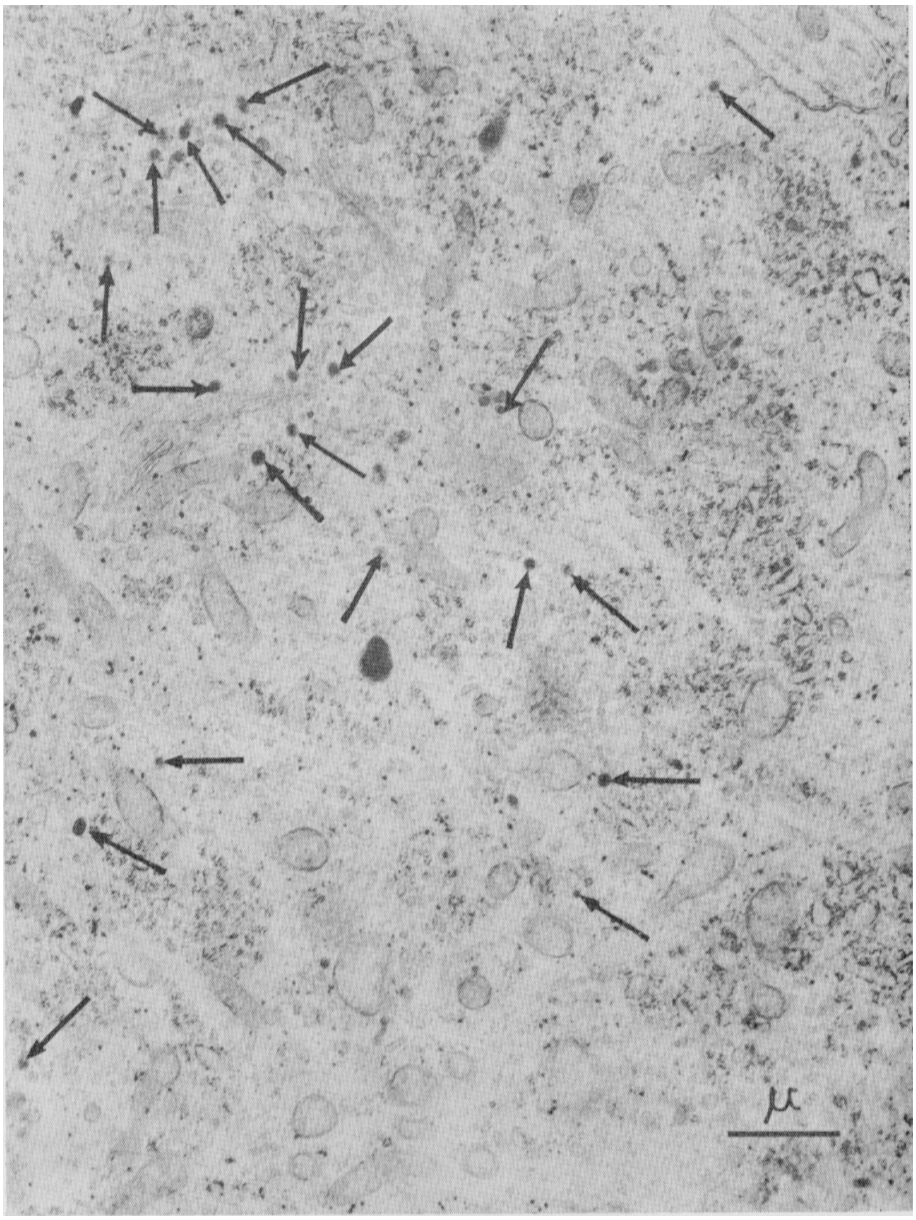

FIG. 10

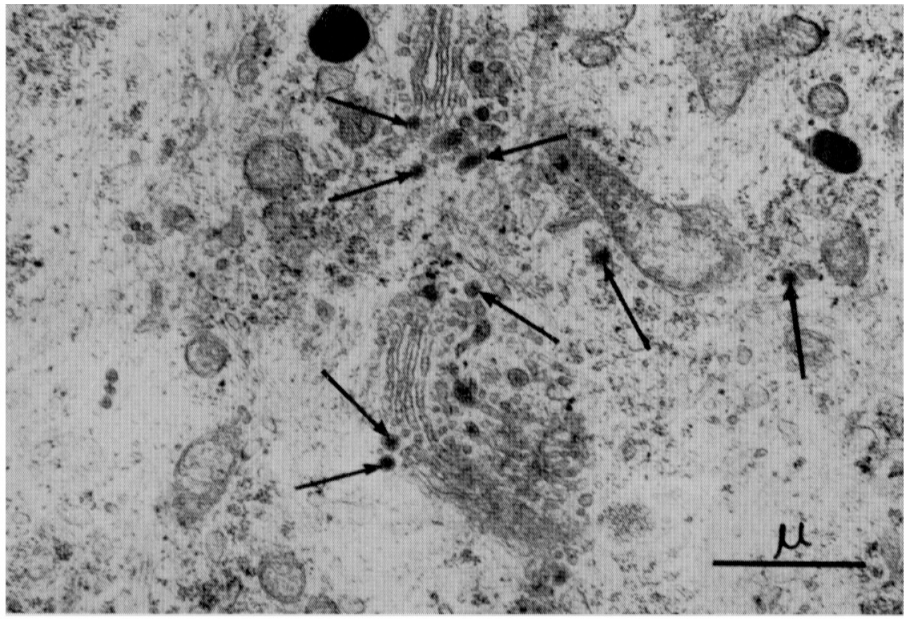

FIG. 11

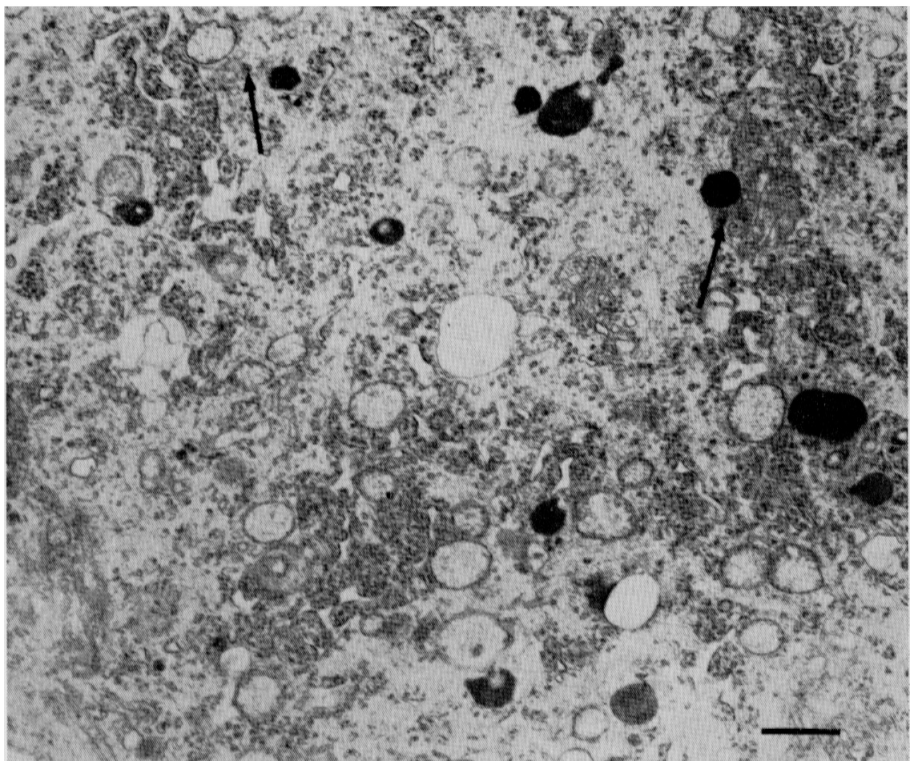

FIG. 12

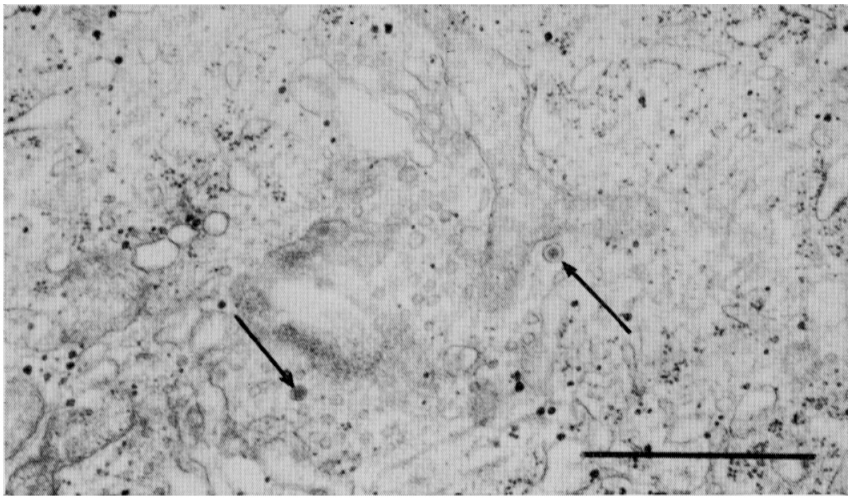

FIG. 13

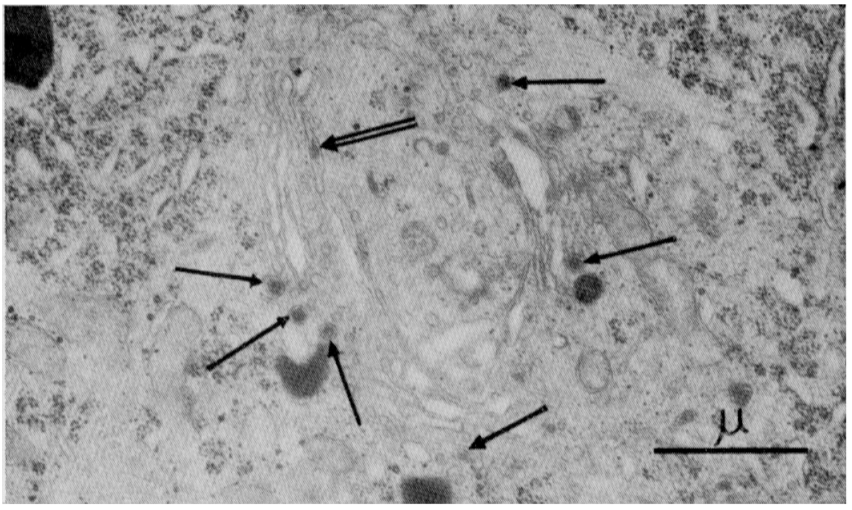

FIG. 14 A

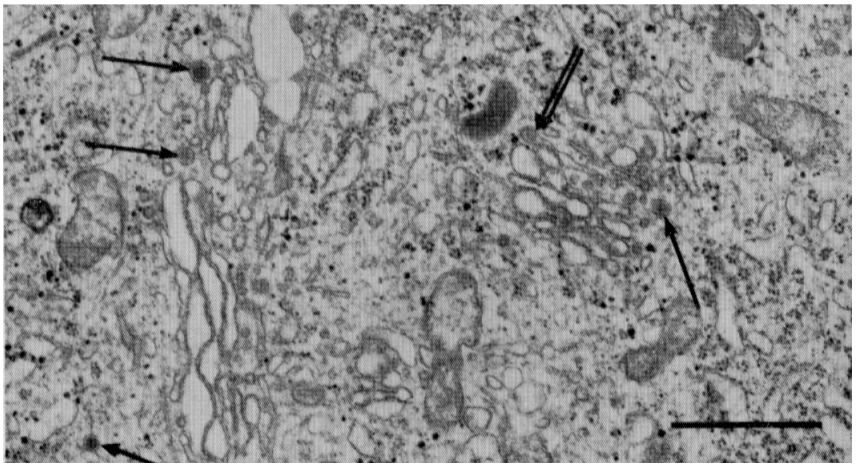

FIG. 14 B