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# Investigations of Familial Benign Chronic Pemphigus Hailey—Hailey's by Electron Microscopy

## Badania w mikroskopie elektronowym łagodnej przewlekłej rodzinnej pęcherzycy Hailey—Hailey

## Исследование ультраструктуры доброкачественной хронической семейной пузырчатки Гейли-Гейли

A disease known as familial benign chronic pemphigus was described by American authors in April 1939 (1). A month earlier Pels and Goodman observed skin lesions which resembled those of familial benign chronic pemphigus. Pels and Goodman considered them a variant of Darier's disease (2). The dispute started then has not come to an end yet. It is mainly based on the interpretation of histological features. On the basis of the presence of acantholysis, corps ronds, and grains in familial benign chronic pemphigus Hailey-Hailey's some authors tend to associate it with Darier's disease. Others do not find dyskeratotic cells and so-called grains under the microscope, and as a result of it they make a distinction between familial benign chronic pemphigus and Darier's disease, and include it in the group of the pemphigus diseases or consider it a new entity. A question arises whether a study of Hailey-Hailey's disease by electron microscopy can solve the problem, i. e. in which group is this disease to be included.

## MATERIAL AND METHODS

A skin specimen was taken from a patient, 32 years old, suffering from Hailey-Hailey's disease for 13 years. The case was described by

Ryll-Nardzewski and Kudejkowa in 1959 (4). A new blister was taken from the patient without anaesthesia. The specimens were cut into sections 0.5—1 $mm^3$ in size. They were fixed at a room temperature for 60 minutes in 1 per cent solution of osmium tetroxide ($OsO_4$) with sucrose (0.14 M). After dehydration through a series of graded ethanol, each block was embedded in a mixture of methyl methacrylate resin which was polymerized at 46°C, for 24 hours. An Omu Reichert Ultramicrotome and glass knives were used to cut ultrathin sections. Observations were made using Elmi $D_2$ Electron Microscope (C. Zeiss, Jena).

## RESULTS

The microelectrophotograms showing the layers of the dermis were as follows:

The horny layer (Sc). Elongated cells without nuclei contained few bundles of tonofibrils (T). No keratohyalin granules were found. Intercellular spaces were narrow, intercellular bridges mostly preserved (Fig. 1).

The granular layer (Sg). There occurred numerous bundles of tonofibrils (T) in the cells. The intercellular spaces were slightly broader than those in the horny layer. Sometimes due to injury of the intercellular bridges there were observed acantholytic spaces (ac), filled-up with electron-dense particles (grains). Some desmosomes were well preserved (d). Here and there were visible small dark staining bodies which by appearance resembled those called by Odland (3) unknown bodies (Ub) (Fig. 2).

The Malpighian layer (Ss). In this layer there were mostly found 3 types of the dermis cells; the cells among which cohesion was not broken yet, the isolated cells (acantholytic) with a large nucleus and a small content of the protoplasm, and lorg spindle-shaped cells with a disappearing nucleus and a protoplasm showing no intercellular bridges (Figs. 3, 4, 5). No preserved desmosomes were found, the intercellular bridges were mostly broken. Apart from them there were visible single, large dyskeratotic cells (corps ronds), oval in shape, with no intercellular bridges, showing bundles of compact tonofibrils. The cells had no nuclei or they were small or flattened. In the protoplasm of those cells there could be found few dispersed bodies similar by appearance to those described by Odland (Ud) (Fig. 6). The nuclei of the Malpighian layer were different in size and shape, some of them being small and degenerate. On the periphery of those cells there were often found numerous invaginations. Some degenerate nuclei had no cellular membrane (Fig. 5). The protoplasm of the cells

was interesting because of the behaviour of mitochondria (M). Some of them were swollen, enlarged and structurless. In some slices the swollen mitochondria (M), specially those placed near the nucleus, exerted pressure upon it and as a result invaginations were formed (Fig. 4). Sometimes enlarged mitochondria were observed to surround a disappearing and degenerate nucleus (Fig. 5). Sometimes parallel mitochondria seemed to bring about a separation of the nucleus containing a small amount of the protoplasm from the rest of it (Fig. 3). It seems that total separation would result in the alterations similar to those of the type of grains. The tonofibrils (T) were contracted and aggregated themselves into irregular bundles more or less dark in colour. They concentrated around the nuclei or on the periphery of the protoplasm, or they were distributed evenly showing no rudiments of the protoplasm. Among the cells there were visible acantholytic spaces (ac) different in size. Often they were found to contain migratory leukocytes.

The basal layer. The cells of that layer showed a large nucleus with numerous invaginations on its periphery, and small amount of the protoplasm. In the protoplasm there were found few mitochondria and scanty bundles of tonofibrils. Some mitochondria showed pathological changes being swollen and enlarged, others demonstrated no changes. The bottom part of the protoplasm was joined to the basal membrane and its top part, deprived of bridges, was attached to acantholytic space (ac).

## DISCUSSION

The most distinct alterations in the skin, e. g. damaged desmosomes, broken intercellular bridges, dyskeratosis, degenerative changes in nuclei were found in the Malpighian layer (Ss). The occurrence of dyskeratotic cells of the type of corps ronds (Figs. 5 and 6) was most interesting. In the above mentioned cells and in some cells of the granular layer (Sg) there could be observed unknown bodies described by O d l a n d (Figs. 2 and 6). Tonofibrils (T) were found to occur as numerous compact bundles in the cells similar to the corps ronds in cells of the granular layer and in some cells with desmosomes partly preserved. Few tonofibrils were observed in the cells of the basal layer and in the isolated cells. Atrophy and degeneration were found in some nuclei (Figs. 3 and 5). Enlargement, swelling and blurring of the structure of mitochondria (M) were observed to occur in the protoplasm. Attention should be paid to the participation of mitochondria in the degenerative process. The enlarged and swollen mitochondria were

observed to surround the nuclei which were hardly visible, and to form the ring of vacuolization around the nuclei (Fig. 5). It may be assumed that in a light microscope the ring of vacuolization could be associated with hydropic degeneration. So far there has been only one report of the research into familial benign chronic pemphigus Hailey-Hailey's (5). Wilgram and his co-workers, who studied the ultrastructure of this disease stated the disappearance of desmosomes, separation and contraction of tonofibrils, the presence of the cells similar to corps ronds which showed the lack of the keratohyalin grains and granules. The authors did not find degenerative alterations in the nuclei, i. e. swollen, enlarged, and structurless mitochondria, the presence of unknown bodies in the cells and the changes inducing grains-formation. The authors report that in Hailey-Hailey's disease, vulgar pemphigus, and in Darier's disease disturbances in the keratonization process and damage of desmosome-tonofibril complex are observed. In vulgar pemphigus no keratonization process is observed because cells turn degenerate very quickly. In Darier's disease and in Hailey-Hailey's disease the acantholytic cells are less damaged and acantholysis occurs simultaneously with dyskeratosis. The fact that there are not specific differences between the two above-mentioned diseases may be supported by our observations, i. e., that in familial benign chronic pemphigus Hailey-Hailey's degeneration of the nuclei may occur as it does in vulgar pemphigus, and corps ronds may also be observed as they are in Darier's disease. The author is of the opinion that so far as the etiology of these diseases remains obscure both Hailey-Hailey's disease and vulgar pemphigus may be associated with a group of dyskeratotic diseases, and there is no reason to include Hailey-Hailey's disease in the group of the pemphigus diseases or that of Darier's disease, or consider it a new entity because of the similarity of the histopathological features.

## REFERENCES

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## ABBREVIATIONS

Sc — *stratum corneum*
Sg — *stratum granulosum*
Ss — *stratum spinosum*
Nu — *nucleus*
n — *nucleolus*
T — *tonofibrillae*
M — *mitochondrium*
ac — acantholysis
d — desmosomes
Ub — Odland's unknown bodies

## EXPLANATION OF FIGURES

Fig. 1. The cells of the horny layer (Sc), granular layer (Sg) and of the Malpighian layer (Ss) are visible. Lack of keratohyalin granules in the horny layer. Numerous bundles of tonofibrils (T) in the cells of the Malpighian layer. Acantholytic spaces (Ac) and enlarged and structurless mitochondria are visible. Magn. 6,600 ×.

Fig. 2. The granular layer (Sg). Some desmosomes are preserved (d). Numerous bundles of tonofibrils (T). At the right bottom corner of the picture unknown bodies (Ub) are present in the protoplasm of the cell. Small acantholytic spaces (ac.) Aggregation of compact bundles of tonofibrils around the nucleus (Nu). Magn. 10,200 ×.

Fig. 3. The Malpighian layer (Ss). Large acantholytic spaces (ac). Aggregation of compact bundles of tonofibrils around the nuclei (Nu). The atrophy of some nuclei. At the bottom of the picture the nucleus seems to be separated from the protoplasm by a range of mitochondria. Magn. 10,200 ×.

Fig. 4. The cell of the Malpighian layer (SS) with numerous tonofibrils (T), and mitochondria (M) around the nucleus (Nu). The mitochondria situated in close vicinity of the nucleus are seen to form invaginations. Magn. 10,200 ×.

Fig. 5. An elongated, spindle-shaped cell of the Malpighian layer without intercellular bridges showing a nucleus similar to a pickaxe. At the top right corner of the picture the nucleus is surrounded with mitochondria. The nucleus shows an advanced stage of degeneration. Magn. 7,000 ×.

Fig. 6. A dyskeratotic cell of the type of the corps ronds cell. The nucleus small and flattened. Numerous compact bundles of tonofibrils. Few granules which may be considered to correspond to Odland's unknown bodies (Ub.) Magn. 13,600 ×.

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## STRESZCZENIE

Skrawek do badań ultrastruktury łagodnej przewlekłej rodzinnej pęcherzycy Hailey-Hailey pobrano od pacjenta w wieku 52 lat cierpiącego na to schorzenie od 13 lat. Najbardziej wyraźne zmiany w postaci uszkodzenia desmosomów, utraty mostków międzykomórkowych, zwy-

rodnienia jąder, powiększenia, obrzęku i zatarcia budowy mitochondriów występowały w warstwie kolczastej. W warstwie tej spotykano trzy rodzaje komórek naskórka: komórki utrzymujące jeszcze łączność między sobą, komórki wyizolowane (akantolityczne) oraz długie wrzecionowate komórki z zanikającym jądrem i wygładzoną linią zewnętrzną protoplazmy a także komórki dyskeratotyczne o typie corps ronds. Zwrócono uwagę, że mitochondria odgrywają rolę w powstawaniu zmian zwyrodnieniowych w jądrze, w tworzeniu się tzw. zwyrodnienia wodniczkowego. W warstwie rogowej brak było ziarenek keratohialiny, natomiast w warstwie ziarnistej i w komórkach typu corps ronds spostrzegano ciałka nieznane Odlanda. Autor sądzi na podstawie własnych badań i obserwacji poczynionych przez Wilgrama i współpracowników, że do czasu wyjaśnienia etiologii chorobę Hailey-Hailey a także pęcherzycę zwykłą należy umiejscawiać w grupie schorzeń dyskeratotycznych. Wyodrębnianie lub zaliczanie choroby Hailey-Hailey do grupy pęcherzyc lub choroby Dariera nie ma większego uzasadnienia, ponieważ istota zmian histopatologicznych w tych schorzeniach jest jednakowa.

## OBJAŚNIENIA RYCIN

Ryc. 1. Widoczne komórki warstwy rogowej (Sc), warstwy ziarnistej (Sg) i warstwy kolczastej (Ss). Brak ziarenek keratohialiny w warstwie rogowej. Liczne pasma włókienek oporowych (T) w komórkach warstwy kolczastej. Widoczne przestrzenie akantolityczne (ac) i powiększone o zatartej budowie mitochondria (M). Pow. 6600 ×.

Ryc. 2. Warstwa ziarnista (Sg). Niektóre desmosomy zachowane (d). Liczne pasma włókien oporowych (T). U dołu po stronie prawej obecne w protoplaźmie komórki ciałka nieznane (Ud). Niewielkie przestrzenie akantolityczne (ac). Pow. 10200 ×.

Ryc. 3. Warstwa kolczasta (Ss). Duże przestrzenie akantolityczne (ac). Skupianie się zbitych wiązek włókienek oporowych wokół jąder (Nu). Niektóre jądra znajdują się w zaniku. Pow. 10200 ×.

Ryc. 4. Komórka warstwy kolczastej (Ss) z licznymi włókienkami oporowymi (T), i mitochondriami (M), wokół jądra (Nu). Mitochondria znajdujące się w bezpośrednim sąsiedztwie jądra powodują w nim wgłębienia. Pow. 10200 ×.

Ryc. 5. Komórka warstwy kolczastej (Ss) wydłużona kształtu wrzecionowatego o jądrze w postaci kilofa, o linii zewnętrznej protoplazmy wygładzonej. U góry po stronie prawej jądro otoczone mitochondriami. Jądro wykazuje daleko posunięty stan zwyrodnienia. Pow. 7000 ×.

Ryc. 6. Komórka dyskeratotyczna o typie corps ronds. Jądro małe spłaszczone. Duża ilość zbitych pasm włókienek oporowych. Nieliczne ziarenka mogące odpowiadać ciałkom nierozpoznanym Odlanda (Ud). Pow. 13600 ×.

## РЕЗЮМЕ

Срезок для исследований ультраструктуры доброкачественной хронической семейной пузырчатки Гейли-Гейли был взят от пациента в возрасте 52 года, страдающего этим заболеванием с 13 лет. Самые выразительные изменения в виде повреждения десмозомов, потери межклеточных мостиков, вырождение ядер, увеличения отека и затушевание строения митохондриев выступали в шиповидном слое. В этом слое встречались три вида клеток эпидермиса: клетки, еще сохраняющие связь между собой, выделенные клетки (акантолитические), а также длинные веретенообразные клетки с исчезающим ядром и сглаженной внешней линией биоплазмы, наконец, — дискератотические клетки типа corps ronds. Обращено внимание, что митохондрий играет роль в возникновении дегенеративных изменений в ядре, в образовании так называемого вакуолярного вырождения. В роговом слое отсутствовали зерна кератогиалина, зато в зернистом слое и в клетках типа corps ronds наблюдались неизвестные тельца Одланда.

На основании собственных наблюдений, и наблюдений сделанных Вильграмом и сотрудниками, автор полагает что до времени разъяснения этиологии, болезнь Гейли-Гейли, как и обыкновенную пузырчатку, следует локализировать в группе дискератотических заболеваний. Выделение или же причисление болезни Гейли-Гейли к группе пузырчаток, или болезни Дариера, не имеет серьезного обоснования, так как сущность гистопатологических изменений при этих заболеваниях одинаковая.


Рис. 1. Видны клетки рогового слоя (Sc), зернистого слоя (Sg) и шиповидного слоя (Ss). Отсутствуют зернышки кератогиалина в роговом слое. Многочисленные полосы тонофибриллов в клетках шиповидного слоя. Видны акантолитические и увеличенные пространства и со сглаженным строением митохондрия. Увелич. 6600 ×.

Рис. 2. Зернистый слой (Sg). Некоторые десмосомы сохранены (d). Многочисленные полосы тонофибриллов (T). Снизу, с правой стороны, находящиеся в биоплазме клетки неизвестные тельца (Wd). Небольшие акантолитические пространства. Увелич. 10.200 ×.

Рис. 3 Шиповидный слой (Ss). Большие акантолитические пространства (ac). Концентрация компактных пучков тонофибриллов вокруг ядер. Некоторые ядра находятся в стадии атрофии. Увелич. 10.200 ×.

Рис. 4. Клетка шиповидного слоя с многими тонофибриллами и митохондриями вокруг ядра (Nu). Митохондрии, находящиеся в непосредственном соседстве с ядром и вызывающие в нем углубления. Увелич. 10.200 ×.

Рис. 5. Клетка шиповидного слоя удлиненная, веретенообразной формы с ядром в виде кирки, со сглаженной внешней линией протоплазмы. Сверху, с правой стороны, — ядро окруженное митохондриями. Ядро обнаруживает далеко продвинутую дегенерацию. Увелич. 7000 ×.

Рис. 6. Дискератотическая клетка типа corps ronds. Ядро небольшое, сплюснутое. Большое количество компактных тяж тонофибриллов. Немногочисленные зернышки, которые могут относиться к неизвестным тельцам Одланда. Увелич. 13.600 ×.

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**Ryc. 1**

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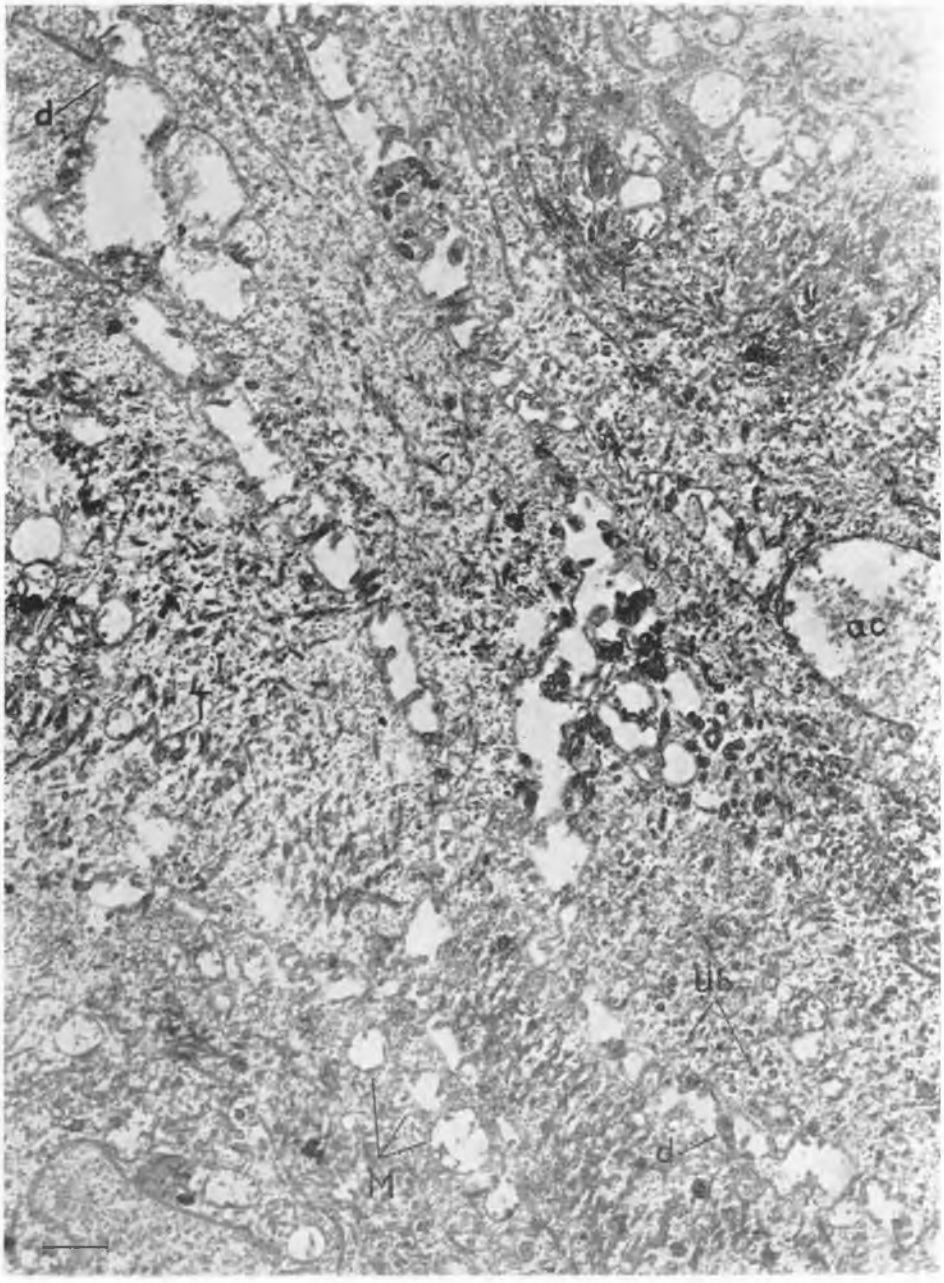


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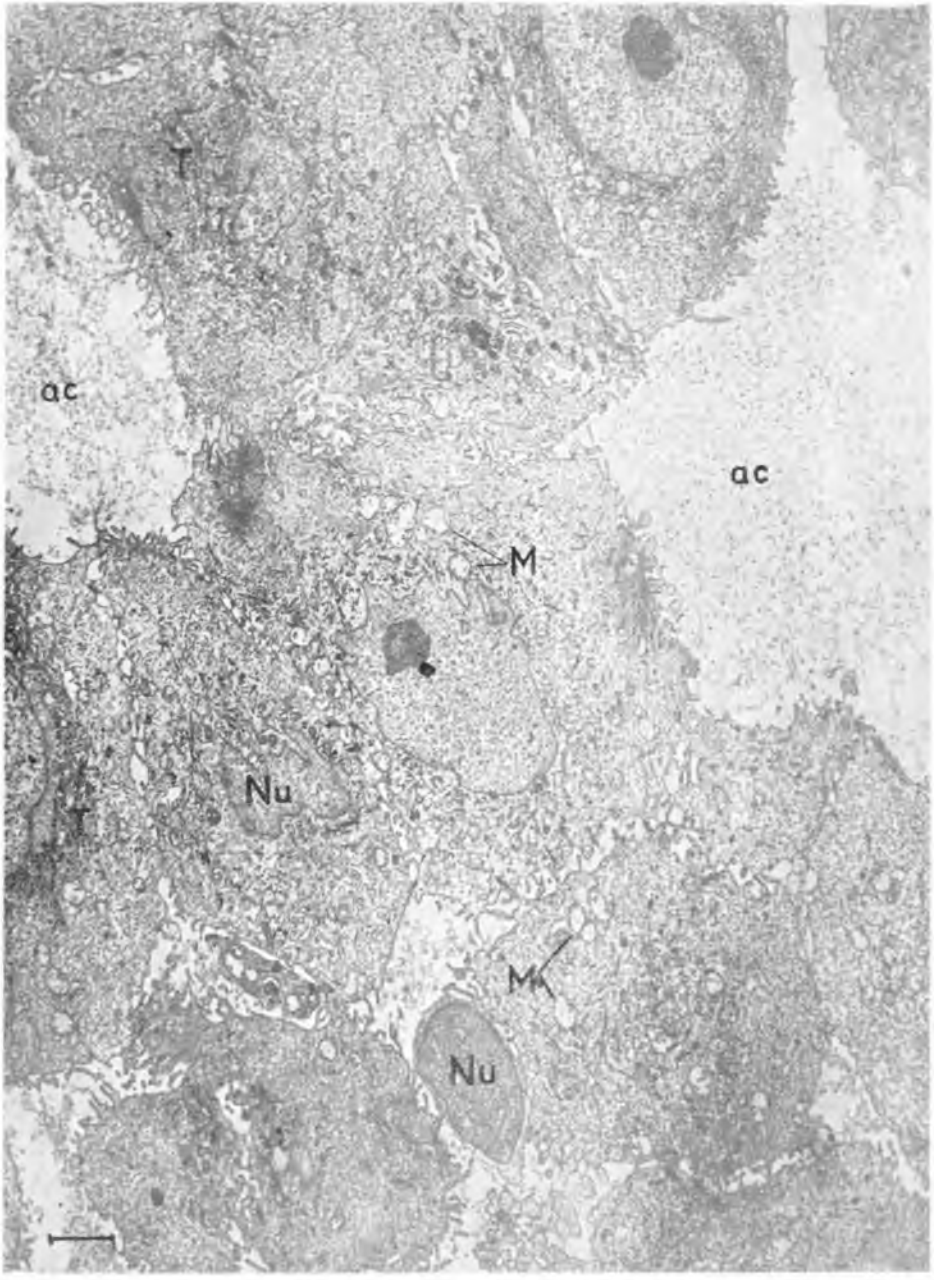


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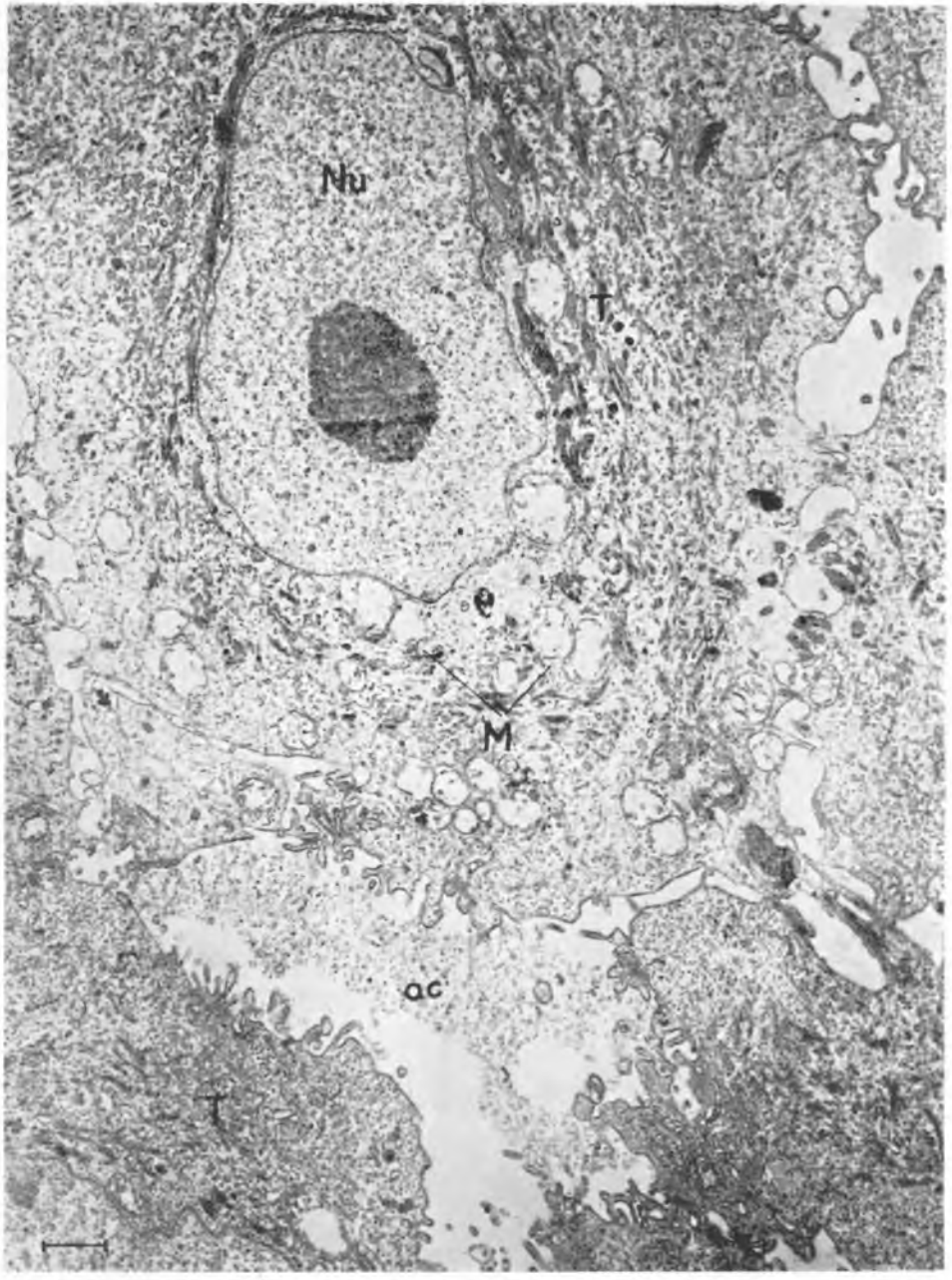


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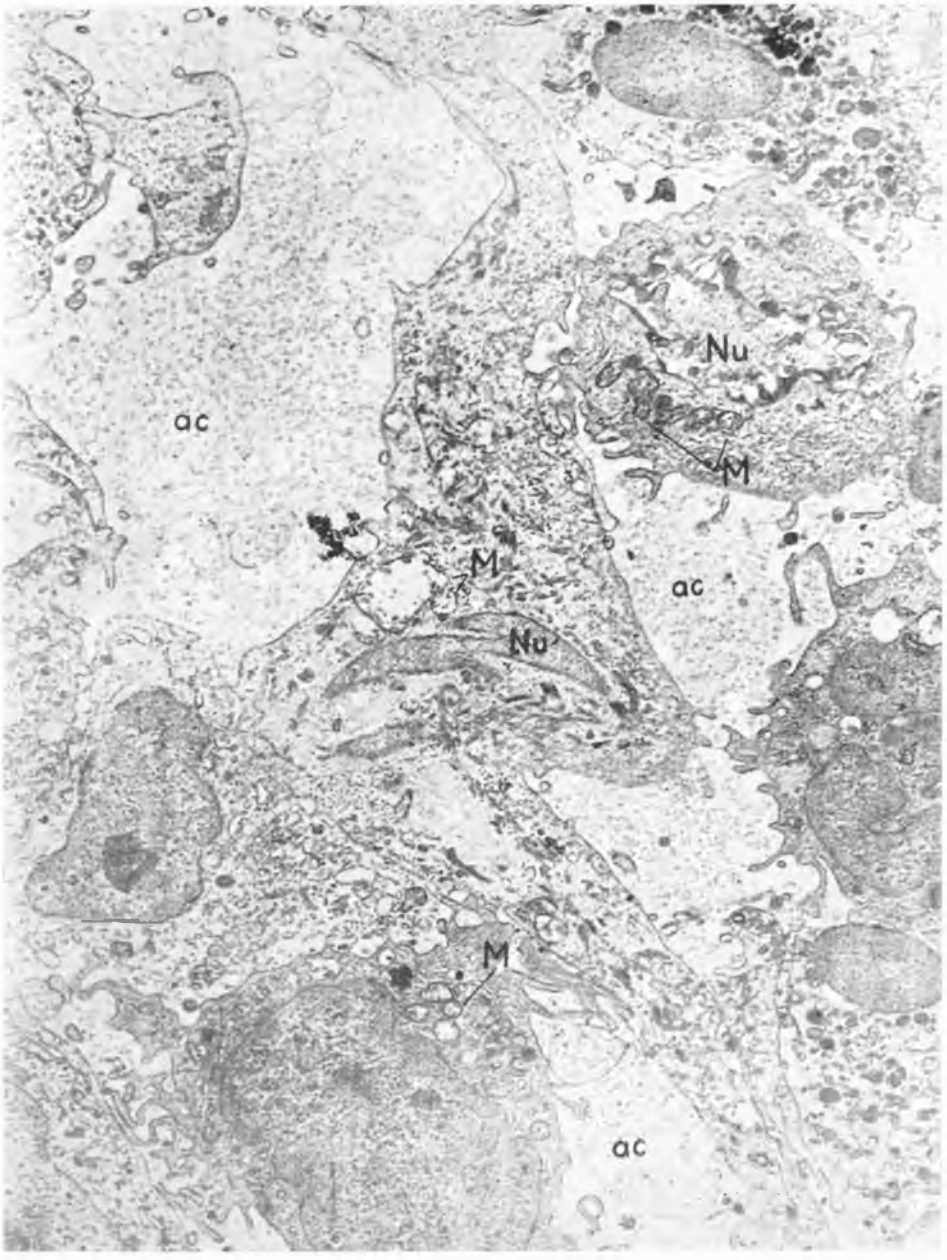


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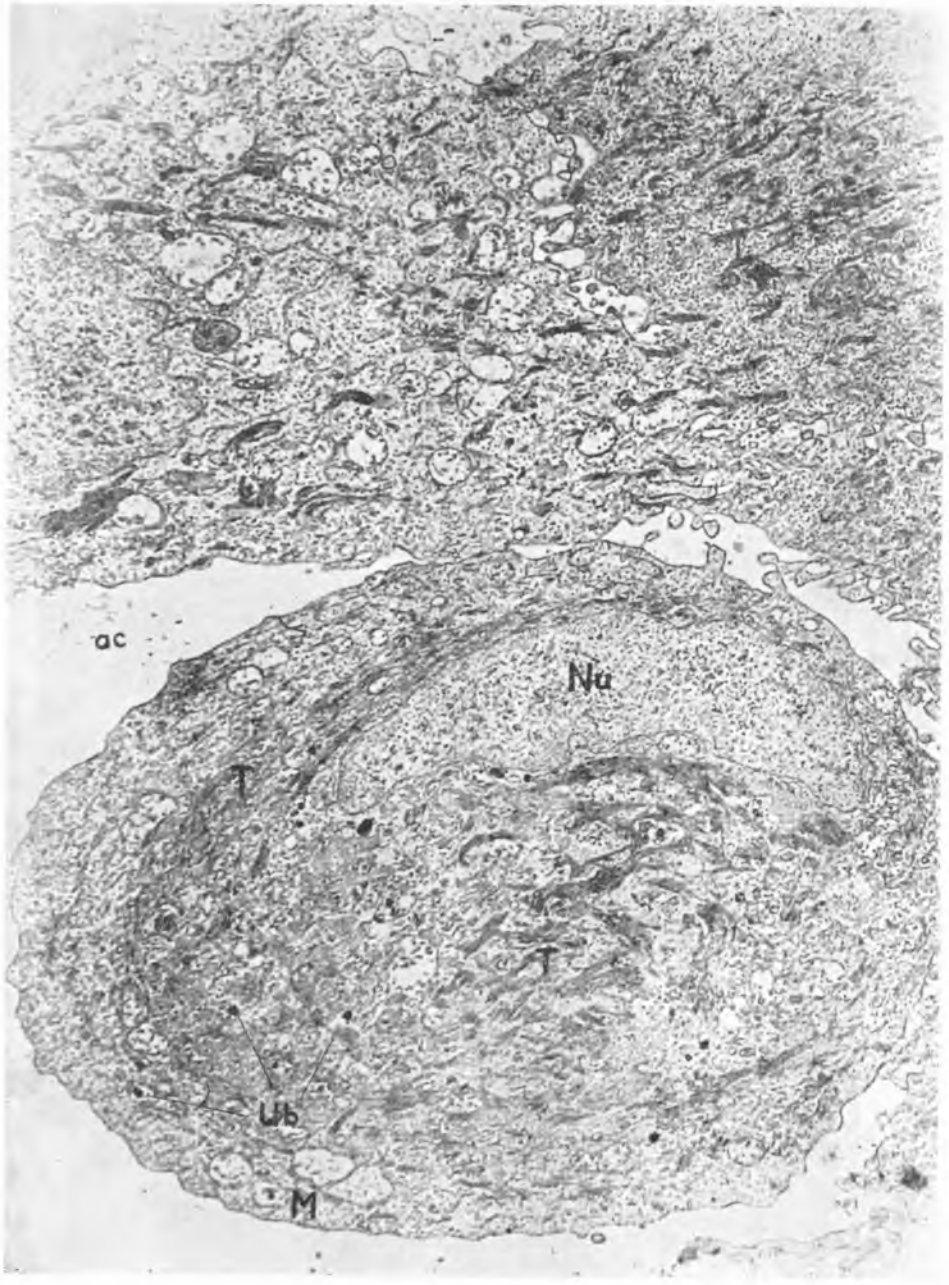


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