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Albinism in Nigeria with delineation of new recessive oculocutaneous type

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Seventy-nine Nigerian oculocutaneous albinos were investigated. Fifty-six had typical tyrosinase-positive albinism (TPA) and 23 had brown albinism (BA), a new oculocutaneous type. The TPA were characterized by localized but no generalized skin pigment, yellow hair, blue to brown irides, nystagmus, and reduced or absent retinal pigment. Localized skin pigment included freckles and lentigines. The iris and skin pigment were the result of the slow accumulation of pigment with age as both were found in older individuals. The most severe skin changes were premalignant keratoses and squamous cell carcinoma of the skin, and the skin malignancies were the major factor in limiting the lifespan for TPA. The BA were characterized by generalized light brown skin pigment, light brown hair, blue to brown irides, nystagmus, and reduced retinal pigment. There was little accumulation or change of pigment in the eyes or skin with age. The generalized light skin pigment was effective in reducing sensitivity to solar radiation and very few BA had premalignant keratoses. Pedigree analysis for BA suggested an autosomal recessive inheritance pattern.

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Defects in human pigmentation are recognized in populations throughout the world. The most common inherited defect is oculocutaneous albinism (OCA), with reduced or absent melanin formation in the skin, hair, and eyes (Witkop 1971, Witkop et al. 1974, 1978). At least six distinct genetic types of autosomal recessive OCA have been described and all share the same clinical manifestations resulting from the hypopigmentation (Witkop 1971, Witkop et al. 1974, 1978). Reduced skin pigment produces increased skin sensitivity to sunlight and increased frequency of skin malignancy. Reduced pigment in the eyes is associated with photophobia, nystagmus, reduced visual acuity, and abnormal optic projections.

Nigeria, located on the western coast of Africa between 4° and 14° latitude north of the equator, has a high frequency of OCA in the different population groups living in this area. Barnicot (1952) found the frequency of albinism in Lagos to be approximately 1:5000 and described several different albino phenotypes, but did not attempt to separate these into distinct types

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of OCA (Barnicot 1952). Okoro (1975) traced 989 albinos throughout Nigeria and documented a shortened life span for this group. All albinos in this study appeared to have a similar phenotype but classification into specific types of OCA was not carried out. We have now studied part of the albino population described by Okoro and have extended these studies to quantitation of clinical manifestations and classification of albino types.

Methods

Albinos and their relatives were examined at the University of Nigeria Teaching Hospital, Enugu, located in the East Central region of Nigeria. All families were members of the Negroid Ibo ethnic group. Radio, television, and mail announcements were used to encourage participation in the studies. Examinations of eye and skin were carried out by two observers (RAK and CJW). Transillumination of the iris and fundiscopic examination with an ophthalmoscope was carried out in the dark without dilatation. The skin was evaluated for generalized and localized pigment production and for acute and chronic effects of sun exposure. The face, ears, neck, upper trunk, and upper extremities were observed. Erythema, areas of thickened skin (pachydermia), solar keratoses, freckles (round, lightly pigmented macules), and lentigines (irregularly shaped, deeply pigmented macules with a serpentine border) were noted. The keratoses and lentigines were graded as follows: absent, 1+ = scattered lesions greater than 2 cm apart, 2+ = scattered lesions between 1–2 cm apart, 3+ = lesions less than 1 cm apart with areas of coalescence, and 4+ = lesions less than 5 mm apart with many areas of coalescence. The freckles were graded as absent, present, and present with areas of coalescence.

Oculocutaneous albinism (OCA) was defined as the presence of generalized hypopigmentation of the skin, hair, and eyes with nystagmus and photophobia. Nystagmus usually had to be present to make the diagnosis of OCA. Albinos were separated into OCA types by clinical examination and a hairbulb incubation test (Witkop et al. 1961). The characteristics used to define tyrosinase-negative OCA (TNA) were the total absence of generalized or localized melanin pigment in the skin, yellow-white hair, blue irides with no iridial pigment on transillumination, nystagmus, lack of any retinal pigment, and a negative hairbulb test (Witkop 1971, Witkop et al. 1974, 1978). No pigmented nevi or sun-induced pigmented spots could be present. The characteristics used to define tyrosinase-positive OCA (TPA) were the lack of generalized melanin pigment in the skin, the presence of localized melanin pigment in the skin in the form of freckles or lentigines, yellow hair, blue to light brown irides with small amounts of radiating iridial pigment on transillumination (cartwheel pigmentation), nystagmus, and markedly reduced or absent retinal pigmentation. The hairbulb incubation test was positive (Witkop et al. 1961). The characteristics used to define brown OCA (BA) were a reduction in generalized melanin pigment in the skin with no evidence of increased pigment formation on sun exposure, brown hair, blue to brown irides with small to moderate amounts of radiating iridial pigment on transillumination, nystagmus, and reduced retinal pigment.

Electrophysiologic (Creel et al. 1974, 1978, 1979) and anatomic (Guillery et al. 1975) evidence indicates that the optic system in human albinos is disorganized in a similar fashion to the anomalous organization documented in albino members of other species of mammals. Twenty-seven TPA individuals were tested electrophysiologically for visual system anomalies (Creel et

Table 1

Age distribution of albinos examined

Age (years)	Number	
	TPA	BA
0– 5	18	5
6–10	9	2
11–15	9	7
16–20	6	8
21–25	4	0
26–30	5	0
31–35	4	1
36–40	1	0
40+	0	0

Table 2

Ocular findings in TPA and BA

Ocular finding	Albino type	
	TPA	BA
Nystagmus	54/54 (100%)*	22/23 (96%)
Strabismus	37/54 (69%)	12/23 (52%)
Iris color:		
Blue	42/56 (75%)	8/23 (35%)
Hazel	11/56 (20%)	5/23 (22%)
Brown	3/56 (5%)	10/23 (43%)
Iris transillumination	54/54 (100%)	20/23 (87%)
Retinal pigment:		
Absent	17/41 (41%)	2/14 (14%)
Present	24/41 (59%)	12/14 (86%)

* Number with specific finding/total number examined (% with finding).

al. 1974, 1978). Ten normally pigmented Nigerians participated as control subjects. Visually evoked potentials were recorded using diffuse flash and a 15′ checkerboard pattern as stimuli.

Results

Albino Types

Seventy-nine albinos from 63 families were examined and classified as follows: Forty-five families with 56 TPA and 19 families with 23 BA. The age distribution is given in Table 1. The average age for TPA was 13 years with a range of 3 months to 40 years, and that of BA was 13 years with a range of 8 months to 33 years. There were 23 female and 33 male TPA and 12 female and 11 male BA. For TPA there was a steady reduction in the number of older individuals, and this was associated with the skin changes described below.

Eyes

All TPA and all but one BA had obvious nystagmus (Table 2). The one BA without nystagmus was a 4-year-old female with blue irides and yellow hair. She was diagnosed as BA because she was from a sibship that included an older brother with typical BA. An alternating strabismus was present in 69 % of the TPA and 52 % of the BA (Table 2). The average age of the TPA without strabismus was 8.3 years and of the BA without strabismus was 11.0 years; iris color was not related to the absence of strabismus. The presence or absence of strabismus did not appear to be related to the age of the individual. Iris color varied from blue to brown (Table 2). Most TPA had blue irides, whereas two-thirds of the BA had hazel or brown irides. The average age of the TPA with blue irides was 11.7 years, with hazel irides was 16.5 years, and with brown irides was 26 years. The average age of the BA with blue irides was 11 years, with hazel irides was 13.8 years, and with brown irides was 14.2 years. Pigmented irides appear to be a function of age with TPA but not with BA. Iris transillumination was present in all TPA and all but three BA (Table 2). The three lacking transillumination had brown irides.

Fundiscopic examination revealed variable amounts of retinal pigment (Table 2). Seventeen (41 %) of the 41 TPA examined had no pigment and 24 (59 %) had evidence of some generalized pigmentation of the retina. Of these 24 TPA with pigment, 13

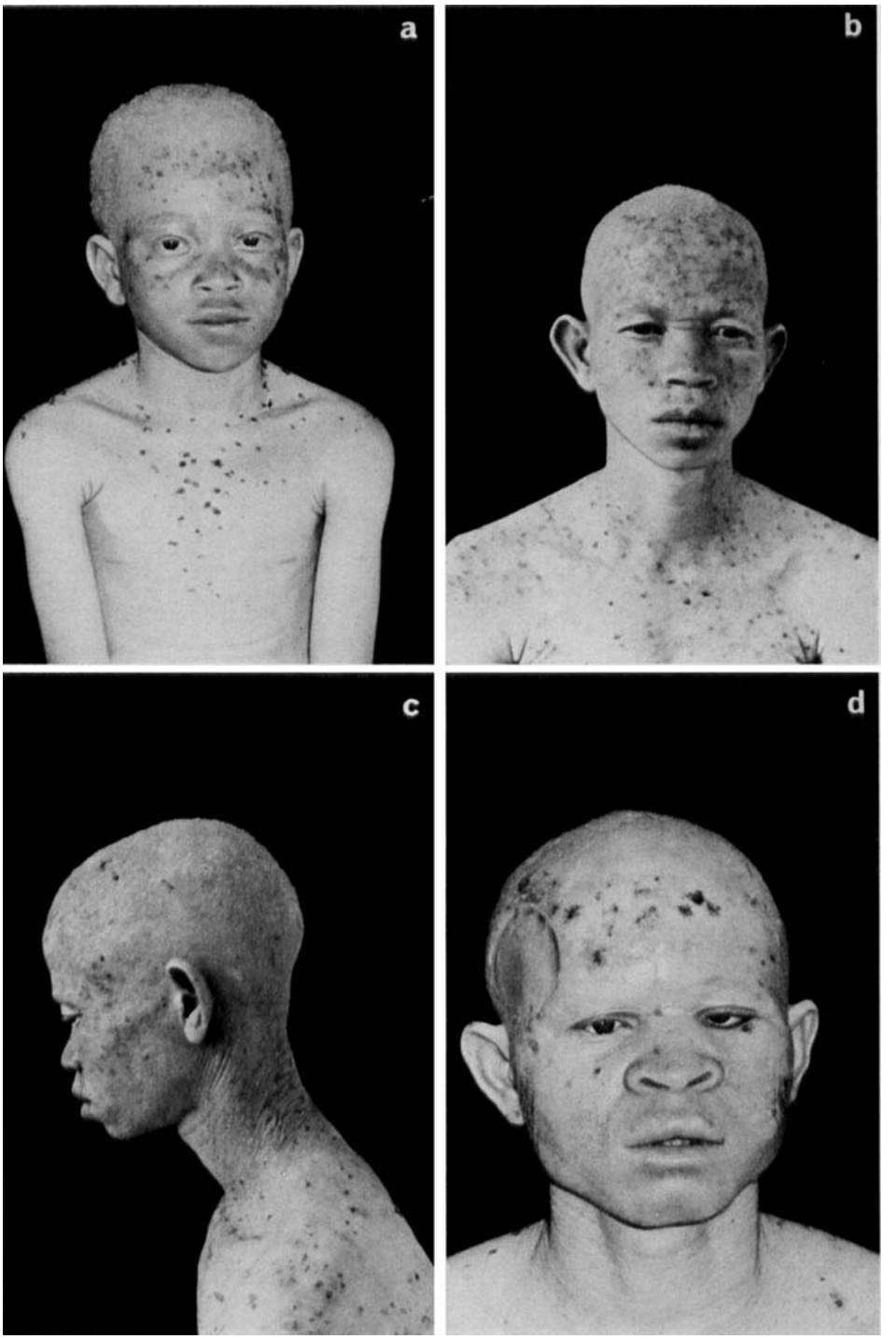
a
b
c
d

Table 3

Skin changes in TPA

Skin change	Number found – by location			
	Face	Neck	Forearm + Hand	Back
Erythema:				
Present	41 (77.4%)	35 (68.6%)	42 (75.0%)	12 (24.0%)
Absent	12	16	14	39
Pachydermia:				
Present	18 (33.3%)	38 (71.7%)	41 (73.2%)	15 (29.4%)
Absent	36	15	15	36
Keratoses:				
1+	9	9	15	6
2+	2	2	5	2
3+	4	1	9	5
4+	7	3	0	4
0	32 (59.3%)	38 (71.7%)	27 (48.2%)	34 (66.7%)
Freckles:				
Present	17	9	18	25
Confluent	1	1	0	0
Absent	36 (66.7%)	41 (80.4%)	38 (67.9%)	26 (51.0%)
Lentigines:				
1+	19	12	14	7
2+	6	2	4	6
3+	4	2	2	5
4+	2	1	0	2
0	25 (44.6%)	35 (67.3%)	36 (64.3%)	32 (61.5%)

had only slight amounts of pigment (classified +/− by the examiner), 10 had small but definite amounts of pigment, and 1 a moderate amount of pigment (equivalent to Caucasian with light complexion). The average age of the TPA with no retinal pigment was 16.1 years, and that of the TPA with small to moderate pigment was 15.8, so the presence of retinal pigment did not appear to be a function of time for TPA. Iris color generally was associated with the degree of retinal pigment. Nine of the TPA with hazel or brown irides had retinal pigment and three had no retinal pigment. Only two of the 14 BA examined lacked retinal pigment (14 %), and 12 had moderate amounts of pigment; none of those with pigment had a normally pigmented retina. Retinal pigment in the BA was fine and generalized and was not granular or irregular in its distribution. There was no obvious effect of age on retinal pigment in BA; the two without pigment were aged 8 and 12 years, and the average age of those with pigment was 14.5 years. Iris color was blue for the two without pigment, and blue for two, hazel for three, and brown for seven with pigment.

Skin

All TPA lacked generalized skin pigment. Examples of skin changes in TPA are shown in Figure 1. The skin was creamy

Fig. 1. Tyrosinase positive oculocutaneous albinos. **a.** Male, age 8 years. Lentigines present over face and on exposed anterior chest. **b.** Male, age 15 years. Erythema, lentigines, and keratoses present on the face and trunk. **c.** Same individual as **b.** Pachydermia visible on neck. Erythema, lentigines, and keratoses present on back. **d.** Male, age 22 years. Erythema, lentigines, and keratoses present on forehead. Squamous cell carcinoma resected from right temple and left cheek with plastic surgical repair following resection.

Table 4

Skin changes in TPA

Skin change	Average age in years – by location			
	Face	Neck	Forearm + Hand	Back
Erythema:				
Present	15.6	16.3	16.5	25.3
Absent	5.6	6.2	4.1	9.4
Pachydermia:				
Present	24.2	17.6	17.6	24.7
Absent	8.3	2.4	2.1	8.3
Keratoses:				
1+	16.3	20.4	15.3	14.7
2+	16.0	37.5	23.0	25.5
3+	25.8	30.0	28.4	26.8
4+	26.6	25.3	0	31.3
0	7.6	9.0	5.6	7.9
Freckles:				
Present	17.7	20.4	19.8	16.1
Confluent	12.0 (n=1)	12.0 (n=1)	0	0
Absent	11.3	11.5	10.4	10.3
Lentigines:				
1+	19.7	23.8	22.5	23.1
2+	20.3	15.5	16.3	18.8
3+	12.3	26.5	26.0	18.4
4+	12.0	12.0	0	26.0
0	6.2	8.5	8.9	8.0

white and the hair color was pale whitish-yellow to golden yellow. Tables 3 and 4 show the number of TPA individuals found with different skin changes and the average age for each skin change. Erythema was present on exposed skin (forearm and hands, neck, and face) in 69–77 % of TPA but on the back in only 24 %. The average age for those with erythema on the exposed skin was 15.6–16.5 years, and 25.3 years for those with erythema on the back. Pachydermic changes were present on the neck and the dorsum of the hands in 72–73 % of TPA, occurring at an average age of 17.6 years. Pachydermia on the back and face was less frequent, occurring in 29–33 % of TPA, and at an average age of 24.2–24.7 years.

Solar keratoses were present on 28–52 % of TPA. Keratoses were most frequent on the forearms and hands and the face, and least frequent on the neck. On the face 13 % had advanced (4+) keratoses. Many of the keratotic lesions appeared to have undergone malignant degeneration, especially on the ears, on the temporal skin, and on the cheek below the orbit. Skin biopsies were obtained from nine TPA individuals in the study. Biopsies from eight of the nine were obtained because of suspected malignant degeneration of a keratotic lesion. Of these eight, five had biopsies that showed squamous cell carcinoma. One of these individuals had a biopsy of three separate lesions and all showed squamous cell carcinoma. The locations of the seven biopsies showing squamous cell carcinoma were the malar region of the face (3), the area just lateral and inferior to the orbit (1), the ear (1), the shoulder (1), and the anterior chest

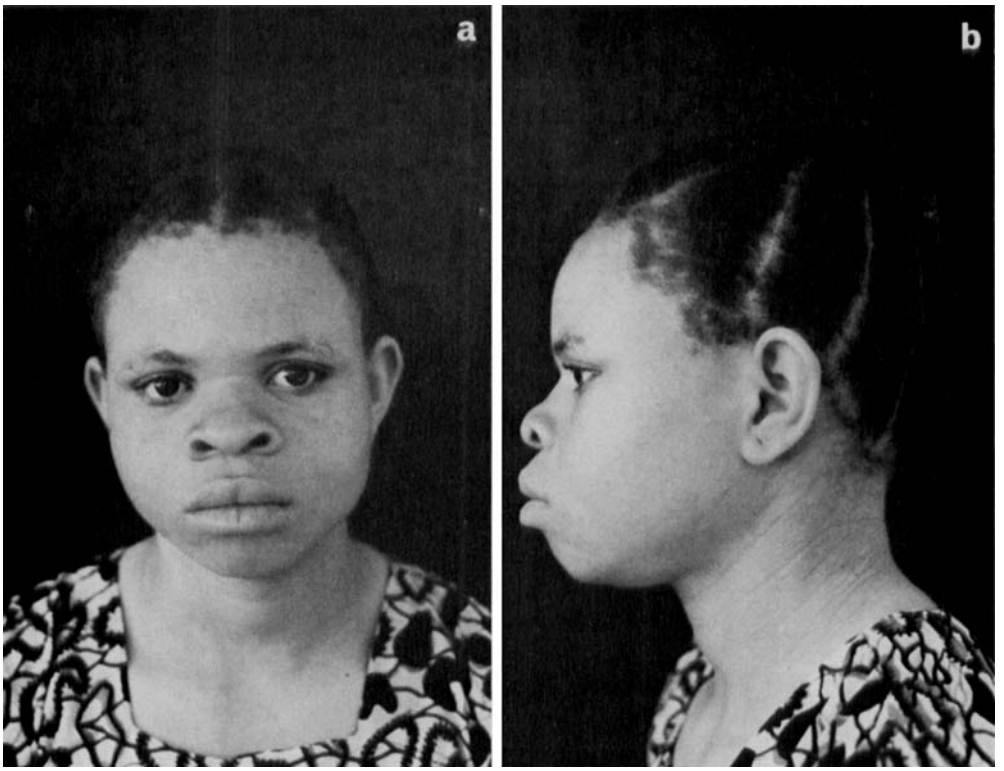

Fig. 2. Brown albino. Female, age 17 years. **a.** Front view. Skin color light brown. No erythema, lentigines, or keratoses present. **b.** Side view.

wall (1). The average age of those with biopsy-confirmed carcinoma was 25.8 years. Biopsies from three of the eight individuals showed solar keratoses. The biopsy of a pigmented lesion from one individual showed a junctional nevus. The average age for those TPA without keratoses at the different sites was 5.6–9.0 years. Early lesions developed at all sites by an average of 14.7–20.4 years, and advanced lesions by an average age of 25.8–31.3 years.

Freckles were present on 20–49 % of TPA, being most frequent on the back and least frequent on the neck. One TPA had confluent freckling over the face and neck. The average age for TPA with freckles was 16.1–20.4 years and 10.3–11.5 years without freckles. Lentigines were present on 33–55 % of TPA. Most had scattered (1–2+) lesions but 11–13 % had coalescent (3–4+) lesions on the face and back. The average age for the TPA with scattered lesions was 15.5–23.8 years and tended to be lower for those with coalescent lentigines, but the numbers were small for these latter groups.

All BA had generalized skin pigment. An example of BA is shown in Figure 2. The skin was light brown and the hair was light to medium brown. Many BA individuals had multiple hypopigmented spots over the shoulder tops and on the forearms that appeared to be the result of sunburning and subsequent scarring. These spots were 1–5 mm in diameter and were irregular in size.

Table 5

Skin changes in BA

Skin change	Number found – by location			
	Face	Neck	Forearm + Hand	Back
Erythema:				
Present	11 (47.8%)	5 (21.7%)	7 (30.4%)	2 (8.7%)
Absent	12	18	16	21
Pachydermia:				
Present	2 (8.7%)	6 (26.1%)	12 (52.2%)	1 (4.3%)
Absent	21	17	11	22
Keratoses:				
1+	2	0	8	2
2+	1	0	0	0
3+	0	0	0	0
4+	0	0	0	0
0	20 (87.0%)	23 (100%)	15 (65.2%)	21 (91.3%)
Freckles:				
Present	17	10	19	18
Confluent	0	0	1	0
Absent	6 (26.1%)	13 (56.5%)	3 (13.0%)	5 (21.7%)
Lentigines:				
1+	1	0	0	0
2+	0	0	0	0
3+	0	0	0	0
4+	0	0	0	0
0	22 (95.7%)	23 (100%)	23 (100%)	23 (100%)

At the time of the examination, no BA had a recent sunburn and most could not remember where or when the hypopigmented spots appeared. Tables 5 and 6 show the number of BA individuals with the different skin changes and the average age for each group. Skin changes in the BA were much less severe than in the TPA, and the BA generally had only mild sun sensitivity. Erythema was most common on the face (47.8 %) and not common on other areas examined (8.7–30.4 %). The average age was similar for those with and without erythema for all areas except the face, where those with erythema were older (15.7 vs. 10.2 years). Pachydermia was most common on the forearms and hands (52.2 %) and not common on other areas examined. The average age for those with and without pachydermia was similar for all areas except for forearms and hands, where those with pachydermia were older (16.0 vs. 9.4 years).

Scattered keratoses were present on only a few subjects and were most frequent on the forearms and hands. No coalescent lesions, premalignant, or malignant lesions were seen on the BA individuals in the study population.

The most common skin change was freckling, which was present with the majority of BA on all areas examined. One BA had confluent freckling over the forearm and hands. The average age for those with freckles was 13.5–14.2 years, and for those without freckles was 2.0–11.8 years for the different areas examined. Only one BA had lentigines, and these were scattered and infrequent.

Table 6

Skin changes in BA

Skin change	Average age in years – by location			
	Face	Neck	Forearm + Hand	Back
Erythema:				
Present	15.7	13.6	14.1	11.0
Absent	10.2	12.6	12.3	13.0
Pachydermia:				
Present	15.0	11.8	16.0	16.0 (n=l)
Absent	12.6	13.2	9.4	12.7
Keratoses:				
1+	21.5	0	15.0	16.0
2+	12.0 (n=l)	0	0	0
3+	0	0	0	0
4+	0	0	0	0
0	12.0	12.8	11.7	12.5
Freckles:				
Present	13.5	14.2	14.2	14.2
Confluent	0	0	20.0 (n=l)	0
Absent	10.8	11.8	2.0	7.8
Lentigines:				
1+	16 (n=l)	0	0	0
2+	0	0	0	0
3+	0	0	0	0
4+	0	0	0	0
0	12.7	12.8	12.8	12.8

Visual Anomalies

The evoked potentials of 18 of the 27 TPA recorded during monocular illumination showed hemispheric asymmetry. In each of the 18 albinos, one or more of the components of the evoked potential was missing or significantly attenuated when recording from the hemisphere receiving the uncrossed optic fibers. The 15′ checkerboard was no more effective than diffuse flash illumination as a stimulus, most likely due to the poor acuity of the albinos.

Discussion

Oculocutaneous albinism (OCA) is an inherited syndrome of congenital hypopigmentation of skin, hair, and eyes (Witkop 1971, Witkop et al. 1974, 1978). The word "albino" came into general use in the Eighteenth Century (Froggatt 1960) and descriptions of albinos have subsequently been made in all races of man (Witkop et al. 1974). The syndrome is recognized by the characteristic cutaneous and ocular changes that are the result of the reduced amount or lack of melanin in these tissues. The skin and hair are light and the skin has an increased sensitivity to the ultraviolet effects of sunlight. The eyes have light irides and reduced or absent melanin in the pigmented epithelial layer of the retina. Photophobia is common, visual acuity is reduced, and nystagmus is a constant feature. Six types of OCA are recognized and have been well characterized (Witkop 1971, Witkop et al. 1974, 1978). Four have hypopigmentation as their major clinical feature and include the common Tyrosinase-Negative (TNA) and Tyrosinase-Positive (TPA)

OCA, and the uncommon Yellow Mutant OCA and Hermansky-Pudlak Syndrome. Two other rare traits, Cross Syndrome and Chediak-Higashi Syndrome, have albinism as a minor feature of the clinical presentation. The six types of OCA are autosomal recessive in inheritance.

OCA has been described in many parts of Africa, including Nigeria (Pearson et al. 1911, Stannus 1913, Knowles 1916, McCrackin 1937, Lowenthal 1944, Barnicot 1952). Barnicot (1952) and Okoro (1975) have presented epidemiological and clinical data on Nigerian albinos and, in fact, the publication of the latter paper led to the initiation of the cooperative studies reported here. Barnicot estimated a frequency for OCA of 1:5000 in Lagos, Nigeria, and Okoro studied 989 albinos collected throughout the country. Most of the albino individuals in these two studies had TPA, but specific classification of individuals into recognized OCA types was not performed. The present study was carried out to extend the studies of Okoro by classification of OCA type and quantitation of clinical features.

Seventy-nine albinos were examined in Enugu, Nigeria. All were Ibo. No individuals with TNA were identified, suggesting that this is an unusual form of albinism in this population. Fifty-six individuals had classical TPA, and most showed the expected secondary effects of the hypopigmentation. The eyes and visual development in all TPA individuals were abnormal. Nystagmus and iris transillumination were found in 100 %, and iris pigmentation, present in 25 %, increased with age. Iris pigment was never normal, as demonstrated with iris transillumination, since normally pigmented irides in non-albino Negro individuals do not transilluminate. The accumulation of pigment was also seen in the retina but none had fully pigmented retinae. Retinal pigment is needed for the normal development of the visual system (Creel et al. 1974, 1978) and the amount was insufficient in all TPA.

In the Nigerian population, the implication of the visual handicap found in OCA is not as great as is the devastation that results from the effects of ultraviolet radiation on the hypopigmented sensitive skin. Almost all TPA individuals had evidence of sun sensitivity, and those with no skin changes were generally young children who had been well protected by their parents. As expected, exposed surfaces such as the face, neck, and hands suffered the most. Acute changes were erythema without tanning and chronic changes were pachydermia, freckles, lentigines, and keratoses. The pachydermia resulted from chronic scarring of the dermis after burning. Both freckles and lentigines appeared to be the result of chronic sun exposure, as both increased in frequency with the age of the individuals and were frequently found in areas of erythema and pachydermia.

The most ominous of the skin changes were the keratoses, for they were often severe and appeared to have undergone malignant degeneration. Five individuals had biopsy-proven squamous cell carcinoma, one with three separate malignant lesions. Four of these had had previous malignancies removed. Cutaneous squamous cell carcinoma was the major cause of death in the TPA population and accounted for the fact that no TPA individuals in the study population were older than 40 years of age. The malignant lesions were located on the face near the orbit, the cheek, the scalp, the ear, and the shoulders, the areas that have been shown to receive the highest ultraviolet radiation dose (Steiner 1954, Urbach et al. 1966, Diffey et al. 1977). In normally pigmented Negro populations, primary skin malignancies are unusual in sun-exposed areas and are found more frequently on the lower extremities in areas of chronic irrita-

tion, infection, and ulceration (Steiner 1954, Oettle 1963). The high incidence of squamous cell carcinoma in the TPA population could be accounted for by sun exposure alone. The highly aggressive nature of the lesions and their occasional location in areas of the skin with little sun exposure, such as the back, suggest that there may be other presently unknown etiologic factors at play in the development of these lesions in the TPA individuals (Cervenka et al. 1979). Chromosomal analysis and sister chromatid exchange with skin biopsy and peripheral lymphocyte samples was performed on a subset of the study population (Cervenka et al. 1979). No significant changes between TPA and control samples could be demonstrated by these methods.

Twenty-three individuals had a form of OCA that we categorize as Brown OCA (BA). BA individuals were not as obviously albino as those with TPA, but they had all of the features necessary to identify them as having a type of OCA. Their skin and hair were light brown and were definitely different from their parents and normal siblings. The light skin pigment in BA individuals was generalized and was effective in reducing the sensitivity to the solar radiation. Erythema and some pachydermia were present, and many had freckles on exposed surfaces, but keratoses and lentigines were absent in the study population. BA eyes were hypopigmented and obviously albino. Iris color varied from blue to medium brown and most had iris transillumination. Fundiscopic examination revealed some retinal pigment but the amount was never normal. Nystagmus was present in all but one BA, and an alternating strabismus was present in many. The ocular changes were the most obvious for classifying these individuals as OCA. The basic defect in this type of OCA is unknown, and the melanocytes have not been characterized by electron microscopy. The pedigrees from the 19 families suggested an autosomal recessive inheritance pattern.

Albinos with a light generalized pigmentation of the skin have been described in previous studies of African albinos. Pearson et al. (1911) described three men with "xanthism" and gave evidence for knowing of 11 boys with xanthism in a sample of 7089 examined by Dr. G. A. Turner in South Africa. One of the three men appeared to have BA with brown skin, hair, and eyes. His photograph is similar to those in our study. The two other men with xanthism were different, with a definite red color to their skin. They had brown hair. Stannus (1913) also described xanthous albinism and characterized this as having "reddish brown, red, or warm brown" skin color of variable degree. He further described another form of albinism characterized by light brown rather than red skin. This latter form is similar to the BA reported here. A description of "semi-albinism" in West Africa is included in a review by Knowles (1916). In this condition, "the skin varies in color between the natural hue of blacks and white." Barnicot (1952) in his review of albinism in Nigeria, included at least four pedigrees containing individuals with BA, although he made no attempt to distinguish the BA from the other more familiar TPA. All of these studies suggest that BA has long been a recognized type of OCA. Our study is the first to characterize the clinical features of this type of OCA.

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