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ELECTRON MICROSCOPY OF WHIPPLE'S DISEASE*

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SUMMARY

Electron microscopy has provided a unique insight into the peculiar morphologic characteristics of tissue affected by Whipple's disease. In the lamina propria of the small intestine, both within and without histiocytes, are abundant bacilliform bodies the fine structure and sizes of which are those of living microorganisms. The present report describes evidence for the fission of these organisms and indicates their asexual reproduction within affected tissues. It also describes observations which support the thesis that their relationship to the histiocytes is that of phagocytosis.

INTRODUCTION

Whipple's disease has attracted and continues to attract far more attention than is deserved by its prevalence. Indeed, the very rarity with which it is encountered in clinical practice undoubtedly enhances its fascination. A more cogent motive for the current meticulous study of Whipple's disease has been based on the hope that it might prove to be one of "nature's experiments" from which something of value might be learned regarding more common disease areas.

With regard to its electron microscopy, it is easy to understand the present activity, for this is a unique disease in which a reproducible configuration of probable etiological significance is recognized and can be studied readily in electron micrographs. Indeed, the presence of the morphological entities and their effects, particularly on the histiocytes of the lamina propria of the small intestine, first reported from electron microscopic studies by us in 1960 (now widely associated with the manifold investigations of Whipple's disease) and variously referred to in the past as "Whipple's bodies", "bacilliform particles", "rod shaped particles", "cylindrical bodies", etc., and now more and more definitely identified as a living organism, can be used as diagnostic aids in the study of the disease. A rereading of Whipple's 1907 classic description[1] of this disease cannot help but impress the reader favourably as he compares Whipple's original thorough light microscopic observations with the new information made available by the higher resolution of the electron microscope.

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The emphasis of this paper is to be on the *electron microscopy* of Whipple's disease in the small intestine and only the barest details will be given in both text and references relative to the clinical and light microscopical features which have been thoroughly covered in many previous publications.

Typically, Whipple's disease generally affects middle-aged men and is manifested by a protracted course, at first remittent, of arthralgia, weakness, cough, fever, steatorrhea, weight loss and progressive debility. Physical findings are chiefly lymphadenopathy and tissue wasting. Earlier cases were rarely recognized before necropsy, but in recent years, by means of lymph node and peroral intestinal biopsies, clinical suspicion of the disease has been readily confirmed by pathognomonic histologic characteristics.

It is now generally recognized that the histologic changes of Whipple's disease may be found by light microscopy in almost all organs and tissues of the body, the distinguishing characteristic of Whipple's disease being the "sickle-form particle containing cell" (SPC cell) described by Sieracki.[2,3] Accumulations of neutral fat are seen both in the intestinal mucosa and lymph nodes (to account for the earlier term, "lipodystrophy") but these accumulations are now considered to be an effect rather than the cause of the disease.

The SPC cell can be recognized in tissue stained with hematoxylin and eosin but is properly identified by the periodic acid schiff (PAS) technique. This SPC cell, which is a large histiocyte with foamy cytoplasm, can be recognized in thin paraffin sections but is best delineated in tissue imprints. Typical PAS-positive SPC cells are easily demonstrated in imprints from biopsy specimens. With the PAS stain the intracytoplasmic, PAS-positive substance appears both as sickle-form particles and as intra- and extracellular amorphous clumps in brilliant magenta. The SPC cells are most abundant in the lamina propria of the small intestine and within the mesenteric lymph nodes. It is from the small intestine that most of our material has been taken for electron microscopy.

Electron Microscopy

We have studied tissue from duodenum, jejunum and ileum and discovered the morphological manifestations of Whipple's disease in all three. In our first attempts to use post mortem material from endocardium, bronchus, trachea, liver and mesenteric lymph nodes which demonstrated the gross effects of the disease we have been unable so far to demonstrate any electron microscopic evidence for it.† The observations reported here and illustrated in the electron micrographs are from jejunum and ileum biopsies taken by Crosby capsule. The specimens were deposited within one minute into buffered 1 per cent osmium tetroxide to be fixed, and later dehydrated, embedded and thin sectioned by the standard techniques. Embedding was accomplished in

†In a private conversation during the 7th Congrès International de Gastro-Entérologie held in Brussels in June 1964, J. Malinsky of Olomouc, Czechoslovakia, demonstrated to one of us the morphological manifestations of Whipple's disease in electron micrographs of mesenteric lymph nodes taken from patients with the disease.

methacrylate mixtures (30 per cent methyl to 70 per cent butyl). Final polymerization of the prepolymerized embedding was done under a dry nitrogen atmosphere. The sections were subsequently stained with lead hydroxide or lead citrate and/or uranyl acetate. A Porter-Blum ultramicrotome, and a Siemens Elmiskop I were the instrumentation used. Specimens were prepared simultaneously for examination by light microscopy.

In many recent papers on electron microscopy a variety of explanations have been offered for the occurrence in Whipple's disease of elongated PAS-positive particles in the lamina propria of the small bowel, lying free about and near the histiocytes or held within these macrophages. In 1960 Haubrich et al[4] postulated that these particles might be an elaboration of an abnormal protein-carbohydrate complex developed by and later expelled from the histiocytes in the form of cylindrical bodies. Again, in 1960, Watson and Haubrich[5] suggested from electron microscopical studies that because of their size (average length about 1.5, width about 0.15 microns) and obviously well-differentiated structure *the rod-like particles could be of the nature of bacteria.* Since 1960 the most significant evidence, including the present paper, has mounted for the identification of these bodies as some type of living organism undergoing phagocytosis by the histiocytes, although as late as 1962 Fisher[6] theorized that the sickle-form particles were derived from mitochondria and that the rod-like particles were not microorganisms. Even in 1963 Adams et al[7] examining tissue by electron microscopy from a case of Whipple's disease in remission concluded that the fine structures of the cytoplasmic bodies were interpretable as compatible with primary synthesis by the histiocytes, although they did not rule out possible phagocytic origin.

Cohen et al[8] in 1960 considered the possibility that the bodies were viral in nature, and in 1962 Cohen[9] commented on the possibility that the PAS-positive inclusion in the microphages was related to the dense rods found at the cell border in a sequence of their phagocytosis and destruction. More recently the same author[10] has presented further electron microscopic experimental evidence, much like our own, that the particles are rod-shaped microorganisms, but although his combined morphologic and clinical data suggest that they are the etiologic factor in Whipple's disease, he stops short of drawing this conclusion.

The possible role bacteria might play in the disease was also commented upon by Yardley and Hendrix[11] and by Chears and Ashworth[12] in 1961 and by Kurtz et al[13] in 1962 who discussed the results of treating the disease with antibiotics. Their results were consistent with those of Perez et al[14] published in 1963, who reported striking improvement in the clinical picture, disappearance of the bacilliform bodies and modification of the abnormal ultrastructure of the histiocytes with antibiotic treatment. Hollenberg[15] also described electron microscopic findings in Whipple's disease, using steroid therapy and antibiotics and reported salutary effects with the latter. Although he did not stress the potential bacterial nature of the disease he did mention that the appearance and size of the cylindrical bodies were somewhat suggestive of rickettsial

or large virus particles. In 1963 Kent et al[16] also described apparent bacterial organisms and their rleationship to the disease. They associated them with the disease because of their persistent presence in active patients, their absence and the regression of the lesions in patients in remission, and their apparent phagocytosis by macrophages with replacement of groups of degenerating intracellular organisms by membranous (PAS-positive) particles.

Attempts were made in our laboratory and by others to culture microorganisms from biopsy specimens but without success. Kurtz[17] has told us that he has probably obtained a pure culture growth but has not yet classified the organism. Kok, et al[18] and Rostgaard[19] recently have reported their work regarding bacteria in Whipple's disease, have discussed the difficulties of proving absolutely which microorganism might be the etiological agent in the disease, and have concluded that the *Haemophili-like* rod might be a better possibility than *Corynebacteria.* Caroli[20] and his group, on the other hand, have also published extensively on the results of their studies and have presented striking evidence that the responsible organism is a gram-positive *Corynebacterium.* That bacteria are present in the jejunal tissue in Whipple's disease is in their view beyond question, as is the importance of these bacteria to the disease and its course as proved by the effect of antibiotics upon them.

Thus the present evidence, our own and that of many others, indicates that the abnormal particles are indeed bacilliform and of the nature of bacteria. The histiocytes then are either phagocytizing these organisms and destroying themselves in the process, or the bacilliform particles are entering the histiocytes, and multiplying therein to destroy the cell. Of these two alternates the overwhelming evidence is for the former phagocytic action.

The evidence for this interpretation will become evident in the following discussion. The Figures 1 and 2 at low magnification are shown for the dual purposes to orient the reader toward the higher magnifications and resolutions inherent in electron micrographs, and to illustrate the basic description of the Whipple's bodies specifically within the lamina propria. Figure 1 shows a section of the *epithelial* cells of human ileum, lead citrate stained. The entire region from the lumen (*L*) *and microvilli* (*Mv*) to the basement membrane (*BM*) is visible and the cells on the luminal side of the basement membrane are found to be normal except for a frequent occurrence of large intercellular lipid droplets (*Li*), among the epithelial cells in the Whipple's material. The number, shape and size of the microvilli, the appearance of the cell walls, mitochondria (*M*) and other cytoplasmic bodies have been identical with those observed in normal mucosa.† Abruptly beyond the basement membrane the abnormal, darkly-staining rod-like bacilliform particles (clear arrow) occur in great abundance in the lamina propria.

Figure 2 is an extension of the field of Figure 1 further into the lamina propria. In this particular area the histiocytes do not contain the bacilliform particles although several of these are seen apparently in the process of invading one such cell at the

†One possible exception to this is reported at the end of this paper.

solid arrowhead. This figure also illustrates electron microscopically the extensive lipid inclusions known from light microscopy to occur in Whipple's disease in the lamina propria both exterior and interior to the histiocytes. These inclusions are very frequently located within a clear area and are often encircled by a membrane, (clear arrow).

Figure 3 shows a swollen, heavily infected histiocyte in which little of the original cell organization, except for a rather malformed nucleus (*N*) and a few scattered mitochondria are recognizable. Other than these the whole cell is full of *nests* of more-or-less oriented oval vacuoles, or elongated sacks, the diameters and widths of which are consistent with those of the extracellular bacilliform particles. These vacuoles and sacks possess a membrane (sometimes recognizably double) and are interpreted as the remains of the phagocytized particles, after their internal content has been partially or completely destroyed. In the examination of many such cells, all stages of degeneration of the bodies are observed. *The nests of phagocytized bacilliform particles constitute the sickle-form particles observed to be PAS-positive in light microscopy. The entire infected histiocyte constitutes the SPC-cell of foamy appearance reported originally by Whipple.*

It is instructive at this point to observe for comparison the appearance of the lamina propria in the *normal* condition. The morphology of the normal cell, Figure 4, is quite different to that of one which is affected by active Whipple's disease. The double-walled nucleus is intact. There are well preserved mitochondria with many cristae, plentiful rough endoplasmic reticulum (RER) and an active golgi complex (Go), all readily indentifiable, Figure 5. The appearance of the cisternae of the endoplasmic reticulum and of the Golgi indicate that the cell is active in the synthesis of protein. A comparison of the organized healthy cell with the vast changes which occur in Whipple's disease, Figure 3 is striking. It would appear that the phagocytosis, instituted by the cell against the rod-shaped, bacilliform particles of Whipple's disease, interferes markedly with the cell's normal processes and it is difficult to find in the cytoplasm of the infected histiocyte any remnant of either the RER or of the Golgi, although the altered nucleus, single ribosomes (*R*) and a few isolated mitochondria are still often recognizable especially in lightly infected cells. At the arrow in Figure 4, (shown again in the insert at higher magnification) is a lysosome (or a mitochondrium) which contains a crystalline inclusion body and has a repeating structure in its membranes.

Figure 6 shows at higher magnification part of an highly infected histiocyte from the lamina propria of ileum stained with lead hydroxide. There are a few remaining mitochondria but very little of the original cell cytoplasm except for scattered ribosomes. There are many vacuolated areas (*V*) and four small lipid inclusions are observed. Many nests of oriented, degenerating bacilliform particles are seen, some in longitudinal, others in cross section, and there is a membrane, often recognizably double, about each nest. The particles themselves are in all stages of phagocytosis, some have dense double membranes and wherever their internal structure is still preserved they are seen to have a relatively heavily staining, vacuolated

interior. Wherever they are relatively unaffected by an early stage of the phagocytic process, the intracellular particles are readily identifiable with those located extracellularly. After prolonged phagocytic action they lose much of their structure and are less readily identified. This is more evident in Figure 7 which shows part of an histiocyte filled with membranous sacks of various diameters, which are judged to be the remains of a very late stage in the phagocytosis of the particles. These usually possess a single observable membrane and scattered among them are the few remaining organelles of the original cell. Groups of fine granules (*Gr*) are seen and an occasional dense body (*B*). Of the membranous structures, there are two distinct families distinguishable by their sizes, the larger ones measuring from about 0.1 to 0.2 microns across, the others with widths of about 0.02 microns. We are of the opinion that the larger membranes are the product of a late stage of degradation of the organisms and that the smaller represent complete collapse of the membranes after complete phagocytic action by the macrophage.

Assuming that a phagocytic action does explain the presence of the Whipple's bodies within the histiocytes, it becomes pertinent to seek locations in the electron micrographs where they are *first* invading, or being entrapped by the cytoplasmic membrane of the histiocytes. It is also pertinent to discover and evaluate their state of preservation in the *lightly* infected cells. If they are better preserved, (i.e. resemble more closely the extracellular bodies) in the lightly infected over the heavily infected cells one could conclude that the bacilliform particle is indeed moving from without to within the cells rather than the reverse.

Figures 8A and B show relatively lightly infected histiocytes where there are many locations where the cell wall is invaginating to enclose an approaching microorganism. At the arrows, single particles are completely enclosed just within the cytoplasmic membrane. The identity in size and appearance (including the existence of the double membrane) between the extra- and intracellular organisms is noted. The tendency for them to be oriented within their nests is also observed again. Since, in the least affected cells they appear to be in better condition, (i.e. with thicker membranes, more cell content, more identifiable appearance) and vice versa, we have concluded that they are enteriing the cells rather than that they are a product of a development process within the cells. Many are demonstrated here extracellularly, where they are invariably densly stained, and show a well differentiated internal structure, leading to the conclusion that they are more viable extracellularly.

Figures 9A and B also show evidence of the phagocytic action at the cytoplasmic membrane of the cell. In Figure 9A at the arrows a particle is being taken into this already infected histiocyte. The cell cytoplasm is vacuolated and has some mitochondria and single ribosomes. In Figure 9B the cell wall is seen to have partly surrounded, and at other places to have completely entrapped the Whipple's bodies. The double walls of both the histiocyte and the body have been preserved and are observed (arrow) as the body enters the cell. One such particle has been completely absorbed by the histiocyte just inside its cytoplasmic membrane.

If, as appears now to be the case, these bodies are organisms of some kind, it might be expected that some evidence of their reproductive processes, such as division by binary fission, would be observable at times in the electron micrographs. Figure 10 shows evidence of cell division and illustrates in addition at higher magnifications the well differentiated nature of these rod-like particles, yielding further evidence that they are indeed living organisms. In Figure 10A, where the tissue is uranyl acetate stained, a single cell just at division is seen at the arrow. The organism is seen to possess a double membrane and outside of this is a rough coating which is striated in repeating distances of about 20 A.U.* and which almost seems to bear a third membrane at some locations. The vacuolated interior is densely stained by the uranyl acetate indicating that it contains nuclear content[21] and supporting the concept that this is indeed a living organism. At the arrow in Figure 10B, which is lead stained, there are two organisms lying end-to-end, the product of a late stage of division. Everywhere there is evidence for a rough, striated coating about 150 A.U. thick, in addition to a heavily stained inner double membrane. Figure 10C shows two examples of very early division, where the wall is only slightly indented (arrows). Figure 10D clearly shows the two dark inner membranes and the rough coat about them. Figures 11A and B represent sagittal sections of the tips of these bacillary bodies in which there is a rough, striated outer coat and two dark inner membranes similar to those in Figure 10.

The highly differentiated nature of the organisms is revealed in cross sections as well as longitudinal sections. This is illustrated in Figures 11C and 12 A, B, C and D of uranyl acetate stained tissue. These fields are extracellular and show also how the structure of the organisms is maintained before phagocytic acceptance by the cell. Our observations on many sections of these organisms have shown that either one of two structures is most frequently seen. The first and most frequent is one in which two layers, separated by a light layer are covered by a rough striated outer coating which itself tends to demonstrate a dark outer density: the central dark core being separated by a clear area from the innermost of the double dark layers. This is illustrated schematically at "A" in Figure 13. The second structure, seen less frequently, is one in which, in addition to the same three dark layers, there is one other dark layer associated with and partly surrounding the central core itself. This is illustrated at "B" in Figure 13 where the average dimensions for three structures are also given. The two dark layers are probably the cell wall in both cases. In no case have we observed anything which could be interpreted as the cytoplasmic membrane. The dark inner nuclear membrane, seen in some locations in Figures 10A, 12A, C, D, could be a result of negative relief, although it appears real enough where it is observed. The rough coat could be capsular in nature but is more likely composed of cellular debri and the outer density seen at times upon it, as in Figures 10A, B, 12A, B, C, and elsewhere does not seem to be a result of negative relief.

Several variations of the two most frequently observed structures are noted. In Figure 11C there appear to be three equally spaced (50 A.U.) dark layers of about

*1 Angstrom unit (A.U.) = 10^{-8} cms.

equal thickness (70 A.U.) and no rough coat; the innermost layer being associated with the periphery of the nuclear content of the body. In others, as in Figure 10D, in addition to a rough outer coat, there are a total of only two dark membranes separated by a clear layer. In still others there is evidence for two outer double layers and two inner double layers as well as a single inner layer associated with the nuclear content, Figure 12C. These structures do not seem to be characteristic of any immediately identifiable genus of bacteria.

This well differentiated complex structure, the evidence of cell division, the differential staining of the nuclear core by uranyl acetate, and their dimensions identify these particles as living but as yet unclassified organisms and confirms their relationship to the PAS-positive staining of the macrophages in Whipple's disease. The study therefore supports the conclusion that Whipple's disease is a type of infection due to a microorganism most closely resembling in size, shape and appearance a very small bacterium or a rickettsia. It is not possible to conclude that the microorganisms are the primary cause of the disease. How they reach the region of the lamina propria so specifically is not known, nor is it explainable why they should be so abundant there and be not at all in or about the epithelial cells. Kent[15] has said that he has observed evidence for them in the lumen. We have not.

Until recently we had observed nothing abnormal about the epithelial cells except the intercellular lipid deposits referred to earlier. The whole effect of Whipple's disease in the small intestine was restricted to the lamina propria. However, recent close examination of our plates, has revealed the presence of infrequent lysosome-like structures within the epithelial cells which contain rounded, membraned structures with a darkly staining core of size and appearance identical with those cross sections of organisms which found so readily in the lamina propria. Figure 14A shows such lysosomes in an epithelial cell from human ileum of a patient with Whipple's disease. The microvilli can be identified. At the arrows are the rounded structures within the lysosomes. Such lysosomes have been discovered[22] in the normal intestinal mucosa of fasting humans, and after overloading with iron, and in pathological mucosa of man during malabsorption syndrome. Further study of these structures and their possible relation to the bacillary bodies is being pursued at this time. Figure 14B of a heavily infected histiocyte of the lamina propria is included to allow convenient comparison of the cross sections of identifiable Whipple's bodies in it with the rounded inclusions in the lysosomes of Figure 14A.

Unanswered Questions

Several important questions remain to be answered more completely by future investigations: 1) what are the genus and specie of these organisms? 2) can they be cultured, and can they reproduce a disease state in susceptible animals 3) are these organisms of primary etiologic significance in Whipple's disease or are they secondary invaders? 4) if they represent primary infection, how do they gain access to the lamina propria, why do they not elicit an inflammatory reaction typical of bacterial infection, and how do they produce the clinical manifestations of Whipple's

disease? 5) do these same organisms occur in all of the variety of organ systems known to be affected by Whipple's disease? 6) if so, how are they disseminated?, and 7) what is the antibiotic most effective against these organisms, and what is the treatment regimen which will assure their total eradication and the cure of Whipple's disease?

LEGEND

BM	Basement Membrane	M	Mitochondria
B	Body (Dense)	Mv	Microvilli
Go	Golgi Complex	N	Nucleus
Gr	Granule (Fine)	Nuc	Nucleolus
H	Histiocyte	RER	Rough Endoplasmic Reticulum
L	Lumen	V	Vacuole
Li	Lipid		

Figures 1 and 2

Low magnification electron micrographs to show the general appearance of the mucosa of human ileum in Whipple's disease from the region of the lumen through the basement membrane to the lamina propria in Figure 1, and further into the lamina propria in Figure 2. The general heavy population of PAS-positive bacilliform particles which begins abruptly beyond the basement membrane and is completely absent from the epithelial cells is noted in both figures. In Figure 1 the intercellular lipid inclusions are shown and in Figure 2 the many lipid droplets both within and without the histiocyte are seen. The tissue is lead citrate stained and the magnification is X10,000.

Figure 3

An heavily infected histiocyte at low magnification, showing little of the original cell content except a malformed nucleus and a few isolated mitochondria. The whole cell is packed with nests of bacilliform particles in various stages of phagocytic destruction. Other particles are observed extracellularly. The tissue is ileum, lead citrate stained and the magnification is X8000.

Figure 4

A *normal* histiocyte from the jejunal lamina propria for comparison with that in Figure 3. It shows well preserved ultrastructure, mitochondria well supplied with cristae, plentiful rough endoplasmic reticulum, and an active golgi complex. The magnification is X15,000. The insert demonstrates at increased magnification (X60,000) a crystalline inclusion body within the lysosome marked by an arrow. This crystal has a repeating structure of the same order in the wall of the lysosome.

Figure 5

A part of Figure 4 at higher magnification to show detail of the cell ultrastructure in the region of the Golgi complex, X55,000.

Figure 6

Part of an heavily infected histiocyte at higher magnification than Figure 3, showing lipid inclusions, nests of bacilliform particles in a variety of stages of phagocytosis and a few remaining cell organelles. The tissue is jejunum, lead hydroxide stained and the magnification is X30,000.

Figure 7

Part of a heavily infected histiocyte demonstrating advanced phagocytosis of the bacilliform particles. Fine granules and an occasional dense body are seen but none of the original cell structure. The tissue is ileum, lead citrate stained and the magnification is X55,000.

Figure 8

Early phagocytic activity by the histiocytes at their cytoplasmic membranes is shown, as well as many viable extracellular bacilliform bodies. The tissue is jejunum, lead hydroxide stained and the magnifications are X16,000.

Figure 9

Early phagocytic activity by the histiocytes at their cytoplasmic membranes is shown. The tissue is jejunum, lead hydroxide stained and the magnifications are A-X36,000 and B-X60,000.

Figure 10

Longitudinal sections of single bacilliform particles at sufficiently high magnifications to show their complex internal structures and their reproduction by binary fission. The tissue is ileum, *A* stained with uranyl acetate, *B* with lead hydroxide, *C* with uranyl acetate and potassium permanganate, and *D* with uranyl acetate. The magnifications are *A*-X125,000; *B*-X150,000; *C*-X75,000; *D*-X170,000.

Figure 11

Sagittal sections of the tips in *A* and *B*, and cross sections of the bacilliform particles in *C* to demonstrate their complex fine structure. The tissue is ileum, *A* and *B* stained with uranyl acetate, *C* stained with uranyl acetate and potassium permanganate, and the magnifications are *A* and *B*, X240,000; and *C*, X170.00.

Figure 12

Cross sections of the bacilliform particles to demonstrate their complex fine structure. The tissue is ileum, *A B C* stained with uranyl acetate, *D*, with lead hydroxide, and the magnifications are *A B C*, X240,000 and *D*, X280,000.

Figure 13

Schematic drawings (not to scale) to illustrate two of the most commonly observed arrangements of membranous structures of the bacilliform particles in Whipple's disease: *A*, with three dense membranes, one of which is associated with a thick striated outer coating; *B*, with a striated outer coating plus three inner dense membranes, one of which is associated with the nuclear content.

Figure 14

In 14*A* is an epithelial cell near the lumen of the jejunum in Whipple's disease showing lysosomes which contain rounded, polymembraned bodies with a dense nucleus, very similar in morphology and size to the Whipple's bodies observed in the lamina propria in Figure 14*B* and elsewhere. The tissue is ileum, stained in *A* with uranyl acetate, and potassium permanganate in *B* with uranyl acetate alone. The magnification is X35,000.

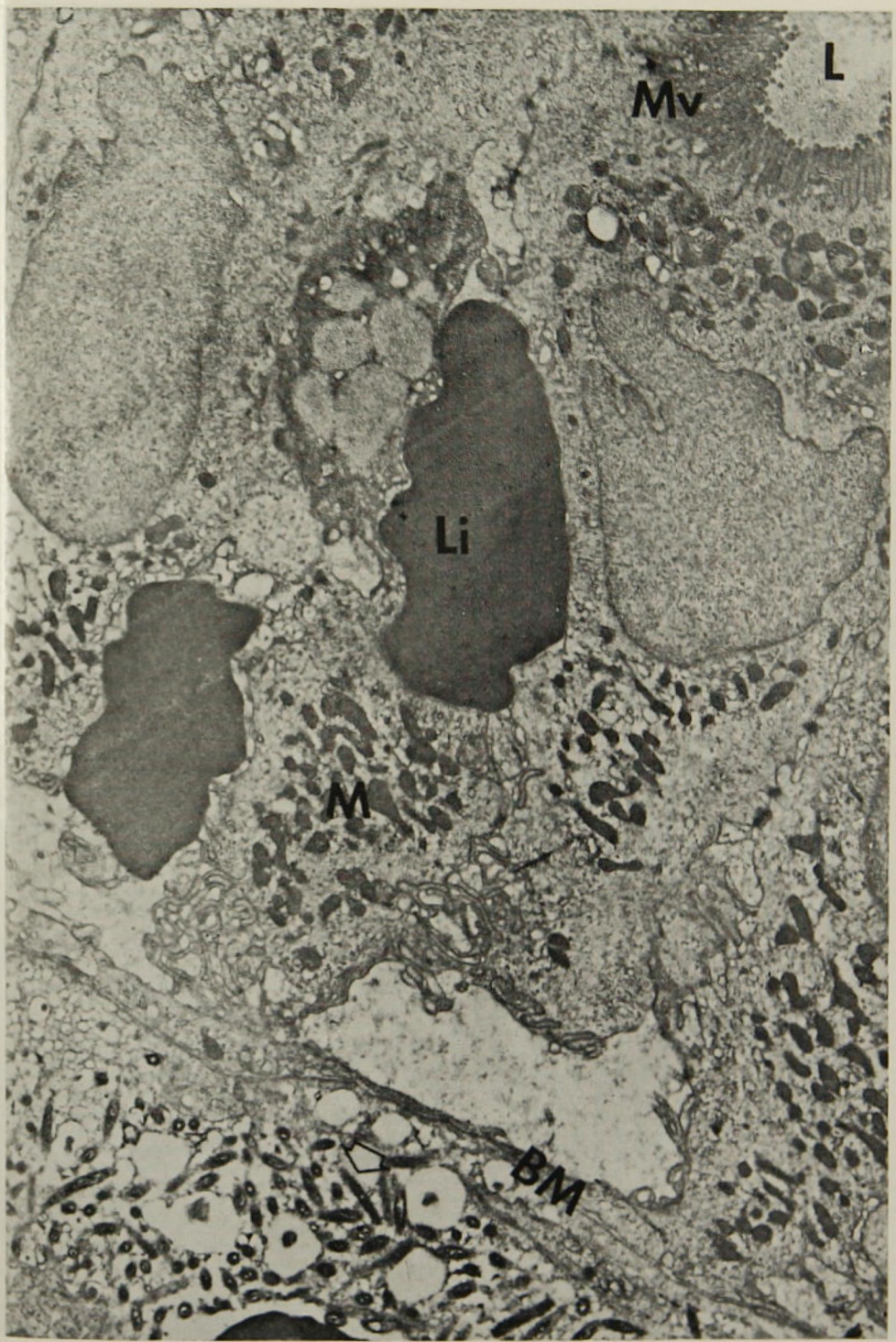

Figure 1

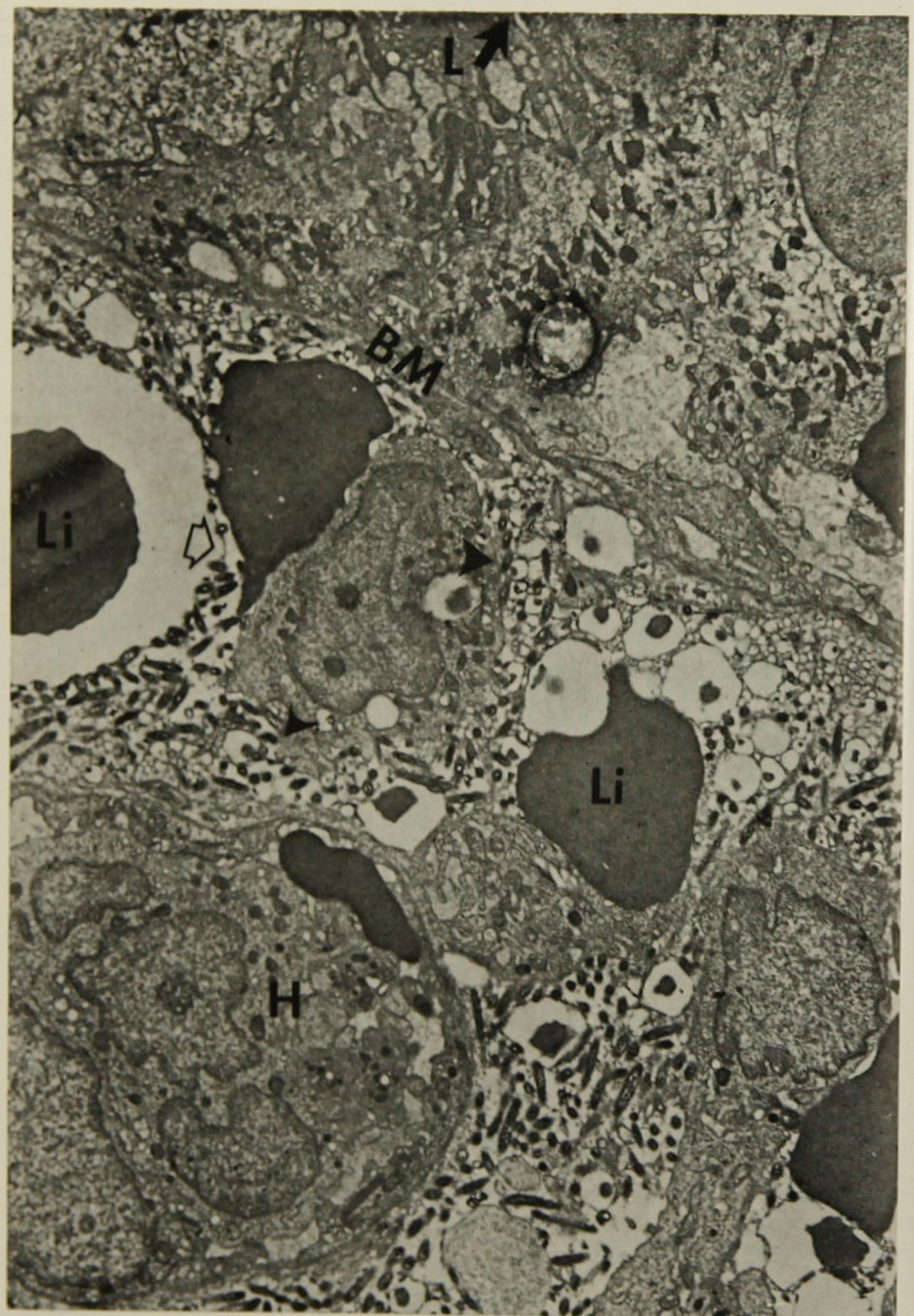

Figure 2

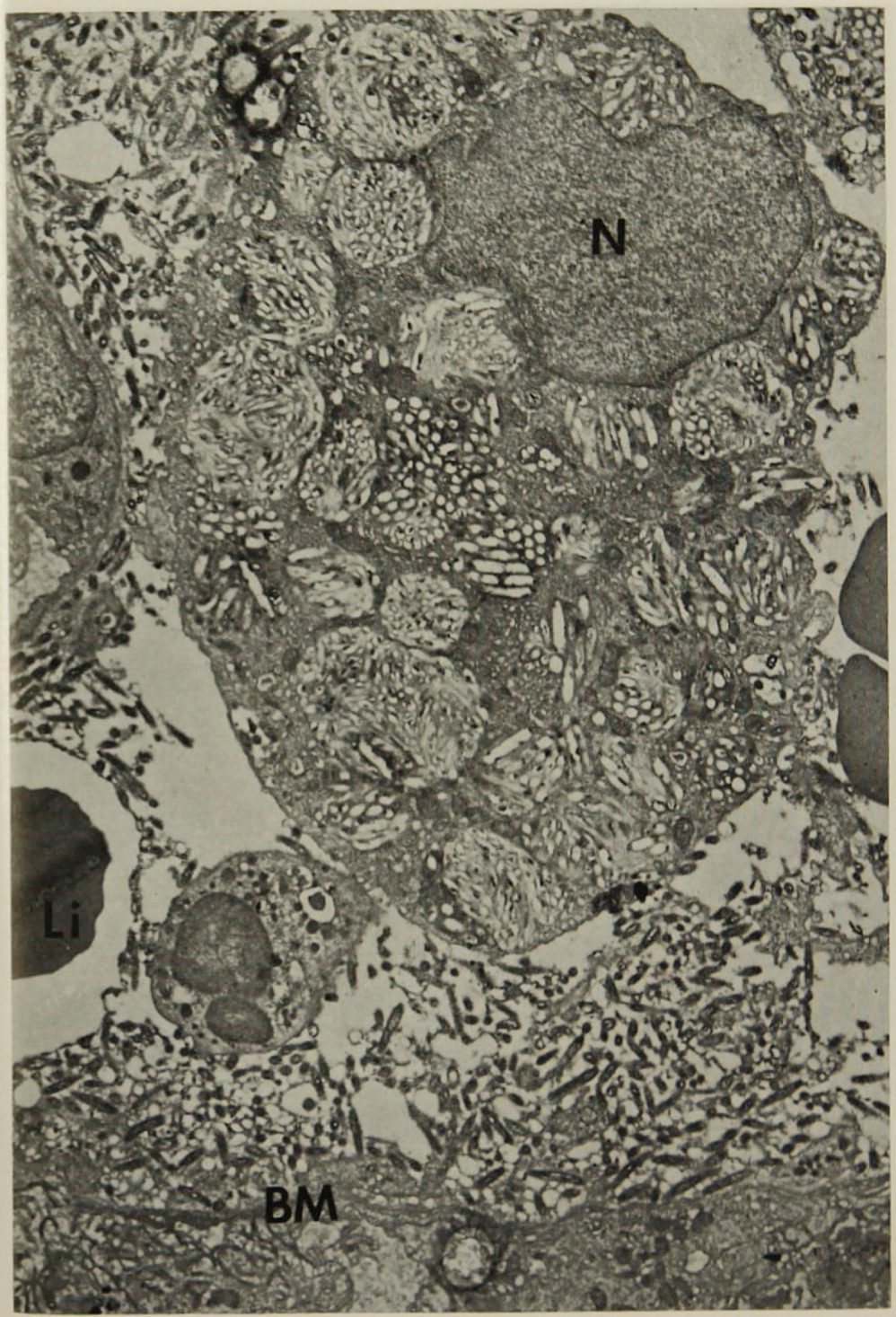

Figure 3

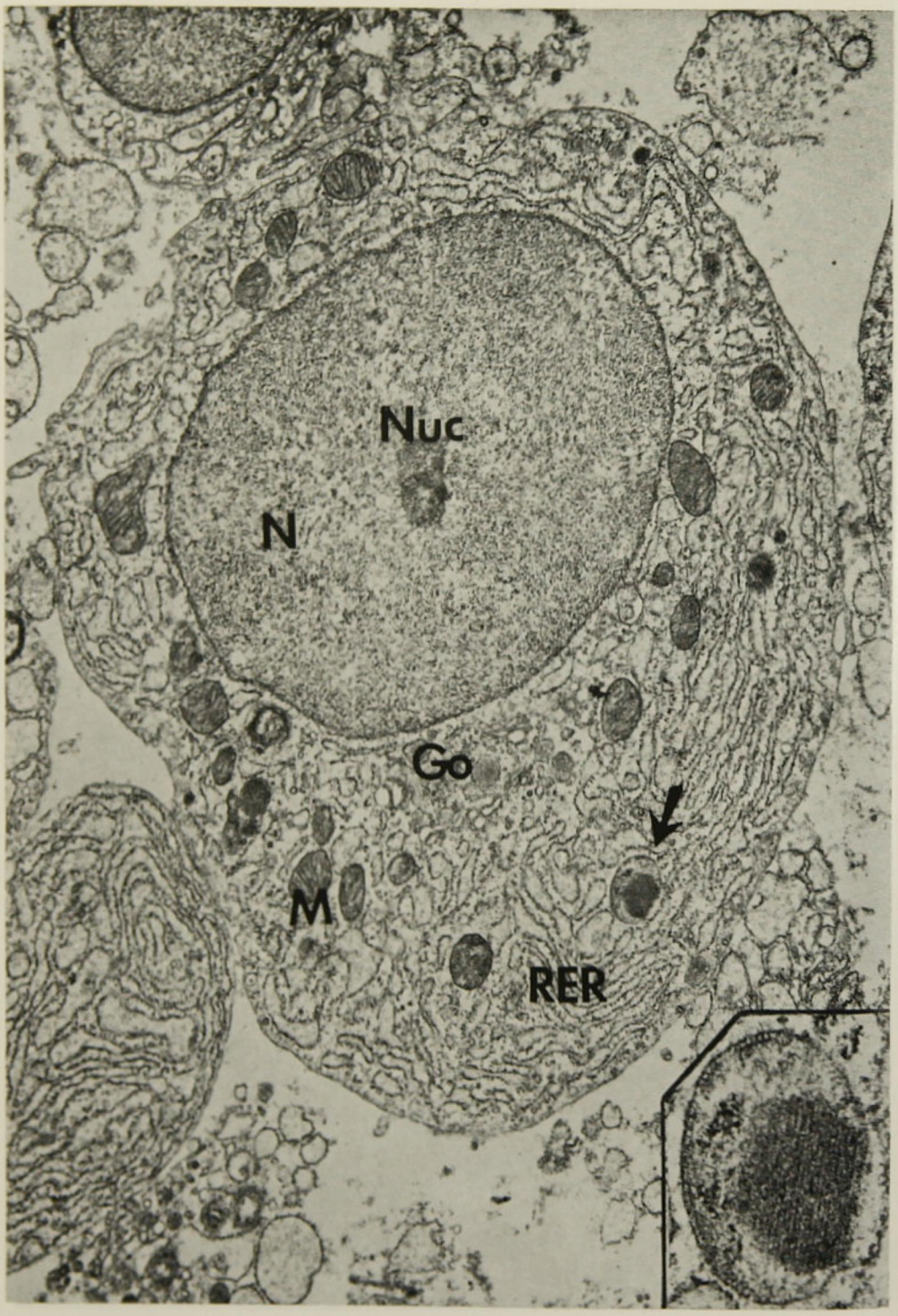

Figure 4

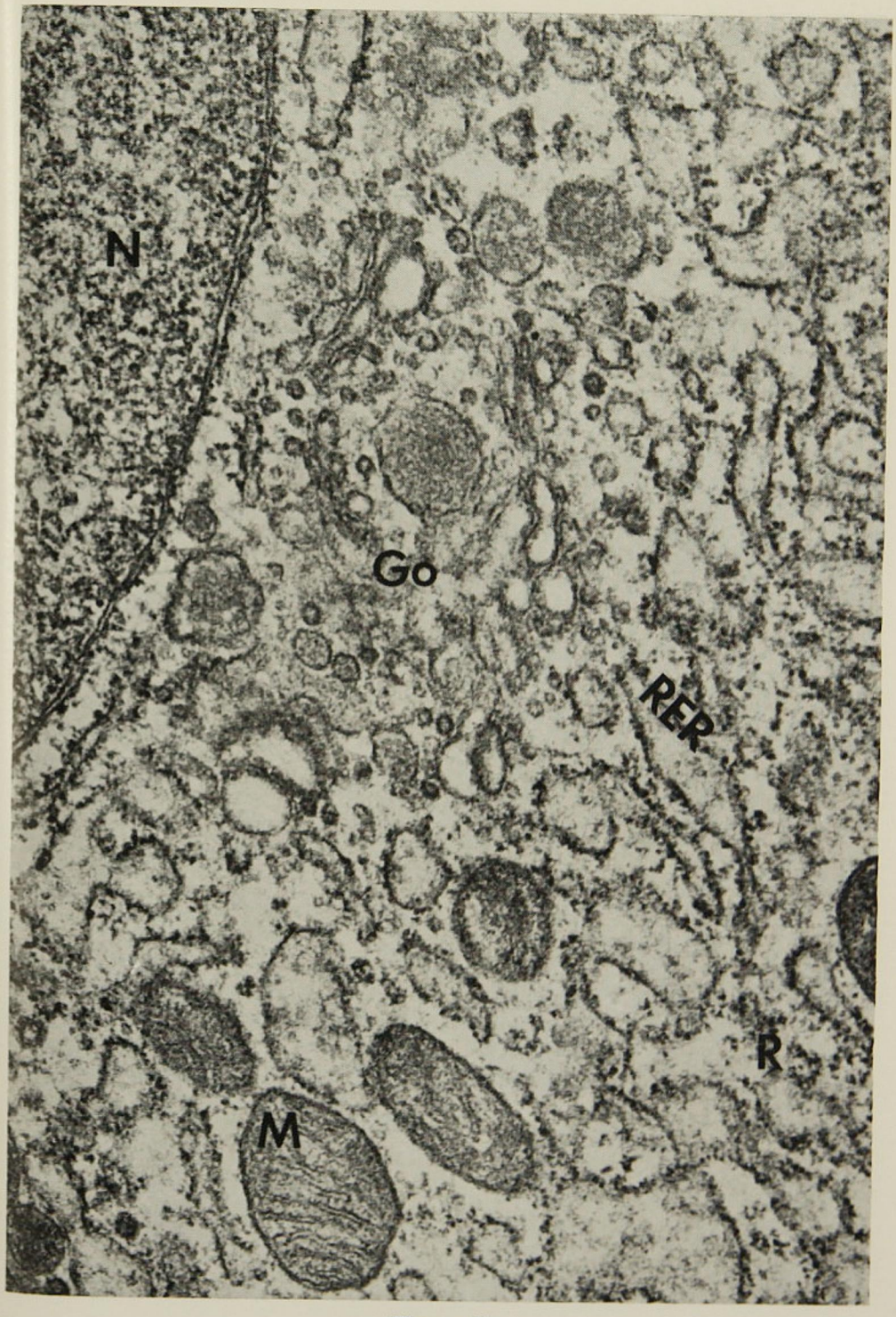

Figure 5

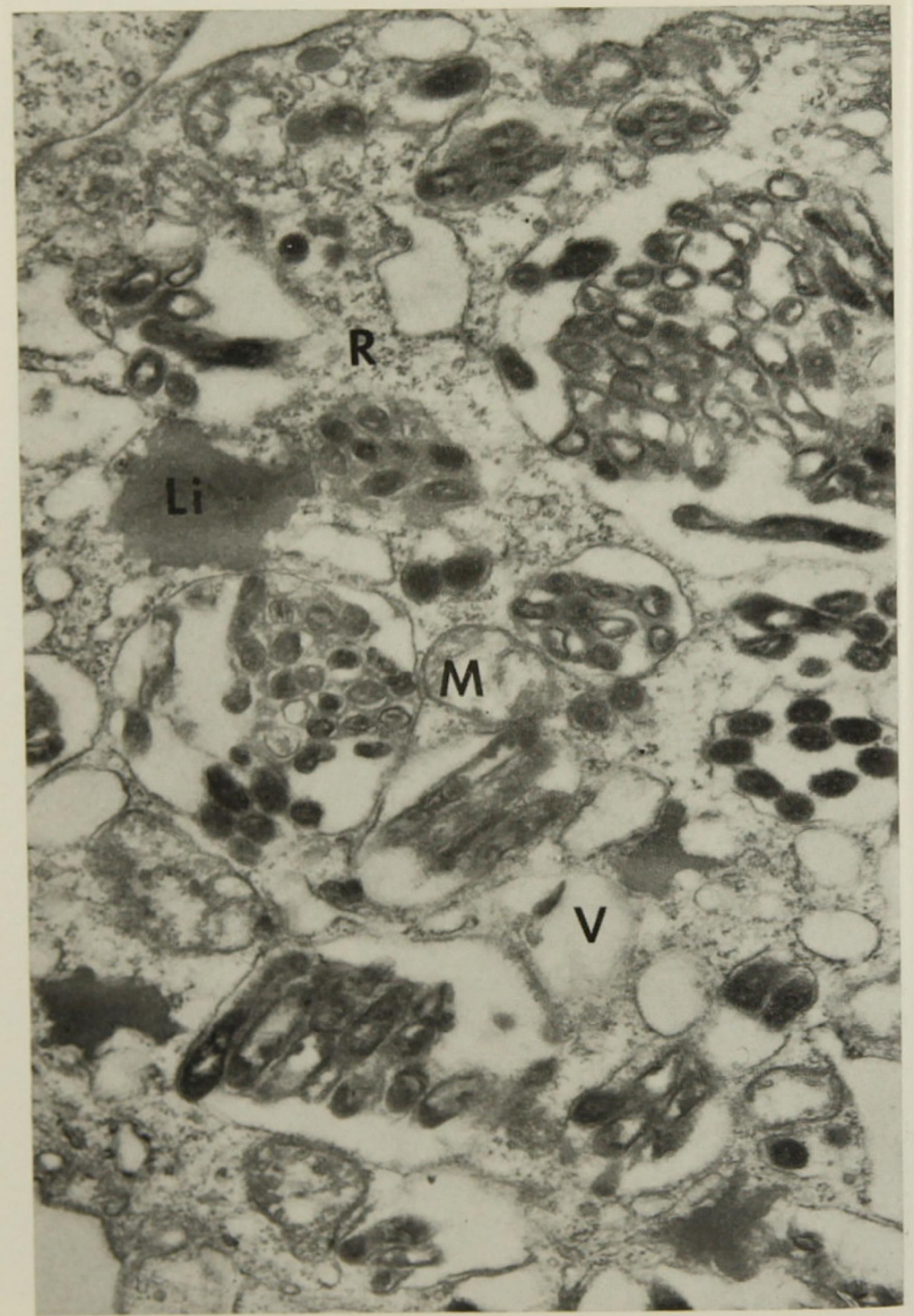

Figure 6

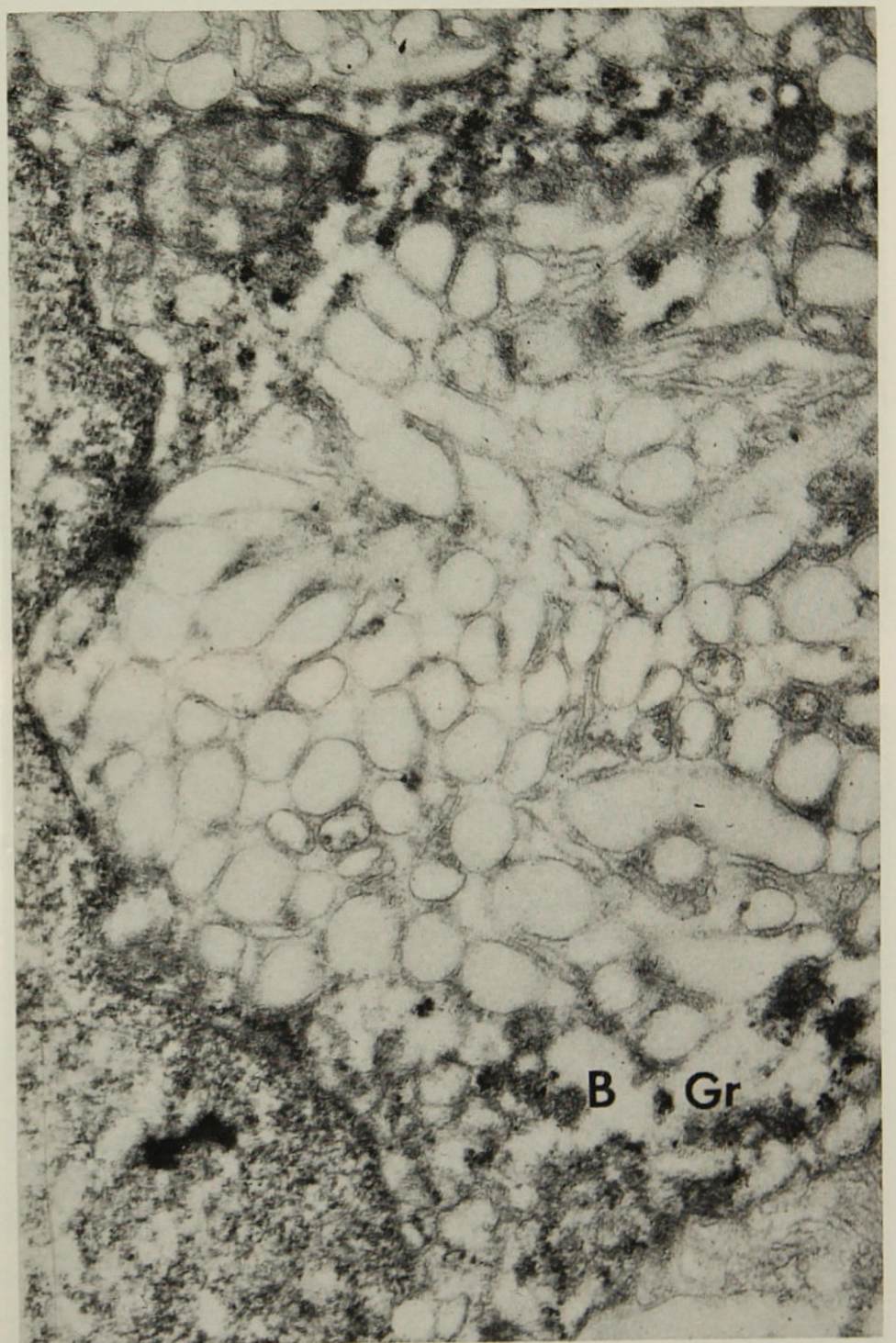

Figure 7

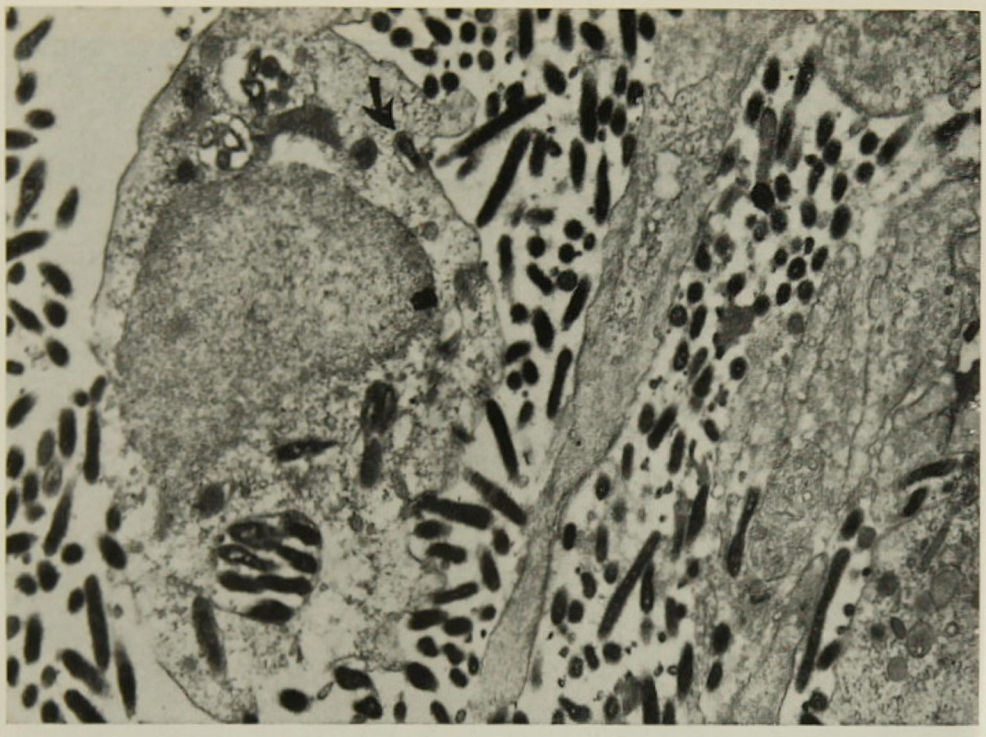

Figure 8a

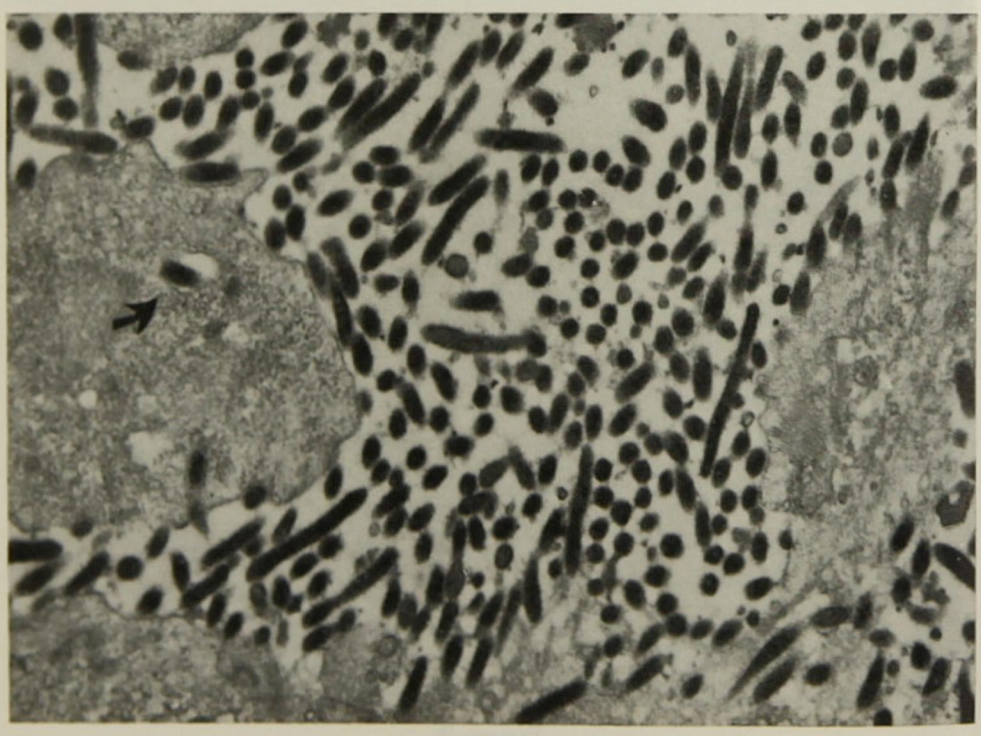

Figure 8b

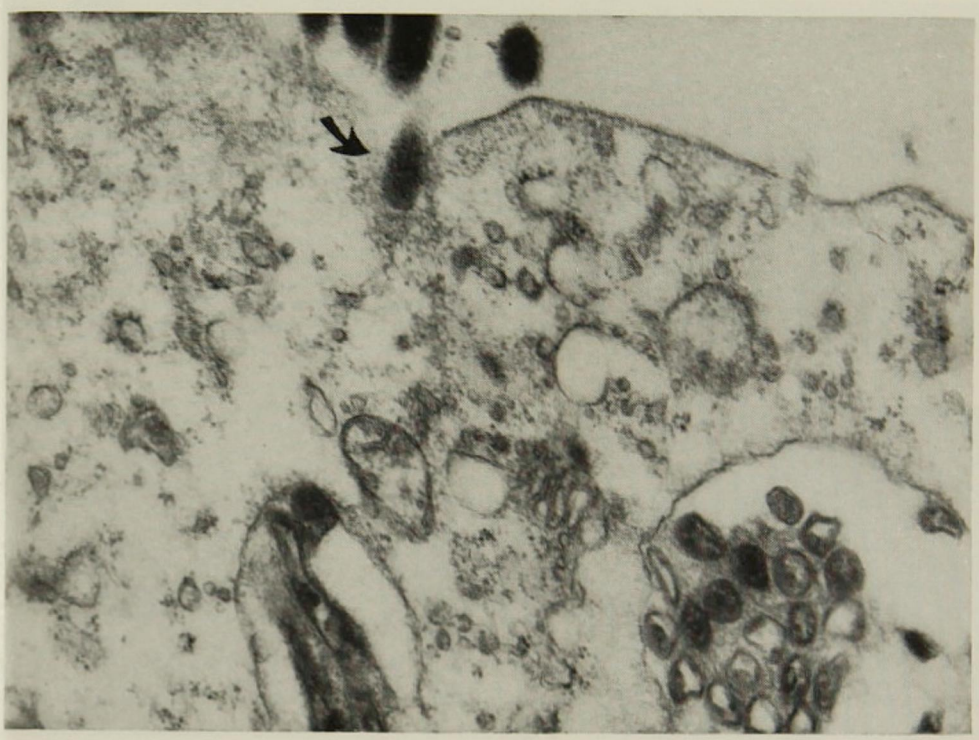

Figure 9a

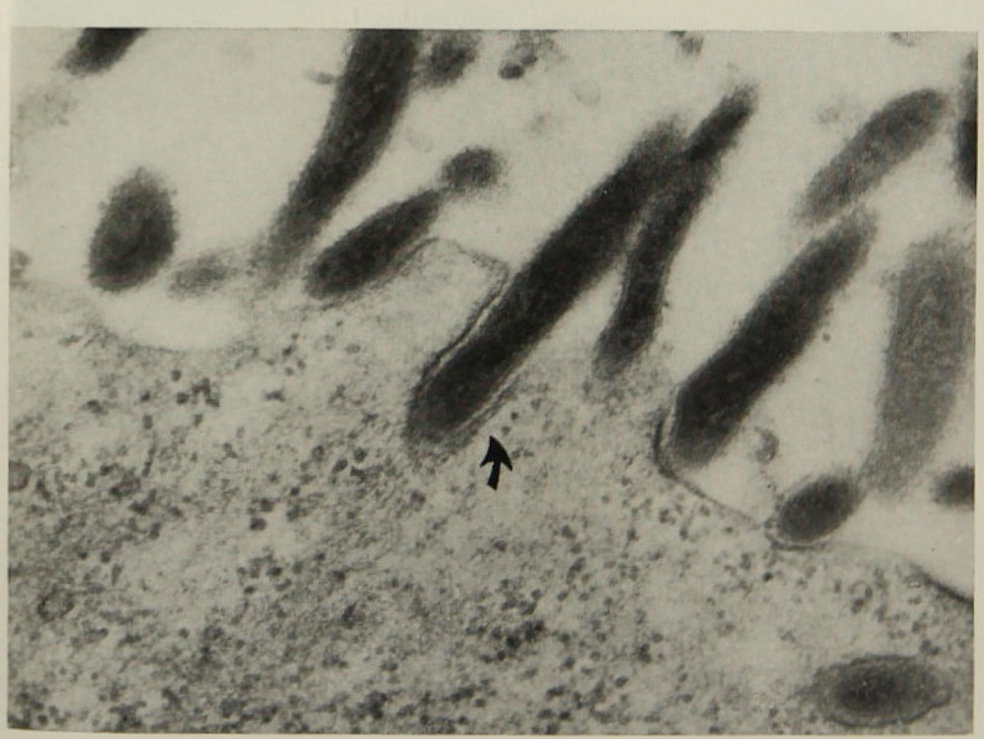

Figure 9b

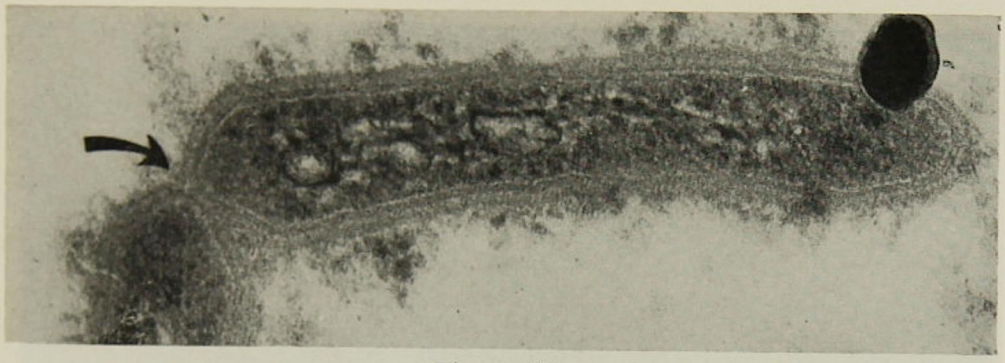

Figure 10a

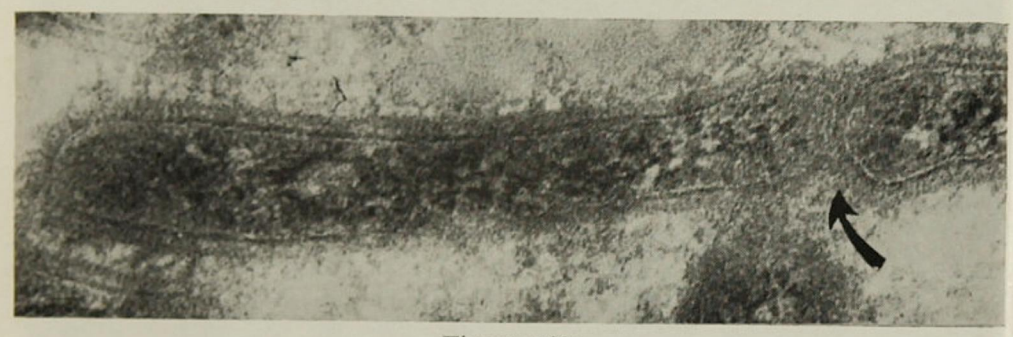

Figure 10b

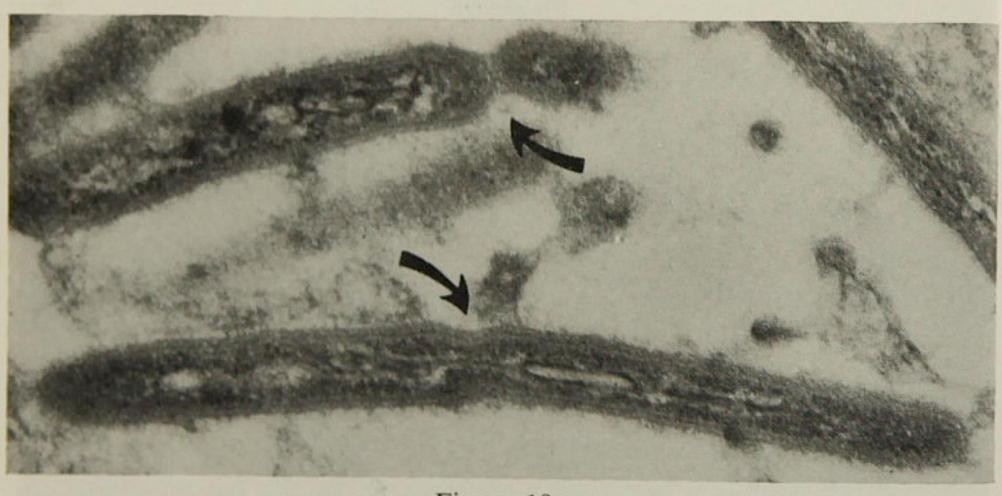

Figure 10c

Figure 10d

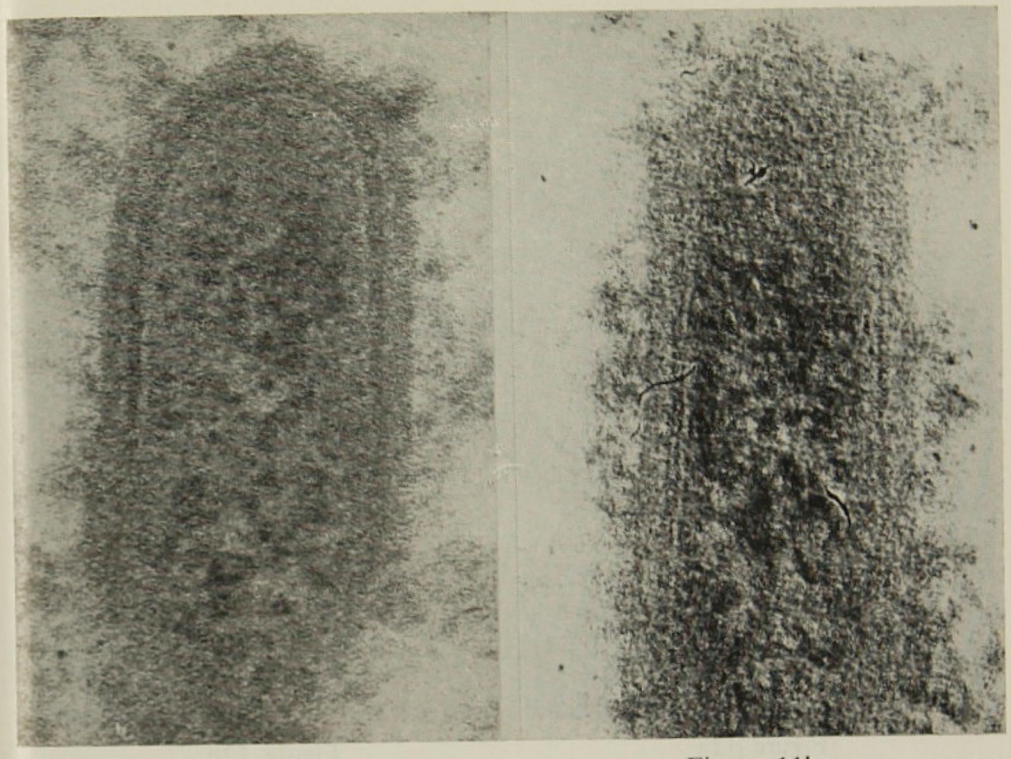

Figure 11a

Figure 11b

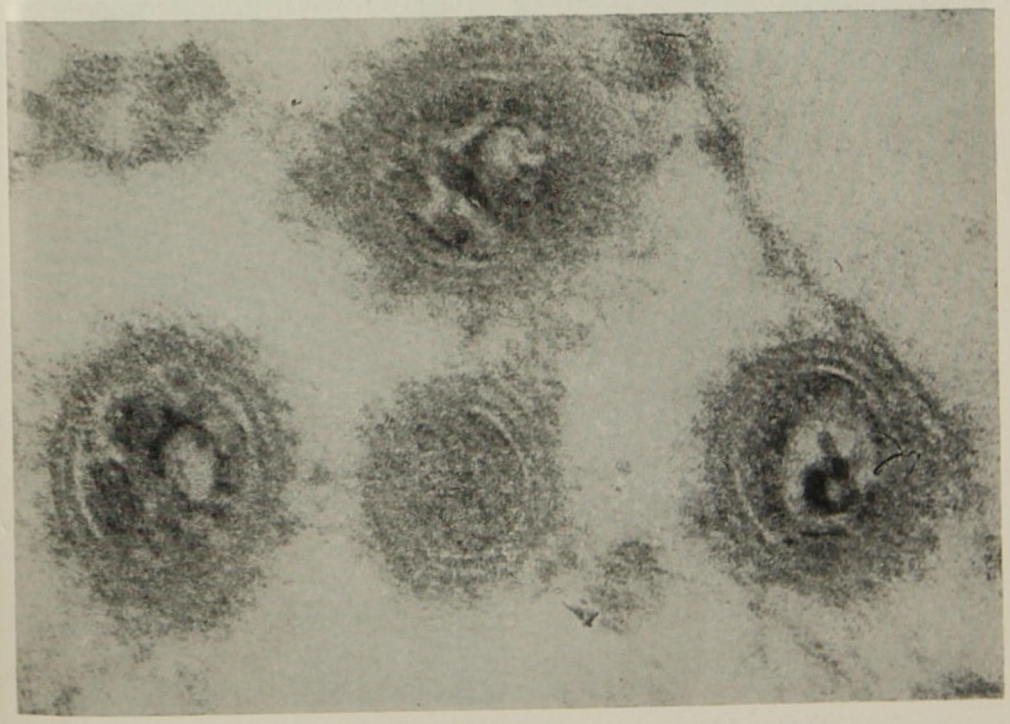

Figure 11c

Figure 12a

Figure 12b

Figure 12c

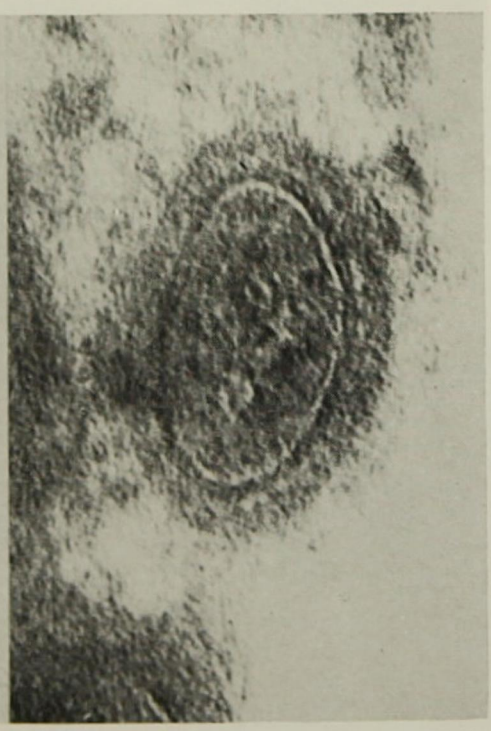

Figure 12d

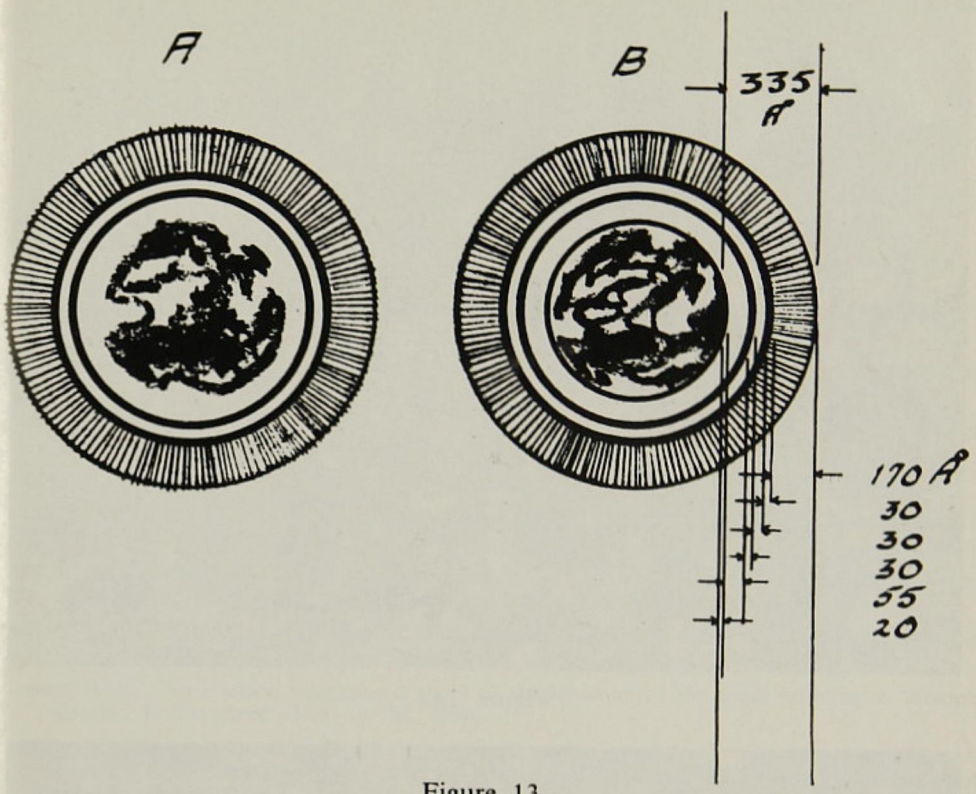

Figure 13

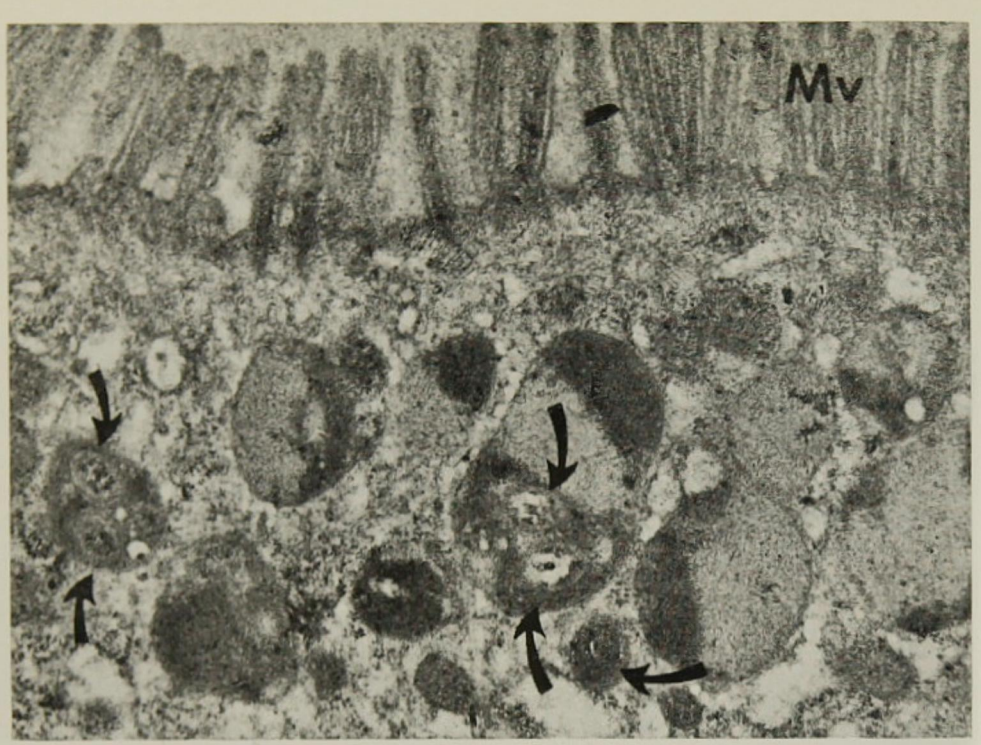

Figure 14a

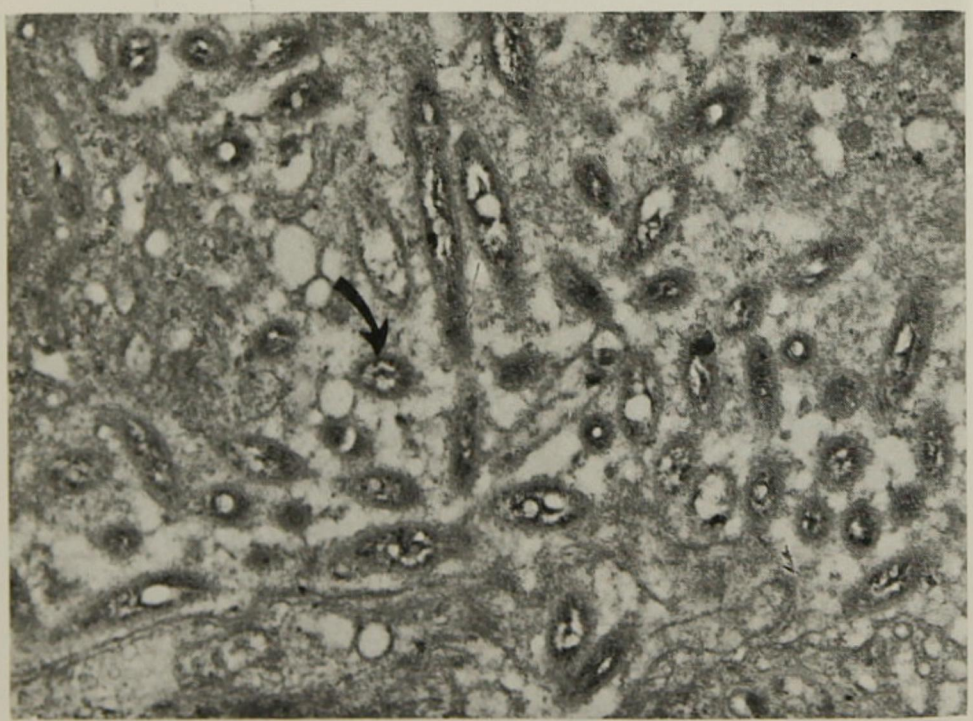

Figure 14b

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