Chediak-Higashi Syndrome: Hereditary Gigantism of Cytoplasmic Organelles

Abstract. *In the Chediak-Higashi syndrome, an anomalous hypopigmentation is associated with large lysosomal granules in the blood leukocytes. Since the inheritance pattern is that of an autosomal recessive trait, we postulated a common mechanism for these two primary features of the disease. Electron microscopy of melanocytes revealed that the pigmentary anomaly is indeed based on giant melanosomes. Since both types of granules, leukocytic and melanosomal, are characterized by limiting membranes, Chediak-Higashi disease may be a genetic disease of membranes.*

The Chediak-Higashi syndrome is a disease of infancy and childhood in which the first finding is an anomalous pigmentation (*1*). Hence it has been termed "oculocutaneous albinism," "partial albinism," and "semialbinism." Uveal pigment is decreased or absent, and there is marked photophobia. The hair is pale gray, blond, or brunette with a distinctive overcast and streaks of gray. The skin is generally pale, but on the exposed parts of children born of dark-skinned parents it may have "slate-gray" coloration or hyperpigmentation (*2*).

Infants with the syndrome are prone to frequent severe infections; smears of their peripheral blood show abnormally large granules in the neutrophils and eosinophils as well as single, large granules in some lymphocytes and monocytes (Fig. 1). Anemia and leukocytopenia are frequent. According to earlier reports, children with this disease usually die in early childhood of infection. More recently, case reports have appeared in which the child lives to be 5 to 10 years old but then dies of a lymphoma-like disease (*3–5*). An autopsy of one child who lived to be 16 has been reported by Kritzler *et al.* (*3*), who found abnormal granulations, containing lipids, in the histiocytes, renal tubules, and neurons.

The occurrence of multiple cases in several large sibships and a high frequency of consanguinity in the parents has clearly indicated that the condition is genetically determined and that it is almost certainly inherited as a simple autosomal recessive trait. Kritzler *et al.* have summarized the genetic information in their excellent review (*3*).

Current understanding of gene action indicates that single genes control the synthesis of single proteins or polypeptides. Hence it would be most revealing to relate the two earliest and most consistent findings of Chediak-Higashi disease—abnormalities in leukocyte granules and in pigmentation.

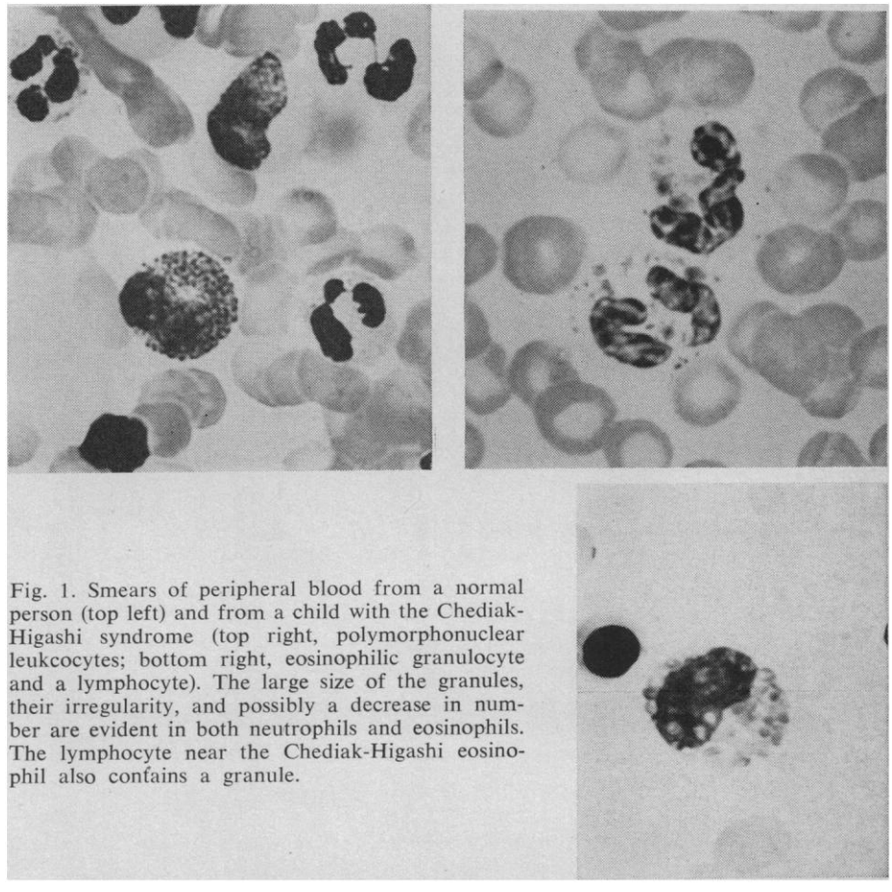

Fig. 1. Smears of peripheral blood from a normal person (top left) and from a child with the Chediak-Higashi syndrome (top right, polymorphonuclear leukcocytes; bottom right, eosinophilic granulocyte and a lymphocyte). The large size of the granules, their irregularity, and possibly a decrease in number are evident in both neutrophils and eosinophils. The lymphocyte near the Chediak-Higashi eosinophil also contains a granule.

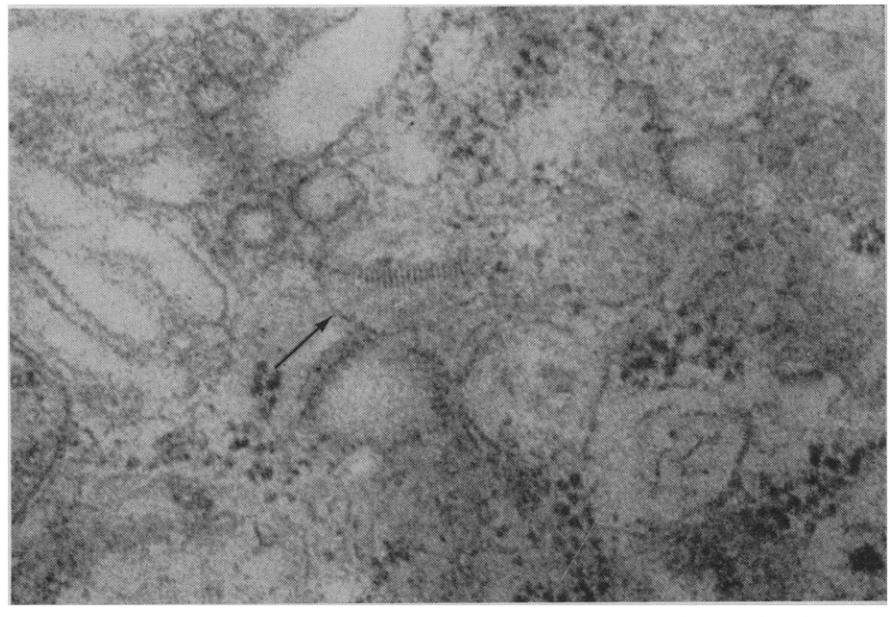

Fig. 2. Melanosome from a human albino. Note the lack of melanin and the character of the matrix of the granule (about × 87,000).

Further, the association of a similar pigmentary characteristic controlled by recessive genes in lower animals with abnormal granulations in leukocytes makes it seem all the more desirable to attempt to link these two major facets of this strange disorder (see *6*).

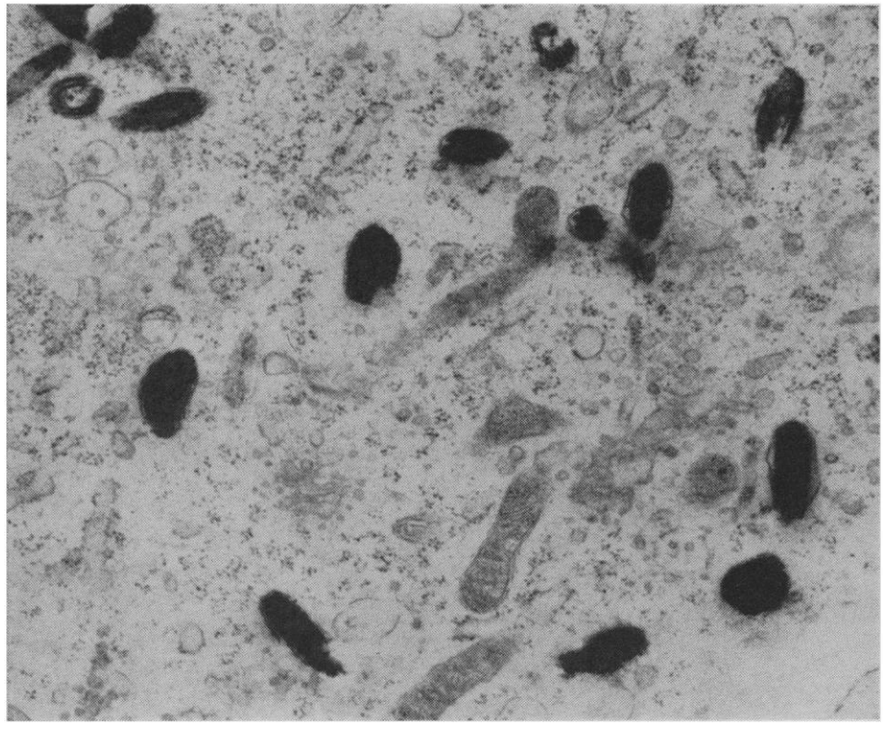

Fig. 3. Melanosomes in normal human hair (about × 27,000).

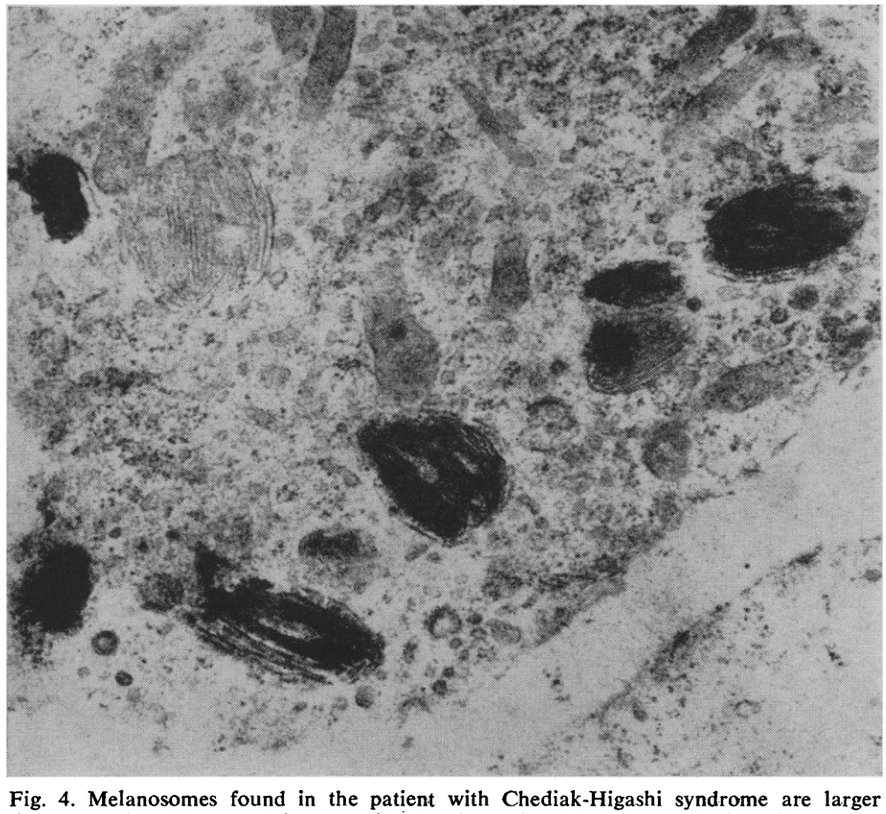

Fig. 4. Melanosomes found in the patient with Chediak-Higashi syndrome are larger than normal and seem to have an increased number of strands forming the matrix. Melanin is present, although the larger granules do not appear to be as heavily melanized as normal mature granules (about × 31,000).

The formation of melanin occurs on a specialized cytoplasmic structure of the melanocyte called the melanosome. There is considerable evidence that the melanosome, a membranous structure, is formed from proteins synthesized on the ribosomes and assembled in relation to the endoplasmic reticulum and the Golgi apparatus. Melanin is synthesized after this basic structure has been formed (*7*).

Granules in the various tissues of children having the Chediak-Higashi syndrome have a wide variety of histochemical and electron-microscopic characteristics. In fact, the one relatively consistent feature has been that the histochemical reactions for each type of granule are compatible with the reactions usually seen in the normal granules of the cell line under study (*8*, *9*). In addition, Bessis *et al.* (*8*) and J. G. White (*9*) report that examination, with an electron microscope, of the abnormal granules found in peripheral leukocytes as well as in granulocytic precursors indicates there are many ultrastructural similarities between the giant granules and normal cytoplasmic organelles coexisting in the same cell. Thus the abnormal granules of the diseased patients can be described as being enzymatically normal but gigantic cytoplasmic organelles.

On the basis of these considerations, we postulated that the pigmentary anomaly in Chediak-Higashi disease might be based on abnormal melanosomes rather than on an absence or inhibition of enzymes in the melanin-forming sequence, as is the case in true albinism (*10*). The observed differences between the clinical appearance in true albinism and Chediak-Higashi disease would then be explainable at a cellular level.

A 10-year-old girl with a well-documented Chediak-Higashi syndrome since infancy was available for study. Her case has been reported previously. together with that of her younger brother, who died of the condition (*5*). Her hair is basically medium to dark brown, with normal variation from hair to hair and the usual tendency to show lighter areas at the temples. Overcasting the entire growth of hair is a "frosted" or hazy appearance which makes even the darkest hairs appear to be incompletely pigmented.

A strand representative of the lightest areas of hair was selected and

plucked for examination. The hair was immediately fixed in buffered 1-percent osmium tetroxide and embedded in Epon 812. The sections were stained with uranyl acetate and studied with an RCA EMU 3G electron microscope. By this technique melanocytes can be readily located in the hair bulb.

The melanocytes were large and contained a well-developed Golgi complex. Surrounding the latter were precursors of melanosomes, melanosomes, and melanin granules. The granules were large and numerous. Each granule was limited by a single membrane and contained a number of strands which made up the granule matrix. The melanosome granules were 2 to 3 times as thick and approximately twice as long as normal melanosomes. The large granules contained approximately twice as many strands as are normally found within a matrix of pigment granules, and in some instances the strands appeared to be more irregular than those found in the typical matrix of melanosomes. Melanin was present, although its relative concentration on the larger melanosomes may have been less than it is in fully developed, normal melanosomes (Figs. 2, 3, and 4).

Thus the morphologic basis of the pigmentary anomaly in this disease is almost certainly based on a defect similar to that responsible for the morphologic abnormalities of the leukocytes. The clinical appearance of the pigmentation defect may be a function of less total quantity of melanin, but the peculiar quality of the color can probably be most easily explained by invoking one of the known properties of melanin: when highly aggregated (that is, on large granules in this instance) it is less perceivable as color.

Melanocytes originate in the neural crest, and melanosomes have been characterized as the products of a cellular secretory process (*7*). Polymorphonuclear cells are mesothelial in origin, and their granules are, by all current criteria, lysosomes (*11*). The common morphogenesis which this work suggests for the organelles of these two diverse cell lines is most intriguing. Possibly the genetic defect is an abnormality of granule formation, including lysosome formation, which may be manifest in most or all cell lines. It is reasonable to postulate that further study may reveal abnormally large organelles having limiting membranes in other tissues, a possibility already suggested by the work of Page *et al.* (*5*) and Kritzler *et al.* (*3*). It then might be useful to look on the disease as a genetic disease of the membranes themselves.

An attractive alternative hypothesis, in view of the known role of some hormones in melanin formation (*12*) and the apparent association of lysosomal structures with hormonally controlled tissue regressions (*13*), is that these giant granules reflect an inherited abnormality of the functioning of a more central process which controls formation of certain membrane-bound structures within the cells.

If this is the case, patients with Chediak-Higashi syndrome may be revealing an important control mechanism or cellular function which plays a telling role in resistance to infection as well as to malignancy of the lymphoid system.

DOROTHY B. WINDHORST
Division of Dermatology and *Variety Club Heart Hospital, University of Minnesota, Minneapolis 55455*
A. S. ZELICKSON
Division of Dermatology, University of Minnesota
ROBERT A. GOOD
Variety Club Heart Hospital, University of Minnesota

References and Notes

1. M. Chediak, *Rev. Haematol.* **7**, 362 (1952); O. Higashi, *Tohoku J. Exptl. Med.* **59**, 315 (1954).
2. Pierini's case as described by O. C. Stegmaier and L. A. Schneider, *Arch. Dermatol.* **91**, 1 (1965); also Higashi's case.
3. R. A. Kritzler, J. Y. Terner, J. Lindenbaum, J. Magidson, R. Williams, R. Preisig, G. B. Phillips, *Am. J. Med.* **36**, 583 (1964).
4. W. L. Donohue and H. W. Bain, *Pediatrics* **20**, 416 (1957); P. Efrati and W. Jonas, *Blood* **13**, 1063 (1958); L. A. Schneider and S. R. McCreadie, *Proc. 7th Int. Congr. Int. Soc. Haematol.* (Grune and Stratton, New York, 1958), p. 1554.
5. A. R. Page, H. Berendes, J. Warner, R. A. Good, *Blood* **20**, 330 (1962).
6. G. A. Padgett, R. W. Leader, J. R. Gorham, C. C. O'Mary, *Genetics* **49**, 505 (1964).
7. M. S. C. Birbeck, E. H. Mercer, N. A. Barnicott, *Exptl. Cell Res.* **10**, 505 (1956); M. Seiji, T. B. Fitzpatrick, M. S. C. Birbeck, *J. Invest. Dermatol.* **36**, 243 (1961); A. S. Zelickson, *Electron Microscopy of Skin and Mucous Membrane* (Thomas, Springfield, Ill., 1963), p. 108; S. R. Wellings and B. V. Siegel, *Ann. N.Y. Acad. Sci.* **100**, 548 (1963).
8. M. Bessis, J. Bernard, M. Seligman, *Nouv. Rev. Franc. Hematol.* **1**, 422 (1961); C. Mauri and V. Silingardi, *Acta Haematol.* **32**, 114 (1964).
9. J. G. White, personal communication.
10. T. B. Fitzpatrick, *Metabolic Bases of Inherited Disease* (Blakiston, New York, ed. 2, 1960), p. 428.
11. Z. A. Cohn and J. G. Hirsch, *J. Exptl. Med.* **112**, 983, 1015 (1960); J. G. Hirsch and Z. A. Cohn, *ibid.*, p. 1005.
12. Various authors, *Ann. N.Y. Acad. Sci.* **100**, 622–719 (1963).
13. A. B. Novikoff, in *The Cell* (Academic Press, New York, 1961), p. 2473.
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Endoplasmic Reticulum in Rat Renal Interstitial Cells: Molecular Rearrangement after Water Deprivation

Abstract. *Cylindrical bodies in renal interstitial cells of dehydrated rats are confluent with membranes of endoplasmic reticulum. The cylinder walls, composed of helically arranged pentagonal tubules, may represent a molecular rearrangement of the membrane structure. The cylinders may represent a morphologic expression of altered ergastoplasmic function possibly related to the production of concentrated urine.*

The renal papilla is important in the process of urine concentration (*1*). We have been studying the morphology of the rat renal papilla during dehydration and water diuresis in order to determine if ultrastructural data can contribute to an understanding of the mechanisms involved in urine concentration.

The rat papilla is composed of large collecting ducts, capillaries, thin limbs of Henle's loop, and an abundant interstitium containing elongated interstitial cells. These cells are oriented perpendicular to the long axis of the tubules and vessels like the rungs of a ladder, and have long, branching cytoplasmic processes that seem to encircle tubules and vessels. The cytoplasm of the interstitial cells is characterized by abundant rough-surfaced endoplasmic reticulum, lipid droplets, and many fine filaments. The cells are partially surrounded by basement membrane material.

Animals were studied in various states of water balance. In one experiment rats were deprived of drinking water for 1 to 13 days. In another, rats with exteriorized urinary bladders were given 8 ml of water or 12.5-percent ethyl alcohol per 100 g of body weight. The presence of a water diuresis was confirmed by a urine output