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OPHTHALMOLOGIC, BIOCHEMICAL, PLATELET, AND ULTRASTRUCTURAL DEFECTS IN THE VARIOUS TYPES OF OCULOCUTANEOUS ALBINISM*

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INTRODUCTION

Mutations Causing Generalized Hypopigmentation in Man

Previous studies have demonstrated that at least six mutations affecting the melanin pigment system in man result in recessively inherited traits with features of oculocutaneous albinism, i.e., a general reduction of pigment in the skin, hair, and eyes with nystagmus, photophobia, and reduced visual acuity (Witkop et al., 1963; Witkop et al., 1970; Nance et al., 1970; Witkop, 1971). In general, these mutations can be distinguished by the ability of epilated hair bulbs to form pigment when incubated in l-tyrosine, by their clinical features, and the ultrastructure of melanocytes. Various features have been described in one or more of these conditions, but a systematic study of all types for all of these characteristics has not been undertaken.

Characteristics of the Types of Albinism

1. The tyrosinase-negative (ty-neg) albino has pink skin, white hair, a prominent red reflex, severe nystagmus, photophobia, and a defect in visual acuity which does not vary with age or race. Hair bulbs incubated in tyrosine do not form pigment (Fig. 1). Melanocytes are present in normal numbers, but no evidence of tyrosinase activity is present in cytoplasmic structures and only stage II early premelanosomes are present (Fig. 2). After incubation in either l-tyrosine or l-dopa, the premelanosomes do not demonstrate increased pigment (Fig. 3).

2. Tyrosinase-positive (ty-pos) albinos have phenotypic features that vary according to age and the degree of pigmentation of the parents. Most Caucasian ty-pos albinos of all ages and infant Negro and Amerindian albinos phenotypically resemble ty-neg albinos. With increasing age small amounts of pigment accumulate in the iris, skin, and hair and they develop flaxen to yellow hair, very slight tanning ability, pigmented nevi, a loss of the prominent red reflex, moderate nystagmus and photophobia, and even brown irides. Hair bulbs incubated in tyrosine produce pigment (Fig. 4). Melanocytes contain early stage III premelanosomes (Fig. 5), which can be converted to normal-appearing, mature stage IV melanosomes by incubation in l-tyrosine or l-dopa (Fig. 6).

Marriages of a ty-pos to a ty-neg albino indicate that the genes are not allelic, since only normally pigmented offspring have resulted from such matings (Witkop, 1971).

3. The yellow mutant (ym) albino resembles the ty-neg albino at birth (Nance et al., 1970) but by 6 months to one year of age has developed yellow-red hair, a moderate tanning ability, a moderate red reflex, nystagmus and photophobia, and visual acuity defect. Hair bulbs incubated in l-tyrosine do not form increased black pigment, but incubation in l-tyrosine plus cysteine produces an intensification of yellow or red pheomelanin. Melanocytes appear to be normally distributed and contain unevenly pigmented stage III premelanosomes resembling those seen in red hair (Fig. 7). After incubation in l-tyrosine, no increase in pigment is seen (Fig. 8).

Recently, Walsh (1971) described "red" albinos among New Guinea natives who phenotypically resemble ym American Negro albinos. Figure 9 is a photograph of a New Guinea native goldminer which was sent to us by a geologist and probably represents the same condition described by Walsh (1971). Walsh (1971) reported that the urinary chromatograms of the "red" albinos contained a compound which stained with ninhydrin with an Rf value similar to that of l-dopa. This compound was absent or present only in small quantities in the urine of the black-skin subjects.

4. Albinism with hemorrhagic diathesis was described by Hermansky and Pudlak (1959) in two sisters. A ceroid-like pigment was found in the reticuloendothelial system, and the bleeding disorder was attributed to a vascular type of hemophilia. Since then about 20 similar cases have been reported or are known (Verloop et al., 1964; Hardisty and Hutton, 1967; Maurer et al., 1968; Mills and Hardisty, 1970; Muniz et al., 1970; White et al., 1971; Logan et al., 1971; White and Witkop, 1972).

The bleeding disorder has now been ascribed to a platelet defect (Mills and Hardisty, 1970; White et al., 1971; White and Witkop, 1972) with low intrinsic levels and poor uptake of serotonin, a decreased amount of nonmetabolic adenine nucleotide, and by electron microscopy a virtual absence of platelet dense bodies (Maurer et al., 1968; White et al., 1971). The addition of concentrations of aggregating agents such as ADP, epi-

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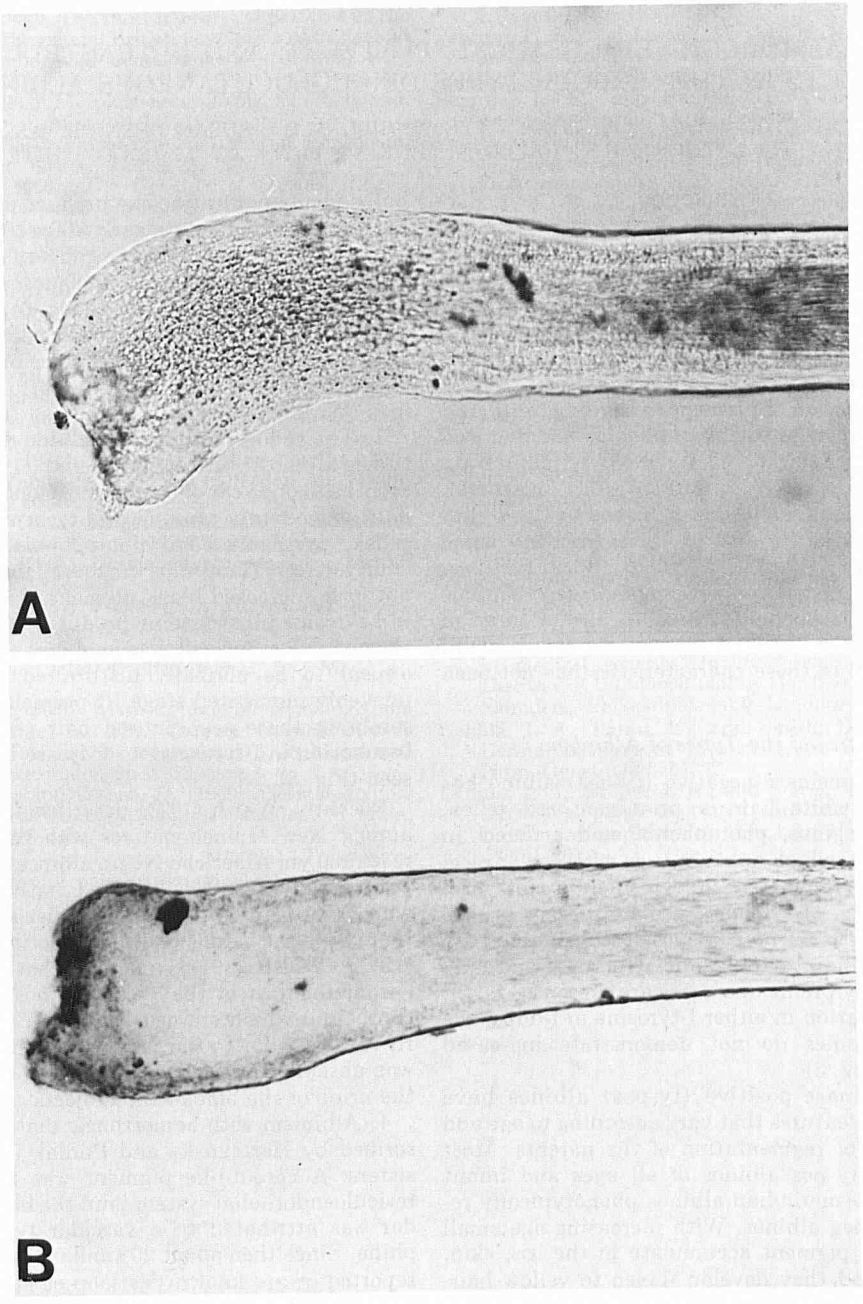


FIG. 1. A. Hair bulb from a tyrosinase-negative albino shows no visible pigment. B. After incubation in l-tyrosine, 80 mg/100 ml of phosphate buffer at pH 6.8, for 12 hr there is no pigment formation.

nephrine, thrombin, collagen, and bacteria to the platelet-rich plasma of patients, which normally produces a biphasic response, results in a monophasic or single wave response instead (White et al., 1971; White and Witkop, 1972).

What has been described as ceroid pigment has been reported in most of the patients examined for this feature but the pigment was absent in the bone marrow of an 18-month-old boy examined by White and associates (1971). One report described a large proportion of peripheral lymphocytes with broken chromosomes in this type of albinism (Maurer et al., 1968).

5. In addition to these four types of albinism, two other recessively inherited hypopigmentary disorders manifest a generalized hypopigmentation with nystagmus and photophobia, the Beguez-Cesar–Chediak–Higashi syndrome (Beguez-Cesar,

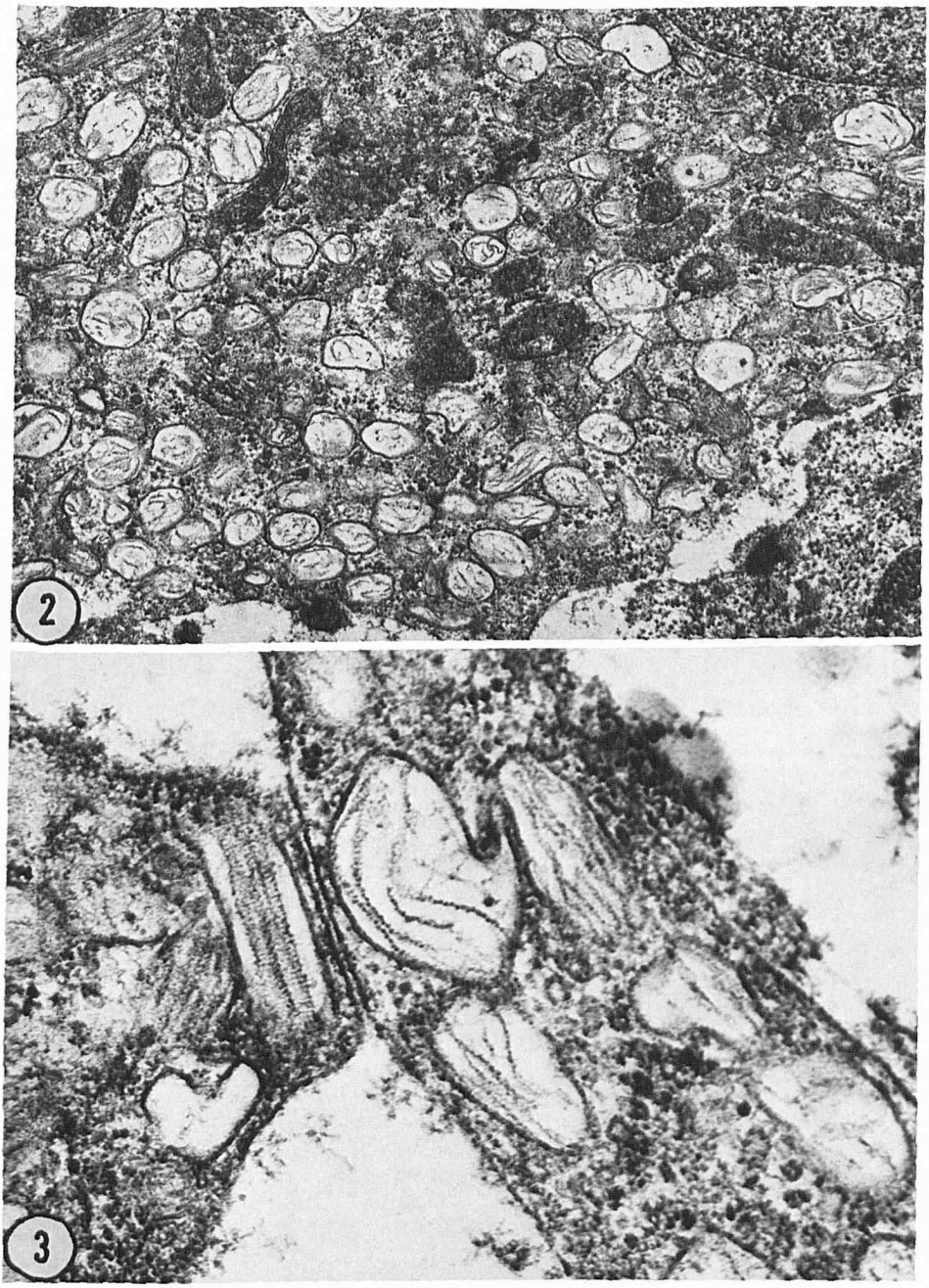


FIG. 2. Electron photomicrograph of a melanocyte from a tyrosinase-negative albino shows intermediate vesicles and Stage II premelanosomes but no evidence of any pigment formation (× 31,710).

FIG. 3. Electron photomicrograph of premelanosomes from a tyrosinase-negative albino after incubation in l-tyrosine, 80 mg/100 ml of phosphate buffer at pH 6.8, for 12 hours shows that the premelanosomes remain depigmented (× 74,700).

1943; Stegmaier and Schneider, 1965) and the Cross syndrome (Cross et al., 1967). In the former, the defect, which is thought to be in the membranes of lysosomal-like particles, results in giant cytoplasmic granules in granule-producing cells. The melanocytes contain giant premelanosomes that cannot be passed properly via the melanocyte dendrites to the keratinocytes. In addition, numerous polyphagosomes in the melanocyte cytoplasm consist of aggregates of giant melanosomes under-

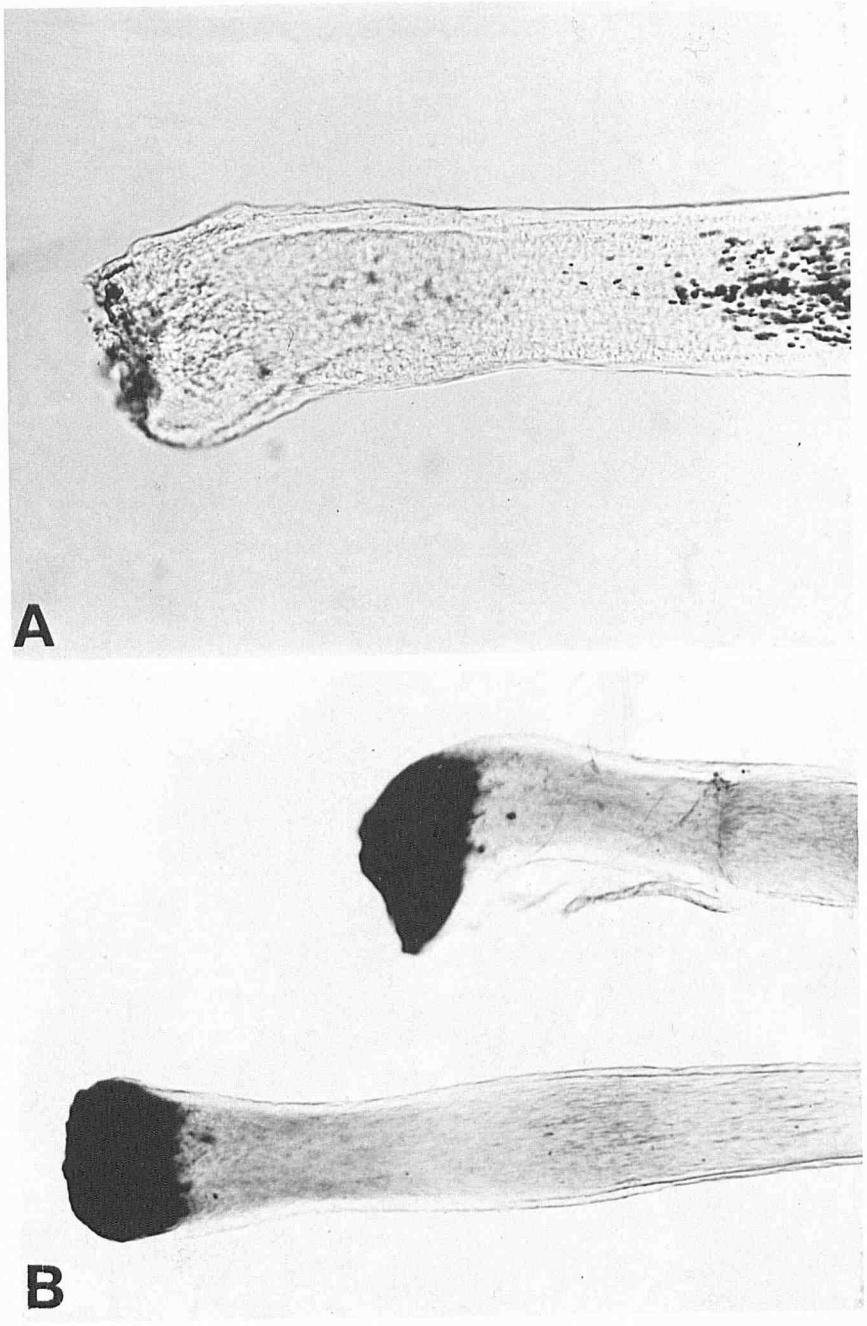


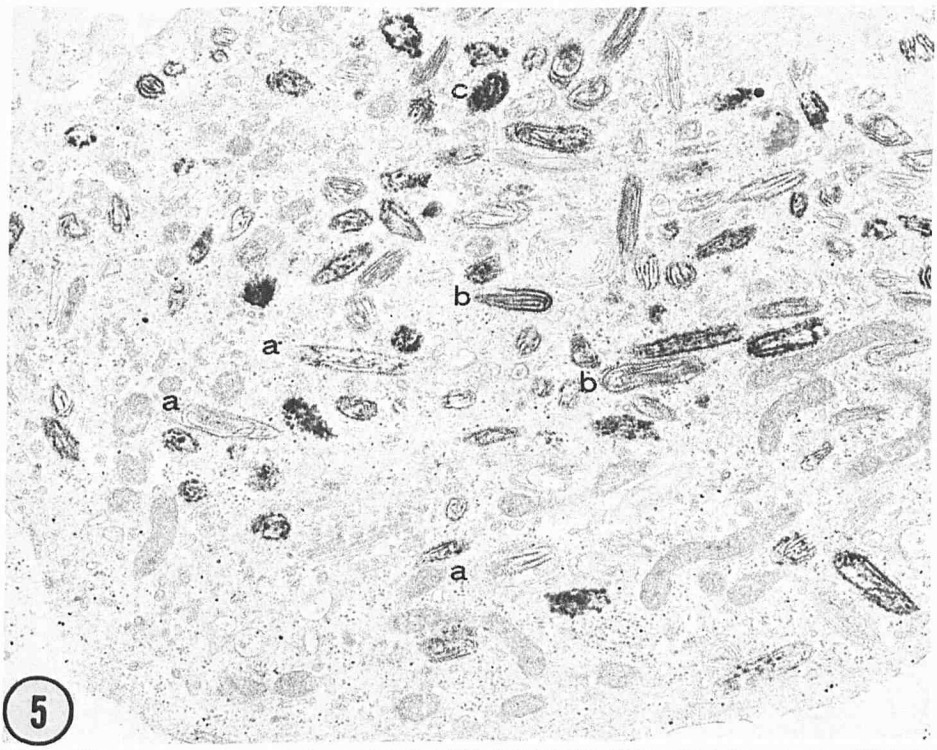
FIG. 4. A. Hair bulb from a tyrosinase-positive albino shows faint yellow pigment granules. Dark area in hair shaft at left is due to light scattering from bubbles in hair. B. After incubation in l-tyrosine, 80 mg/100 ml of phosphate buffer at pH 6.8, for 12 hours, there is intense pigmentation.

going destruction by the surrounding lysosomes (Windhorst et al., 1968).

6. Children with Cross syndrome are hypopigmented with melanocytes in which scanty melanosomes respond with increased pigmentation in vitro to added l-tyrosine or l-dopa. In addition, the children have microphthalmia, athetosis, severe oligophrenia, and gingival fibromatosis (Witkop, 1971).

Present Study

A study of ty-neg, ty-pos, ym, and albinos with bleeding tendency was undertaken to determine which of the previously described abnormalities



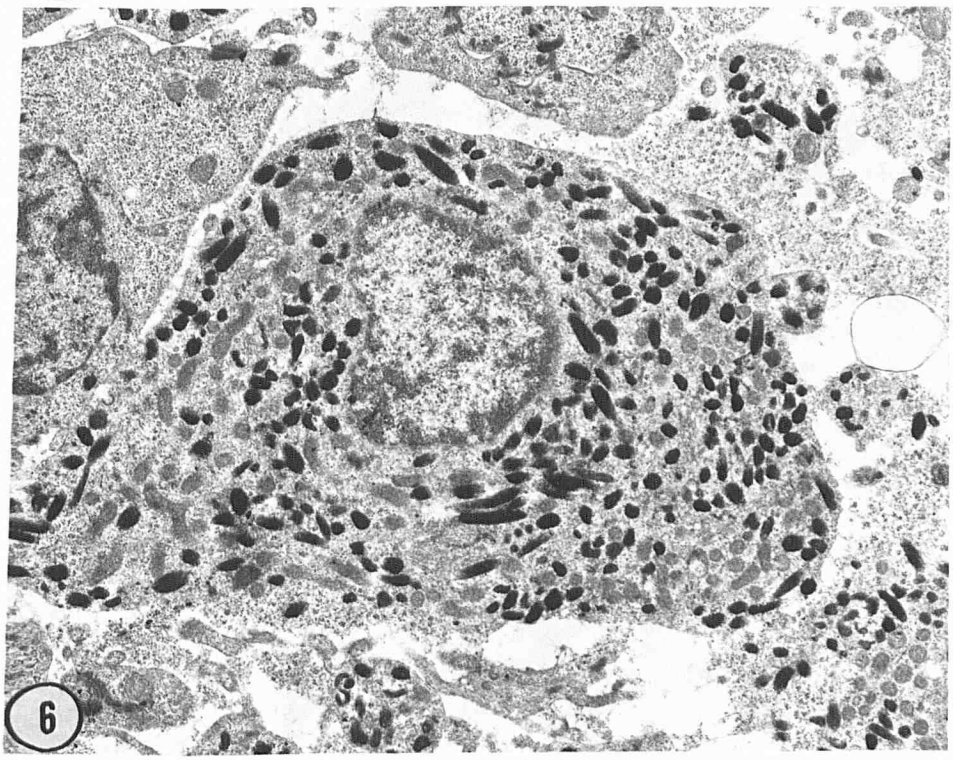
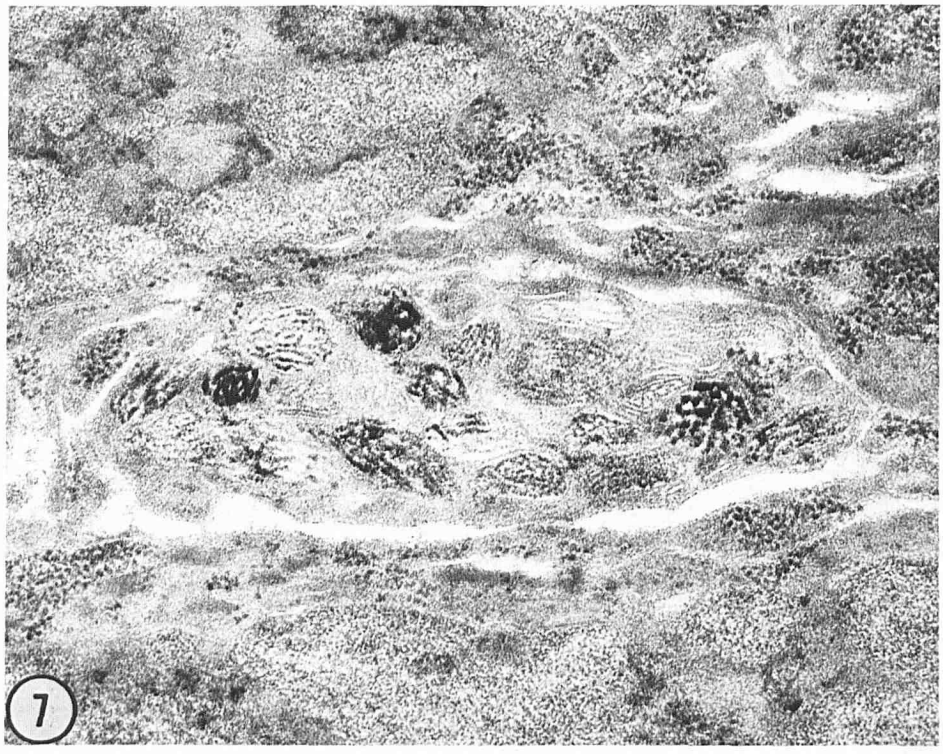


FIG. 5. Melanocyte from a tyrosinase-positive albino shows intermediate vesicles, premelanosomes Stage II (a) and lightly pigmented premelanosomes Stage III (b). Rarely are mature Stage IV melanosomes (c) observed (× 16,500).

FIG. 6. Melanocyte from a tyrosinase-positive albino prefixed in 2% glutaraldehyde and incubated in 80 mg of l-tyrosine/100 ml phosphate buffer at pH 6.8 for 12 hours, refixed and stained in osmic acid : glutaraldehyde shows that most of the premelanosomes have converted to mature melanosomes Stage IV (× 10,250).



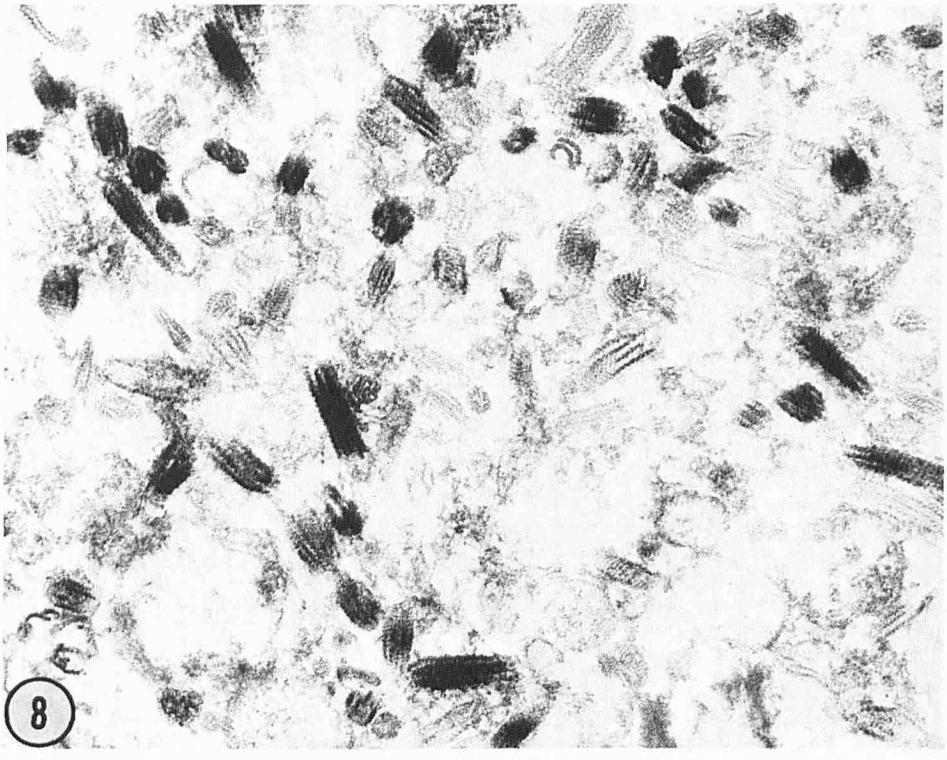


FIG. 7. Melanocyte dendrite from a yellow mutant albino shows unevenly pigmented premelanosomes similar to those seen in persons with red hair (× 41,500).

FIG. 8. Melanosomes from a yellow mutant albino after incubation in 80 mg of l-tyrosine/100 ml of phosphate buffer pH 6.8 for 12 hours show only questionable increase in pigmentation (× 37,500).

were shared among the various types. In addition, obligate heterozygotes for each type were examined ophthalmologically to determine whether they had diaphanous irides as a possible sign of the carrier state.

METHODS

All albinos had a physical examination and were photographed. They were tested with the hair bulb incubation test (Witkop, 1971) and had their hair bulbs examined by electron microscopy (Witkop et al., 1970). Ophthalmic examination was made with dilation and included near and far visual acuity and Ishihara color vision. Transillumination of the irides was done in a dark room with a Finnhoff light that had been shown to elicit iris transillumination in albinos and in some obligate heterozygotes for ty-neg type albinism. Iris transillumination and nystagmus were graded on an arbitrary scale of 0 to 4+. All observations were made by the same investigator (C.W.H.) who had no previous knowledge about the type of albinism affecting the patient or the obligate heterozygotes. Slit lamp examination and fundus photographs were obtained.

FIG. 9. New Guinea native gold miner with "red" type albinism probably similar to that reported by Walsh (1971).

Chromosome analysis (for breakage) of cultured peripheral lymphocytes was carried out by the inspection of 100 metaphase cells of each patient.

Citrated platelet-rich plasma (C-PRP) was prepared and the effects of various aggregating agents (collagen, thrombin, adenosine diphosphate (ADP), epinephrine, and serotonin) added to C-PRP on the platelet aggregometer were noted and samples fixed for electron microscopy as detailed elsewhere (White, 1968). Serotonin determinations were made by the method of Murayama and Takemori (1970). All patients were instructed to avoid any drug intake for at least 10 days before testing.

Urinary glycolipids were determined by the method of Desnick et al. (1970) and two-dimensional paper chromatography was done for urinary amino acid (O'Gorman et al., 1970).

RESULTS

Clinical Studies

Results of the ophthalmologic examination are given in Tables I–III. In general, proceeding from the severely affected ty-neg to the ty-pos to the ym type albinos, there was a lessening of severity of visual acuity defects. This was accompanied by evidence of differential pigment accumulation in the various types: the ty-neg albino—no accumulation of melanin pigment and severe nystagmus and visual acuity defect; the ty-pos albino—some pigment accumulation and a less severe nystagmus and visual acuity defect; the ym—the most pigment, the least nystagmus, and the best visual acuity.

Only among the Caucasian ty-neg heterozygotes was the number with iris translucency substantially increased. In one subject with a variant of the Hermansky–Pudlak syndrome, only one melanocyte was found in serial electron microscopic sections of 10 hair bulbs. Both of his parents had the most prominent translucent irides seen in any

TABLE I

Ophthalmologic findings: Ty-neg albinos

	No. Tested	Mean Acuity	Range Acuity	Mean Transillum	Mean Nystagmus	Fundus Pigment
Homozygotes						
Caucasian	7	20/300	200–400	3.0	2.9	0
Negro	3	20/400	400	3.0	3.0	0
Heterozygotes						
Caucasian	10			0.8 (8 individuals were +)		
Negro	7			0.3 (3 individuals were +)		

TABLE II

Ophthalmologic findings: Ty-pos albinos

	No. Tested	Mean Acuity	Range Acuity	Mean Transillum.	Mean Nystagmus	Fundus Pigment
Homozygotes						
Caucasian	9	20/225	70–400	1.9	2.0	0
Negro	52	20/200	70–400	1.4	1.8	+
Amerindian	10	20/200	60–300	1.5	2.0	+
Heterozygotes						
Caucasian	17			0.3 (5 individuals were +)		
Negro	72			0		
Amerindian	13			0		

TABLE III

Ophthalmologic findings: ym and H–P albinos

	No. Tested	Mean Acuity	Range Acuity	Mean Transillum.	Mean Nystagmus	Fundus Pigment
Homozygotes						
ym						
Caucasian	6	20/200	25–400	1.5	1.0	+
Negro	1	20/200	—	1.0	1.0	++
Hermansky–Pudlak						
Caucasian	2	20/300	—	3.0	3.0	+
Heterozygotes						
Caucasian H–P	2			2.0		

TABLE IV

Laboratory findings in various types of albinos (no. tested/no. with abnormalities)

Type	Chromosome Breaks	Polyphagosomes in Melanocytes	Absent Platelet Dense Bodies	Abnormal Platelet Aggregometry	High Urinary GI-1	Abnormal Urinary Chromatography
Ty-neg	2/0	6/0	1/0	—	3/0	—
Ty-pos	13/1*	11/7	4/0	—	4/2	3/0
ym	2/1*	5/0	1/0	—	0/0	4/0
H–P	1/0	2/0	2/2	2/2	2/0	1/0

* Patients with infectious mononucleosis; when retested, no breaks.

obligate heterozygote of any albino type. Another subject, however, had yellow-brown hair, pigmented lentigines in his skin, and hair bulb melanocytes that contained numerous melanocytes with many stage II and early stage III phaomelanosomes; his irides were yellow-brown and showed only one plus transillumination. His relatives were not available for testing.

Laboratory Findings

The laboratory findings are summarized in Table IV. Increased chromosome breakage was seen in only two individuals (ty-pos, 40 percent of cells; ym, 12 percent of cells). The day after the study, the ty-pos subject was found to have infectious mononucleosis, and the ym subject had a possible exposure to the same viral infection and to drugs. When retested later, the cells from both patients showed less than 2 percent breaks.

In electron photomicrographs of melanocytes from 7 of 11 ty-pos albinos there were giant polyphagosomes in the cytoplasm showing aggregates of phagosomes, melanosomes, and endoplasmic reticulum undergoing destruction (Fig. 10). In addition melanocytes from these patients were packed with premelanosomes. These cells contained one to several giant melanosome complexes, some of which were in various stages of destruction in autophagic vacuoles.

Platelets from the subjects with Hermansky–Pudlak (H–P) syndrome showed a marked decrease in dense bodies (Fig. 11), which could not be recruited by incubation in serotonin-rich media. Platelets from subjects with ty-pos, ty-neg, or ym albinism appeared to have normal numbers of dense bodies.

Two subjects with the H–P syndrome showed abnormal aggregometry with collagen, thrombin, epinephrine, and ADP (Fig. 12). Samples of C-PRP from patients with this disorder manifested a normal primary response to aggregating agents, but the second wave of aggregation, which is

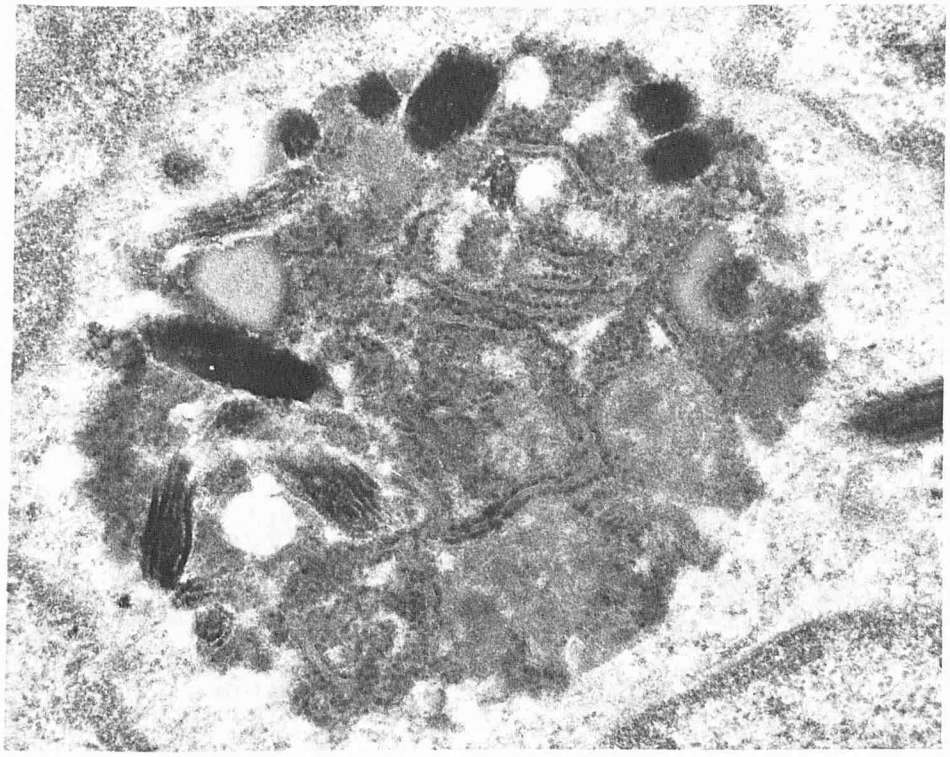


FIG. 10. Melanosome complex from a tyrosinase-positive albino hair bulb melanocyte appears to be undergoing destruction. Elements which appear to be endoplasmic reticulum are seen throughout the complex (× 41,500).

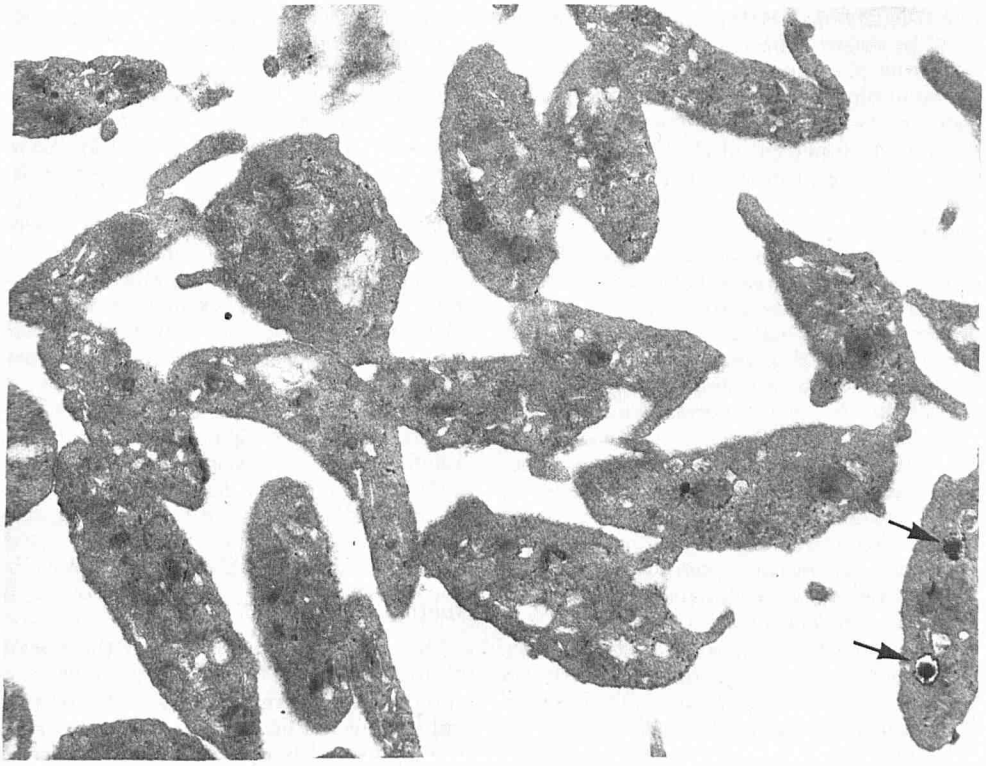


FIG. 11. Platelets from a Hermansky–Pudlak type albino showing the lack of dense bodies which are storage organelles for serotonin. Only two dense bodies are seen in this photomicrograph (arrows). Normal cells contain about 1.4 dense bodies/platelet in thin section (× 21,500).

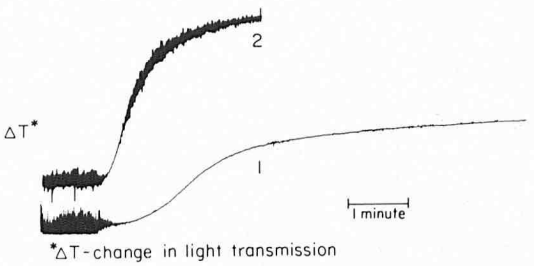


FIG. 12. Response of patient's C-PRP to addition of collagen in tracing 1 is compared with the reaction of a normal sample of C-PRP to same agent shown in tracing 2. Collagen induced early changes in patients as in normal cells, indicated by a narrowing of the baseline. However, instead of rapid increase in light transmission followed by irreversible aggregation evident in tracing of the normal sample, patient's C-PRP developed a modified pattern of response, Light transmission increased steadily for the first 3 min, then slowed to a gradually ascending phase, which did not reach a maximal decrease in optical density during the period of recording. The pattern evident in the patient's tracing suggests inadequate availability of secretory products essential for rapid development of irreversible aggregation.

entirely dependent on chemical products secreted by the cells, failed to occur. As a result the aggregated cells disassociated, as indicated by the return of the tracing toward the base line. Platelets from these patients adhered to collagen but did not aggregate. The addition of 10 percent normal C-PRP to C-PRP from a H–P patient corrected the defect and produced a normal biphasic response. Aspirin-treated platelets from normal individuals showed monophasic responses to aggregating agents similar to those of the H–P patients. However, combining 50 percent of H–P C-PRP and 50 percent of normal aspirin-treated C-PRP restored the aggregation curves to normal biphasic responses (Fig. 13).

High urinary excretion of Gl-1 fraction was observed in 2 of the 4 ty-pos subjects tested: 0.691 and 0.650 mmoles/24 hrs respectively, compared with the normal range of 0.225 to 0.459 mmoles/24 hrs. The subject with H–P variant had high urinary Gl-1 fraction excretion on initial examination, but was well within the range of normal when retested (0.372 mmoles/24 hrs).

None of the subjects tested had an abnormal amino acid pattern nor an abnormal amount of l-dopa excretion products on two-dimensional paper chromatography. If dopa itself accumulated in an albino, excessive 3-methoxy-4-hydroxyphenylacetic acid and 3,4-dihydroxyphenylacetic acid would be found in the urine from individuals who have ingested dopa (O'Gorman et al., 1970). No such abnormalities were detected with the diazotized p-nitroaniline method of O'Gorman et al. (1970) in urine from patients with ty-pos, ym, and H–P albinism.

Investigation of the bone marrow of one adult male subject with albinism, bleeding tendency, and a platelet defect (Fig. 13) showed the extensive

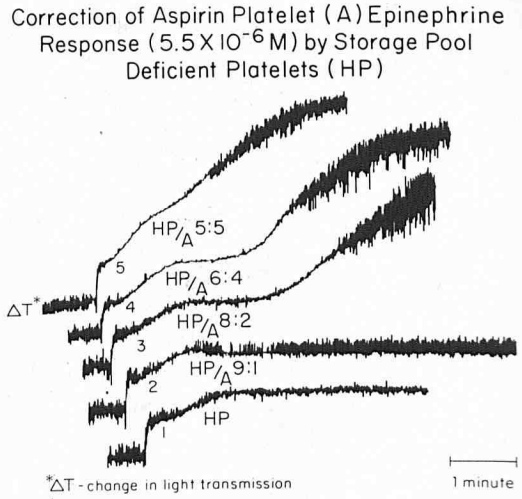


FIG. 13. Effects of C-PRP from a normal individual after the ingestion of aspirin on the defective secondary aggregation of a patient with H–P syndrome to epinephrine. Tracing number 1 of the patient's C-PRP alone is identical to the reaction of C-PRP from the aspirin-treated control, and the combination of 10 percent aspirin platelets (A) in tracing 2 does not alter the defect in secondary aggregation. A mixture of 20 percent aspirin platelets and 80 percent H–P cells develops a slightly delayed, but otherwise normal-appearing second wave of aggregation in response to epinephrine in tracing 3. Tracings 4 and 5 obtained from samples combined in ratios of HP6:4A and HP5:5A respectively are identical to biphasic responses observed in samples of normal C-PRP alone following addition of epinephrine.

accumulation of lipid deposits in macrophages (Fig. 14); the lipid appeared to be neutral, i.e., it stained intensely with Sudan black B and, in addition, deposits of golden yellow ceroid-like material. Figure 15 is an electron photomicrograph of ceroid deposits in bone-marrow macrophages from a patient with ceroid storage disease (Levine et al., 1968). Figure 16 is an electron photomicrograph of a bone-marrow macrophage from the subject with H–P albinism. In the latter the lipid deposits are in droplet form, have a smooth, uniform appearance, and are relatively electron translucent. The ceroid deposits do not have a smooth droplet configuration, appear somewhat granular with a vermicular pattern, and are relatively more electron dense than the deposits of neutral lipid.

DISCUSSION

Ophthalmologic Findings

The ophthalmologic findings in the various types of albinos indicate in general an inverse relationship between the amount of pigment accumulation and the severity of the defects in visual acuity and nystagmus. Although the relationship between pigment accumulation, nystagmus, and decreased visual acuity follows this general pattern by albino type, variation depends upon the ethnic back-

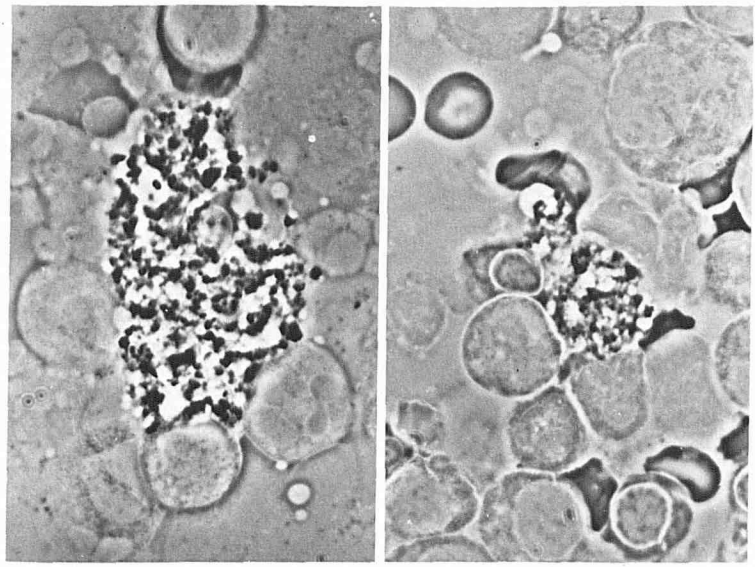


FIG. 14. Phase contrast photomicrographs of bone marrow cells from a patient with H–P albinism. The macrophages contain a bluish-green material which stains intensely with Sudan black.

ground of the patient. Thus, ty-pos Negro albinos have more pigment, seen in hair bulbs, skin, and iris color, with less nystagmus and better visual acuity than some Caucasian ym albinos. Some Caucasian ty-pos albinos cannot be distinguished by phenotypic pigment accumulation from ty-neg Negroes, and have ocular defects of the same degree of severity.

Iris translucency as an indicator of the carrier state for albinism is probably not a reliable indicator of carriers for ty-pos and ym albinism. It was absent in about half of the Negro ty-neg obligate heterozygotes in this series. Among the Zuni Indians, we have examined 11 obligate heterozygotes for ty-pos albinism but have failed to find any with diaphanous irides (Witkop et al., 1972).

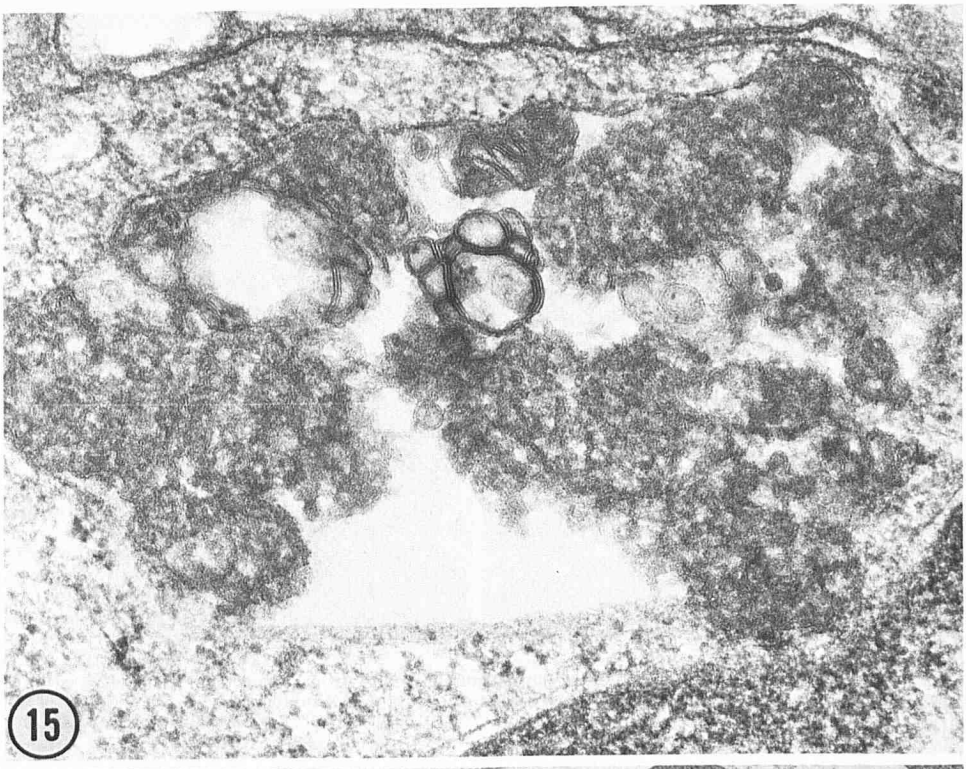
Waardenburg (1947) first reported that obligate heterozygotes for albinism could be detected by diaphanous irides, but Dodinval and associates (1965) failed to corroborate this finding. Later Waardenburg (1970) emphasized that examinations for iris translucency must be made with a special light, no longer manufactured, and that the use of any other device invalidates the results. In retrospect, this controversy probably arose not from a difference in technique but from the use of different types of albino heterozygotes. Our experience indicates that iris translucency is not a consistent trait in the heterozygote of any type of albinism; hence we do not use it as a basis for genetic counseling.

Chromosomal Breaks

At one time we entertained the possibility that breaks in the chromosomes of circulating lymphocytes reported in H–P syndrome (Maurer et al., 1968) are not limited to this type of albinism and postulated that all albinos have this defect because of increased ultraviolet radiation of the dermal capillary bed insufficiently protected by melanin pigment in melanocytes and keratinocytes. However, we were unable to find chromosome breaks in any of the types of albinos tested, including those with H–P syndrome. We plan to test albinos in the tropics to determine whether sunlight is a factor involved.

Polyphagosomes in Ty-pos Albinism

Although we found giant polyphagosomes in melanocytes of only seven of the 11 albinos tested (Table IV), serial sections of hair bulbs from the other four subjects could have shown them since the keratinocytes of these subjects contained premelanosome complexes as well as normal-appearing melanosome complexes. Mottaz, Thorne, and Zelickson (1971) demonstrated that after minor trauma induced by cellophane tape stripping of the stratum corneum of human epidermis melanocytes from normal subjects contain numerous melanosome complexes, many in autophagic vacuoles. They attributed this phenomenon to the production of edema around the melanocytes and to the inhibition of the passage of melanosomes to keratinocytes. This suggests a defect in the passage of melanosomes from melanocytes to keratinocytes in the ty-pos type of albinism. Although some keratinocytes of ty-pos albinos contained melanosomes and the dendrites of melanocytes also had numerous premelanosomes, increased numbers of premelanosomes and polyphagosomes suggest that failure to transfer melanosomes in adequate numbers is related to the albinism in this disorder.



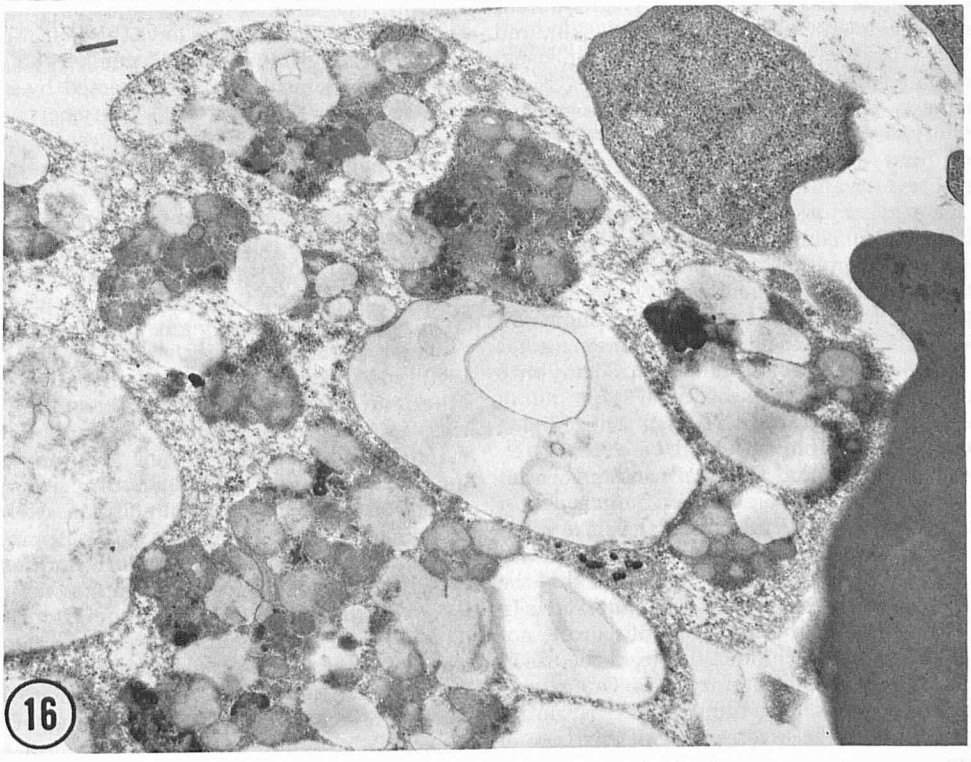


FIG. 15. Electron photomicrograph of a portion of a bone marrow macrophage from a patient with ceroid storage droplets. This stored lipid does not have the laminated appearance of phospholipid present in Fig. 15. Electron dense ceroid-like material lies adjacent to the clear vacuoles ($\times$ 16,150).

FIG. 16. Electron photomicrograph of a bone marrow macrophage from a patient with H-P albinism. The macrophage cytoplasm contains partially digested cellular debris, some erythrocyte fragments, and large clear droplets. This stored lipid does not have the laminated appearance of phospholipid present in Fig. 15. Electron dense ceroid-like material lies adjacent to the clear vacuoles ($\times$ 16,150).

Platelet Abnormalities

The basis for the platelet abnormality in H–P syndrome is now partially established. To date it is the only known platelet defect in which a morphologic abnormality has been correlated with a chemical defect. In platelets of patients with H–P syndrome, Maurer et al. (1968) observed intrisically low levels and poor uptake of serotonin and defective availability of ADP-induced platelet factor 3; similar findings were reported by Mills and Hardisty (1970). Measured by the Takemori method (Murayama and Takemori, 1970) the serotonin content of one of the H–P patients in the present series was 0.059 mg/10^9 cells, about one tenth the concentration found by this technique in normal platelets (0.6–0.8 mg/10^9 cells) from children of similar age (White et al., 1971). Platelets from H–P patients rarely contain dense bodies, which are the storage organelles for serotonin. About one dense body per 40 platelets was observed in thin sections of H–P platelets compared with about 1.4 per platelet in cells from normal persons.

The rationale for examining the effect of aspirin-treated platelets from normal persons on H–P platelets was based on the inherent difference responsible for abnormal release in the two cell types. H–P platelets have an intact, operating contractile mechanism but fail to release because secretory products are present in relatively minute amounts. Aspirin platelets contain secretory products but fail to secrete them because of an impaired response of the contractile mechanism to the usual concentrations of aggregating agents. The fact that equal volumes of H–P and aspirin-treated platelets mixed together corrected the release defect of aspirin platelets by storage pool-deficient H–P cells indicates that different mechanisms are involved in the failure of the release reaction in the two cell types.

Aspirin-treated normal platelets mixed in appropriate proportions with H–P platelets will correct their mutual defects, but these studies suggest that aspirin given to a H–P patient will cause him to regress from a fairly mild bleeder to a more serious one. Aspirin would be expected to block the release of the small concentration of secretory products present in the H–P cells. The clinical histories of H–P patients sometimes show what events first brought them to medical attention. Of the first 18 H–P patients reported in the literature or known by these investigators, 15 were brought to medical attention after prolonged bleeding from tooth extraction or tooth injury. There is a distinct possibility that in these situations the patient took aspirin for toothache or was given aspirin by the dentist.

Urinary Glycolipid-1 Fraction

According to our data, patients with any type of albinism do not have abnormal levels of urinary glycolipids. The slight increase in the levels of the Gl-1 fraction in two patients could not be repeated in patients with the same type of albinism. Despite the large amounts of lipid in macrophages in the bone marrow studies, it has the characteristics of neutral lipid rather than of a glycolipid.

Urinary Amino Acids

The failure to find any evidence of l-dopa or the metabolic products of l-dopa in the urinary chromatograms of albinos of any type prompted us to communicate this finding to Dr. Walsh, who had previously reported a ninhydrin staining compound with an Rf value similar to l-dopa in "red" albinos from New Guinea (Walsh, 1971). Dr. Walsh replied that in further investigation he was unable to substantiate his previously reported findings.

Lipid in Bone Marrow Macrophages

One 18-month old male albino patient with a bleeding disorder and abnormal platelet function and morphology gave no evidence of lipid accumulation in bone marrow macrophages. A ym albino subject also had a normal-appearing bone marrow, and one adult H–P albino patient had extensive deposits of what appeared to be neutral lipid associated with ingested erythrocytes in various stages of disintegration in bone marrow macrophages and, in addition, extensive deposits of ceroid-like material in bone marrow macrophages, urine, and buccal mucosa.

SUMMARY

In summary, our findings indicate that the ty-neg, ty-pos, ym, and H–P forms of albinism share the clinical features of a generalized decrease in pigmentation of the skin, hair, and eyes as well as decreased visual acuity, nystagmus, and photophobia. In general, there is an inverse relationship between the amount of pigment produced in the various syndromes and the severity of the ophthalmologic defects; however, this may be modified in the ty-pos, ym, and H–P albino by the general ethnic pigmentary background of the patient.

Ty-pos albino melanocytes show dense accumulations of premelanosomes and melanosome complexes, which may indicate a defective ability to pass their products to keratinocytes.

In addition to a pigment defect, the H–P albinos show mild bleeding tendencies and the accumulation of lipid in bone-marrow macrophages. The platelets do not undergo secondary wave aggregation with the addition of aggregating agents, lack dense bodies, and are low in serotonin and nonmetabolic nucleotides; however, they have an intact release mechanism. The use of aspirin by this type of albino may cause him to regress from a mild bleeder to a more serious one by the blockage of the release mechanism in chemically deficient platelets.

None of the various types of albinos had consistently abnormal urinary glycolipid values and no abnormal products were detected in their urine by two-dimensional paper chromatography. The lipid in the bone marrow of one H–P albino had the characteristics of neutral lipid and ceroid.

Chromosome breaks were not found in any of the four types of albinism.

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