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THE CHEDIAK-HIGASHI SYNDROME: FORMATION OF GIANT MELANOSOMES AND THE BASIS OF HYPOPIGMENTATION*

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The Chediak-Higashi (CH) syndrome is a rare familial disorder characterized by variable clinical manifestations including defective pigmentation, and massive anomalous granulations in leukocytes and other cells (1–6). We have previously reported the occurrence of giant melanosomes in this condition (7) and have now examined the manner of formation of these massive melanosomes and the nature of the associated defect in pigmentation.

MATERIALS AND METHODS

A 10-year-old girl with a well-documented CH syndrome was available for study. Specimens of skin, hair and nevi from this patient were removed by punch biopsy, cut in one millimeter cubes and immediately fixed in buffered 1% osmium tetroxide, dehydrated in alcohols and embedded in Epon. Sections were cut with an LKB ultrotome, stained with lead and uranyl acetate and examined in an RCA EMU electron microscope.

RESULTS

Melanocytes seen in patients with the CH syndrome are similar to normal melanocytes except for the presence of massive melanin granules and degenerating cytoplasmic residues. The melanocytes contain one or more large melanin granules in addition to normal sized particles. Mitochondria, Golgi vesicles, and other cytoplasmic elements are present in their usual numbers and distribution. The enlarged pigment particles are surrounded by a unit membrane and present a broad spectrum of bizarre appearances (Fig. 1).

The giant granules appear to form in close relation to the Golgi complex. The particles develop from a series of spiral-like lamellae, made up of repeating protein units which are enveloped by a unit membrane. Development continues with proliferation of the lamellae within the unit membrane, until a massive granule is formed. As the particles increase in size they become more osmiophilic. Some of the massive granules are also formed by the fusion of several smaller granules resulting in a grouping of premelanosomes within a single unit membrane (Fig. 2).

Enlargement of the giant particles does not continue indefinitely. At some point in their development the granules begin to show signs of deterioration. Degenerative transformation of CH granules can readily be detected. The internal substructure of the granule is often vacuolated and converted into membranous or myelin-like configurations. As transformation and degeneration occur one finds lipid droplets (Fig. 3) within the large granules. There is also an apparent increase in the granularity of the pigment granules. Later this gives way to vacuolization and formation of residual bodies (Fig. 3). The degenerating granules fuse with one another resulting in huge, vacuolated areas honeycombing the cells (Fig. 4 and 5).

The epidermal cells also show an apparent aberration in their packaging mechanism. The pigment granules that are passed to the epidermal cells are located in lysosome-like structures, often surrounding the nuclei (Fig. 6 and 7). These membrane bound masses of pigment particles are many times larger than similar components in normal epidermal cells. All granules passed appeared normal and none were noted free in the epithelial cell cytoplasm. The massive, bizarre granules which formed in the melanocyte were not found in the epithelial cells, and, therefore were presumably not passed.

DISCUSSION

Under normal conditions two stages are evident during the development of melanin granules. These are so distinct that each is given a name. The first stage is the premelanosome which consists of an organized protein matrix upon which melanin will be deposited. The struc-

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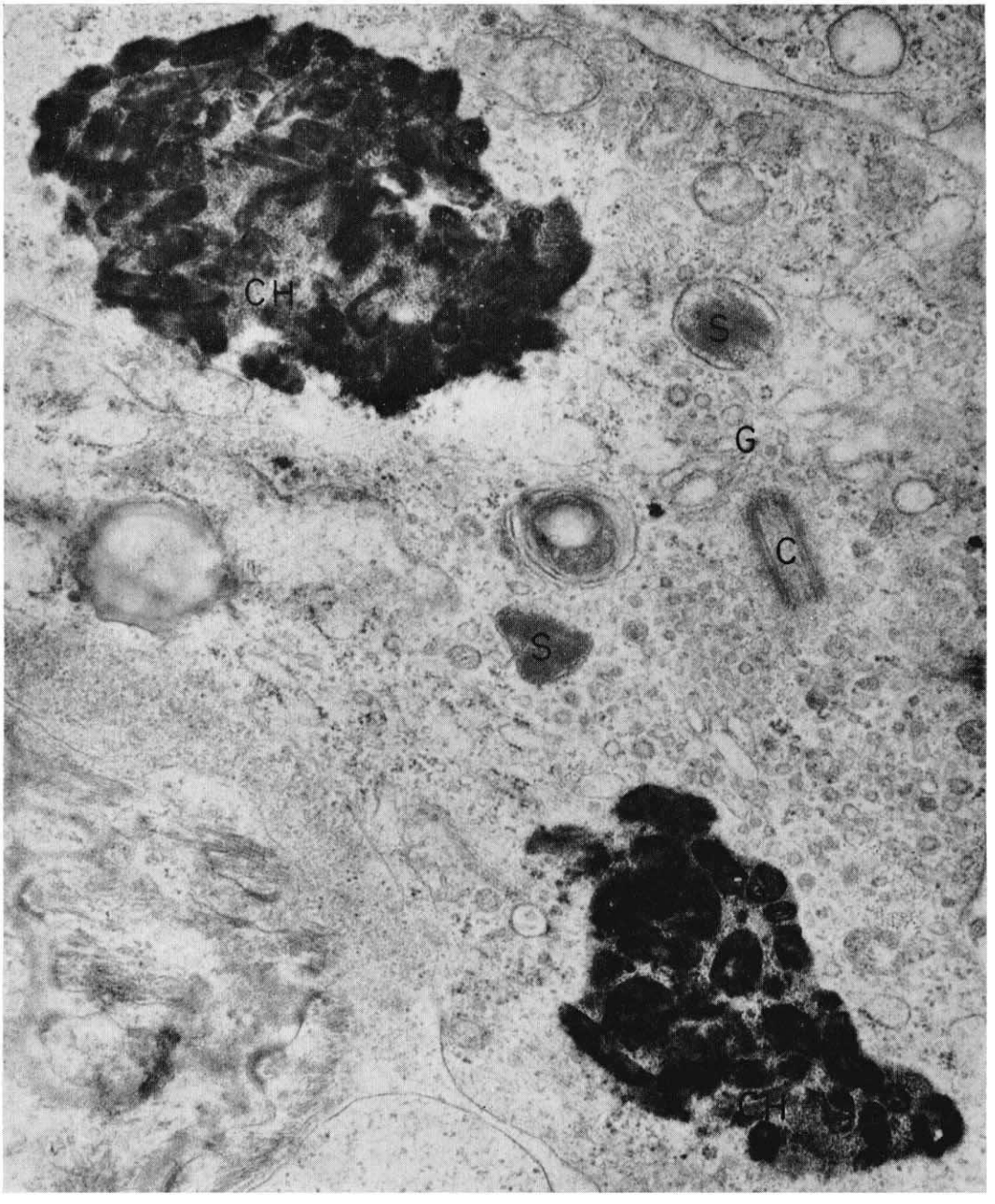

FIG. 1. The massive Chediak-Higashi granules (CH) have a bizarre pattern and reach tremendous proportions. C, centriole; G, Golgi complex; S, smaller pigment particles. × 30,448.

ture consists of several spiral-like lamellae which are made up of repeating protein units and are surrounded by a unit membrane. Melanin synthesis apparently begins with the deposition of small particles on the fibers of the matrix. This process continues until each fiber becomes a thickened, dark lamella, at which point the whole particle is referred to as a melanosome (8).

Apparently the massive melanosomes in this

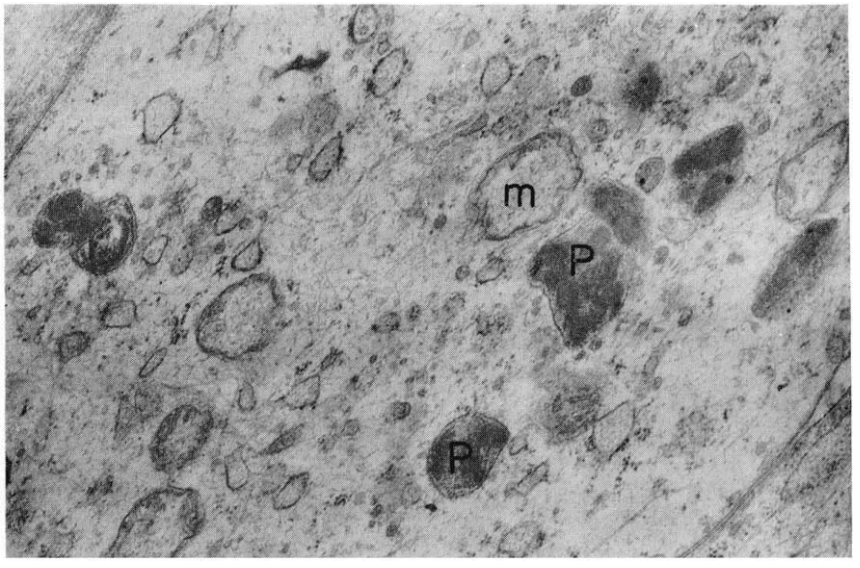

FIG. 2. The massive CH granules are the result of either continued growth of single abnormal granules and/or of fusion of numerous granules until the giant size is reached. m, mitochondrion; P, pigment granules in varying stages of growth. × 11,365.

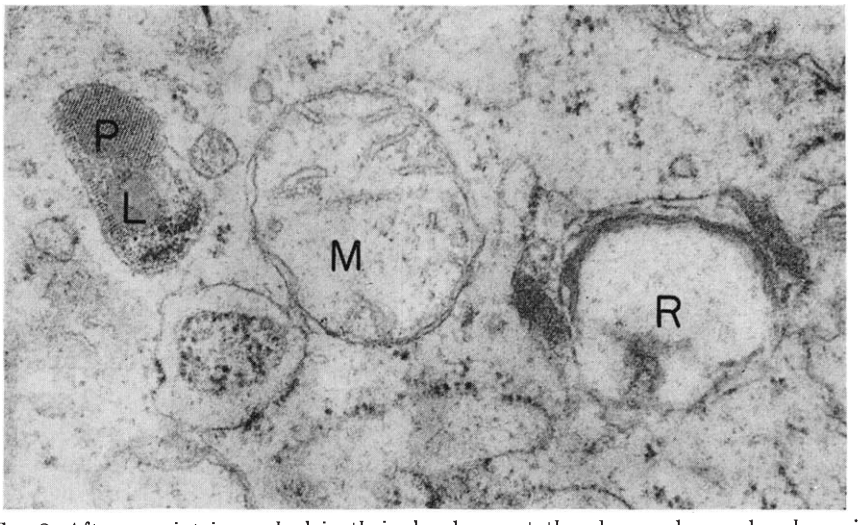

FIG. 3. After a point is reached in their development the abnormal granules show signs of deterioration. M, mitochondrion; L, lipid droplet; P, pigment particle; R, residual body. × 45,000.

condition are formed from either single premelanosomes which continue to grow, probably due to some defect in their limiting membrane, or by fusion of numerous abnormal premelanosomes. The continued growth of these premelanosomes is probably due to continued transport of nutrients into the particle. Apparently the membrane is unable to "shut off" in a normal manner and the particles continue to enlarge. As mentioned, continued growth by fusion of particles cannot be ruled out.

It has been suggested by several authors that the unusually large granules formed in the CH syndrome have some defect in their unit membranes which is probably not resolvable with the electron microscope. Studies have shown that the membranes surrounding the massive CH granules are unusually permeable to substrates

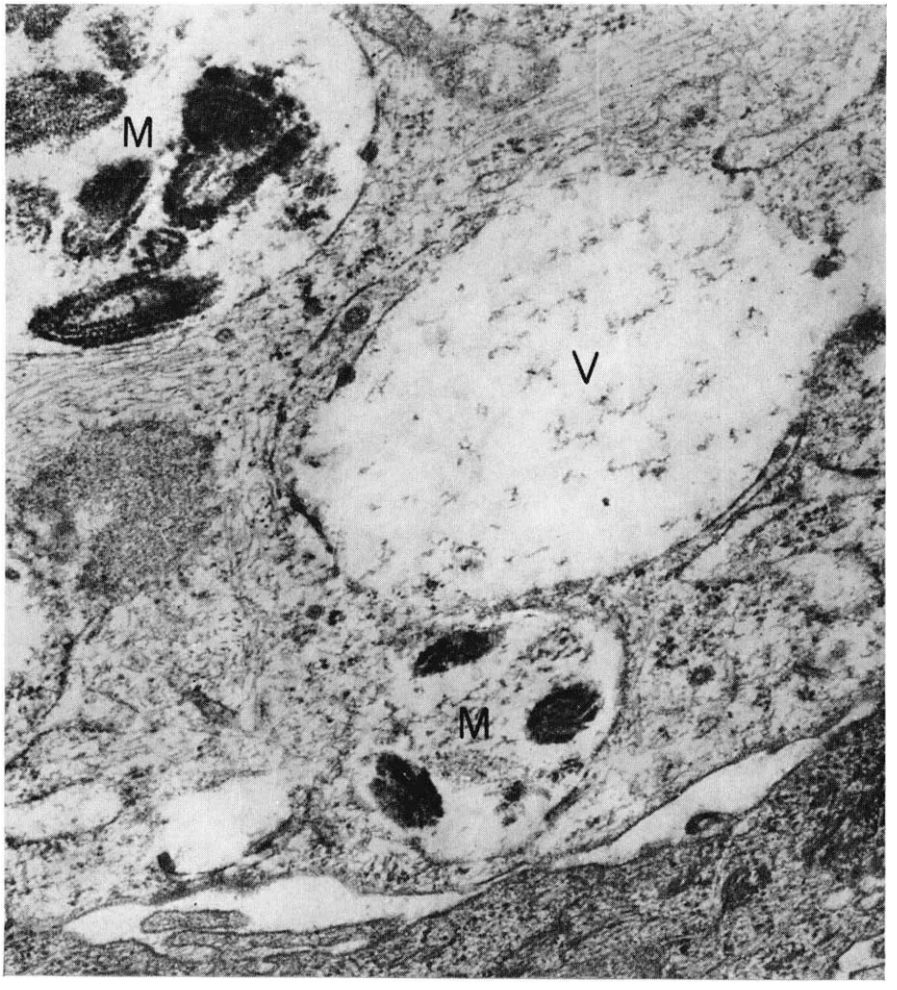

FIG. 4. Continued destruction of the massive particles results in a vacuolated cytoplasm. M, deteriorating melanin particles; V, vacuole. × 48,760.

and fluorescent stains suggesting that there may well be a defect in the unit membrane surrounding this abnormal particle (9, 10). The aforementioned most likely underlies the structural changes noted in the giant pigment granules seen in this syndrome.

Leakage of injurious substances from the granules to the surrounding cytoplasm might act as the stimulus which brings about their ultimate destruction. The observation that the cell can destroy the very resistant pigment it has produced is intriguing. We know of no hydrolases in the lysosomal network of the cell that are capable of destroying melanin, but morphologically the protein matrix apparently degenerates first and subsequently the osmiophilia (melanin?) associated with it also disappears, leaving a vacuolated cytoplasm.

Ultrastructural studies of albinism indicate that melanocytes are present in this condition and that the cell is capable of producing, in the usual numbers, premelanosomes which are normal in structure. Melanin deposition does not occur and thus a melanosome is never formed. In the CH syndrome the premelanosomes are at times gigantic granules, thus differing greatly from what is seen in true albinism. It is quite likely that this disorder represents an hereditary pigmentary anomaly based on a structural defect of the premelanosome.

As was shown, the epidermal cell forms giant lysosomes from normal sized granules. This con-

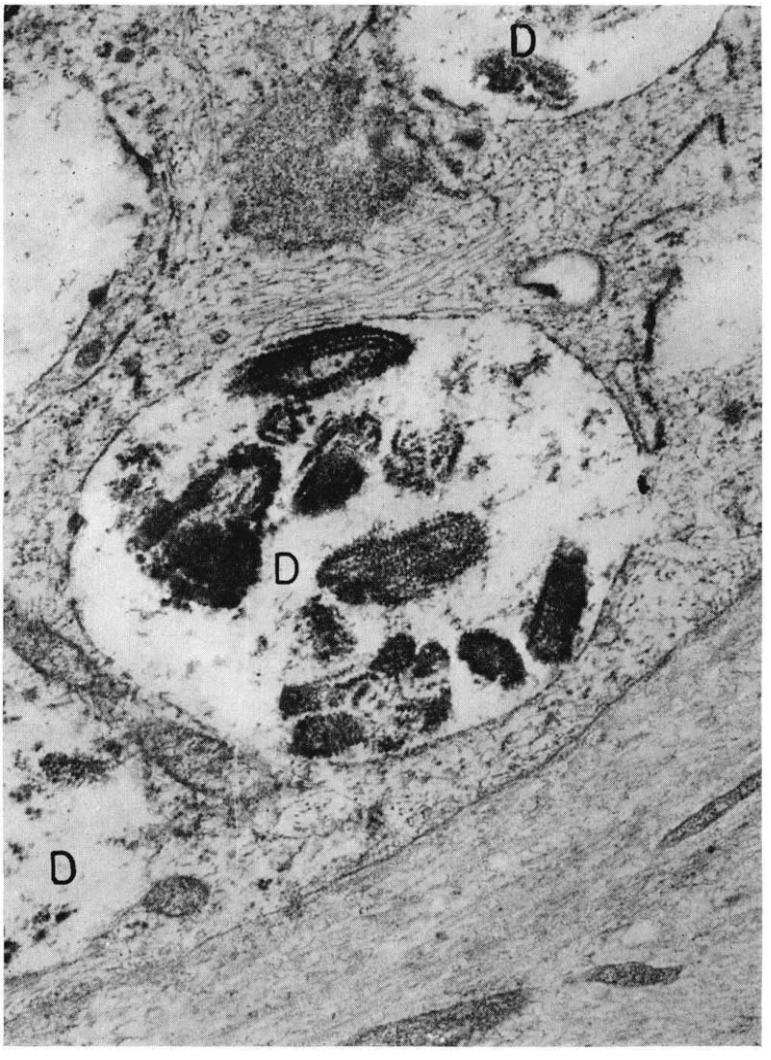

FIG. 5. Lysis of the Chediak-Higashi granules gives the cytoplasm a honey-combed appearance. D, deteriorating particles. × 47,840.

cept, of the failure of the epidermal cell to disperse the melanin in a normal fashion, most likely is the cause of the hypopigmentation seen in the CH syndrome. Therefore while the giant melanosomes demonstrate a defect in premelanosome formation due to defective membranes, the hypopigmentation is probably due to abnormal packaging of normal melanosomes in giant lysosomes of the epidermal cells.

The characteristic decrease in color demonstrated by these patients may also be directly related to the defective structure of the abnormal granules. The possibility exists that due to the huge size of these granules they cannot respond to adaptive stimuli. The massive organelles may have a limited ability to move or be moved and they are recognized as "foreign" by the melanocyte and destroyed. Significantly, after their formation, degeneration of the massive granules takes place, creating numerous vacuolated areas, and disappearance of much of the osmiophilia associated with large pigment granules. The internal substructure of the granules is often converted into membranous or myelin-like configurations. Many of the particles undergo internal destruction and the degenerating granules fuse forming large, vacuolated areas honeycombing the cells. These massive granules

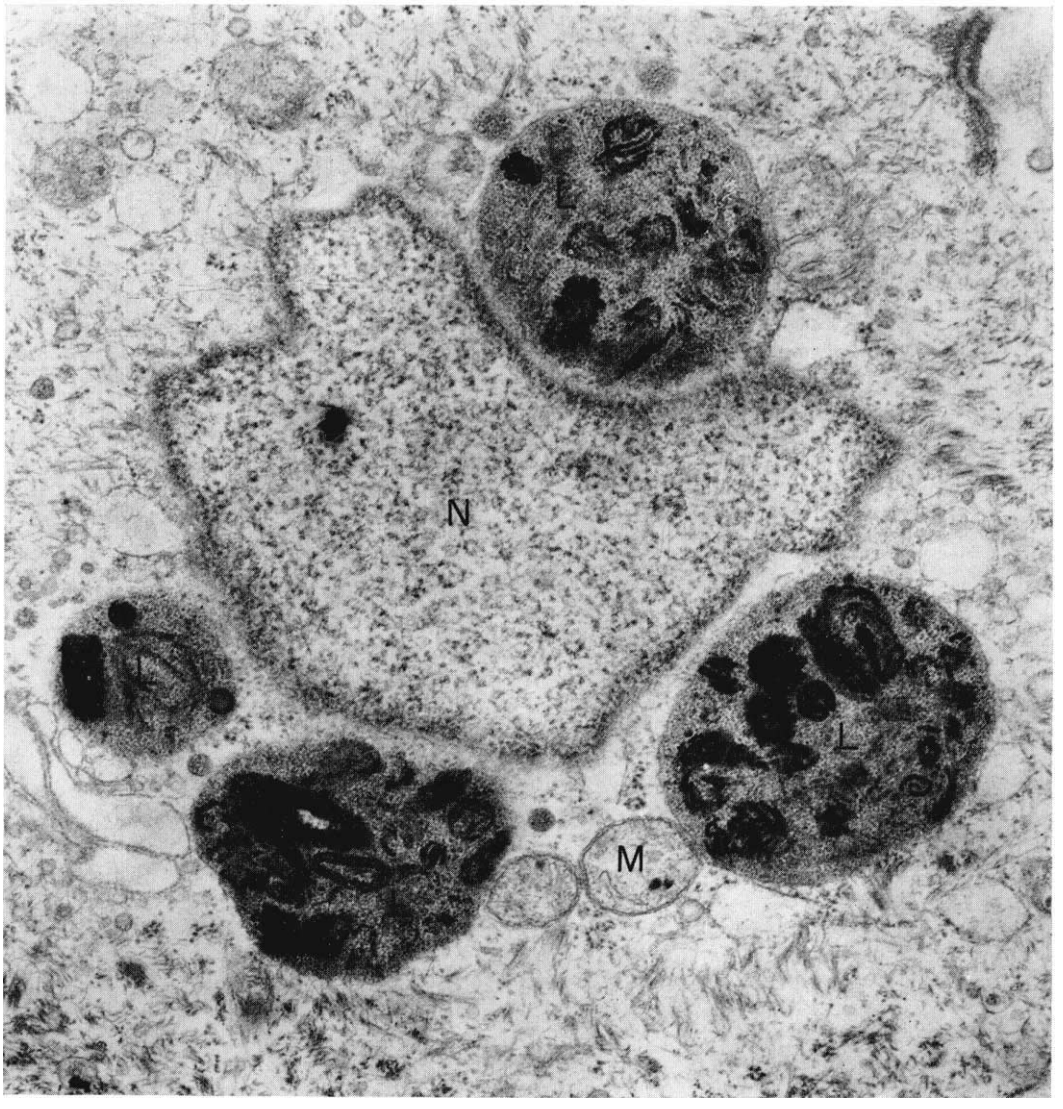

FIG. 6. The pigment granules that are passed to the epidermal cells are located in lysosome-like structures, often surrounding the nucleus (N). L, lysosome-like structure containing numerous pigment particles; M, mitochondrion. × 29,410.

have not been noted in epithelial cells and are probably not transferred from the melanocyte.

SUMMARY

A previous report demonstrated that melanocytes from the skin of patients with the CH syndrome contain giant melanosomes. The present study has examined formation of the massive melanosomes, and the basis of the hypopigmentation in CH disease. Giant particles in CH melanocytes appear to arise from defective premelanosomes. Their continued growth and/or fusion results in enormous particles which eventually degenerate. Destruction of the giant melanosomes may dilute skin color. However, abnormal packaging of normal sized melanosomes into large lysosome-like structures in the epidermal cells may provide a more likely basis for the hypopigmentation.

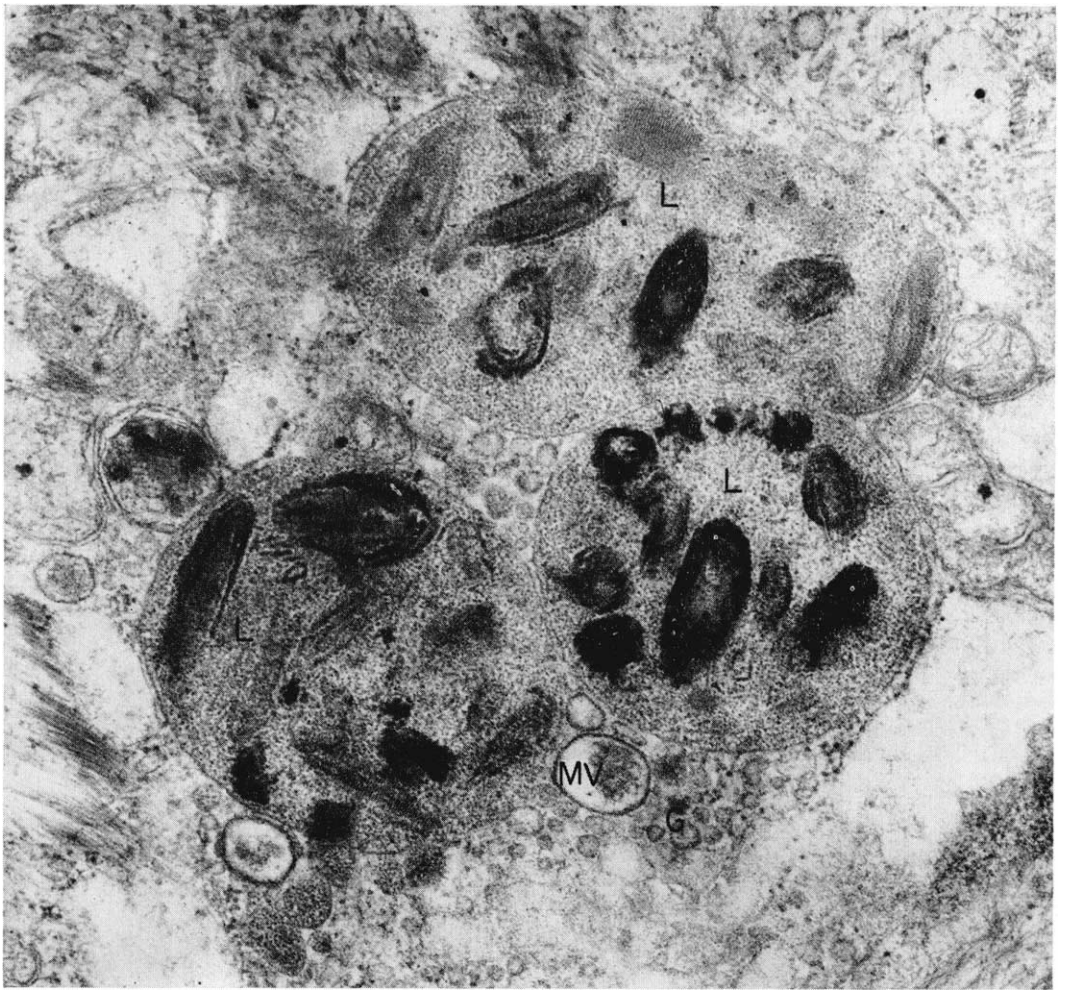

FIG. 7. The hypopigmentation in this condition is most likely due to abnormal packaging of normal melanosomes in giant epidermal cell lysosomes (L). G, Golgi vesicles; MV, multivesicular body. × 39,825.

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