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ALBINISM IN BLACK SOUTH AFRICANS

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A report submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg in fulfilment of the requirements for the degree of Master of Medicine in Dermatology.

This report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

J.E. Bothwell

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J.E. BOTHWELL

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ABSTRACT

The physiology of melanin production and features of albinism are reviewed. The purpose of this study was to establish the clinical features, prevalence, nature and significance of the pigmented lesions in sixty one South African Negroid tyrosinase positive albinos. The ultrastructure of their skin and hair bulbs was examined and its correlation to their clinical features determined.

Although many of the clinical features of South African tyrosinase positive and rufous albinos have previously been described, the ultrastructure of skin and hair from this group has not been documented. Pigmented lesions have previously been noted in tyrosinase positive albinos but the nature, prevalence and significance of these lesions has not been clearly defined.

The albinos came from Johannesburg and its surrounding areas. Sixty two normal South African Negroids were used as controls. They were examined for skin, hair and eye colour and the presence and distribution of naevi, lentigines, palmoplantar pigmentation and freckles. Biopsies of naevi and freckles were examined histologically. The presence of solar elastosis, solar keratoses and skin cancers was noted.

The anagen bulbs of 28 tyrosinase positive albinos and 5 rufous albinos were examined in a Hitachi H-600 electron microscope. Skin biopsies of 2 tyrosinase positive and 2 rufous albinos also were examined ultrastructurally. The findings in the rufous albinos were compared to those in 5 red-haired Caucasoids.

Clinically South African Negroid tyrosinase positive albinos were found to be similar to Negroid albinos elsewhere in the world. South African rufous albinos were found to most resemble rufous Nigerians rather than Papua New Guineans.

Pigmented naevi were found in 80% of tyrosinase positive and 70% of normal Negroids and the mean number per person was 12 and 17 respectively. The trunk was the main site involved in both groups. Dendritic freckles were found on sun-exposed parts in 43% of the albinos. These were distinguished by their irregular, branched shape, light to dark brown colour and large size (0.5 to 3 cm). Solar keratoses occurred more frequently in albinos without freckles (73% versus 50%) confirming the sun-protective role of the increased albility to form pigment in this group. There was no correlation between the number of naevi and the number of keratoses. Racially determined palmoplantar pigmented macules were found in 75% of controls and in none of the albinos.

On ultrastructural examination of the skin of the tyrosinase positive albinos eumelanosomes were found in stages I to II, singly in the melanocytes and singly or in groups in the keratinocytes. In the hair bulbs, these melanosomes were found singly or grouped in stages I to late stage III. In the skin of rufous albinos, eumelanosomes were found singly in the melanocytes in stages I to IV and singly or in groups in the keratinocytes in stages III and IV. In the hair bulbs only eumelanosomes in stage I to early stage III were seen singly and in groups. In comparing our findings in tyrosinase positive albinos to previous reports, the melanosomes in the hair bulbs were identical, but those in the skin were slightly less melanised. Our rufous albinos seem to be a distinct genetic entity since they failed to demonstrate the phaeomelanosomes previously described in rufous albinos.

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INTRODUCTION

Tyrosinase positive albinos are relatively common in South Africa. [Kromberg & Jenkins (1982)] Because the normal mechanism of melanisation has failed to take place, they are clinically pale. However, despite a generalised decrease in pigmentation, they are able to produce pigment at certain sites viz. in naevi, freckles and lentigines. Rufous albinos are far less common. They also are paler than normal Negroids, and characteristically demonstrate a reddish tinge in skin and hair.

Although the clinical features of both types of albinos have previously been described, the prevalence and nature of the pigmented lesions in tyrosinase positive albinos are poorly documented. The ultrastructural findings in tyrosinase positive albinos and rufous albinos in the other countries have been published, but not those in South Africa.

Section I discusses the normal mechanism of pigmentation, in particular the ultrastructural features of melanogenesis. The different types of albinos are described and the mechanism for the disturbance in normal pigmentation in each type is documented. Albinos are particularly important in South Africa because of their high prevalence. The problems they develop as a result of their pale skin are described i.e. premalignant and

malignant lesions. The pigmented lesions previously reported in tyrosinase positive albinos are also documented.

Section II deals with the present study where a group of tyrosinase positive and rufous albinos were examined. The prevalence and nature of pigmented lesions in the tyrosinase positive groups was established. An attempt to correlate the presence of the pigmented lesions with the degree of sun damage was made. Ultrastructural examinations of the skin and hair bulb in tyrosinase positive and rufous albinos were performed to establish the degree and type of melanisation and to correlate this with the clinical features.

SECTION I

NORMAL PIGMENTATION VERSUS THE HYPOPIGMENTATION IN ALBINISM



CHAPTER I

PHYSIOLOGY OF PIGMENT FORMATION

The normal skin colour is different in Negroids and Caucasoids because of various factors which include the amount of oxyhaemoglobin (red), deoxygenated haemoglobin (blue), carotene (yellow) and melanin (brown). This chapter will concentrate on the role played by melanin.

The melanocyte is the cell responsible for melanin production which occurs in an organelle called the melanosome. Melanin formed on the melanosomes is transferred to the keratinocytes which make up the epidermis. The amount of melanin formed in an individual is genetically determined and is referred to as the person's constitutive colour [Bolognia & Pawelek (1988), Mosher et al (1987)]. Three to four gene pairs are responsible for the production and dilution of pigment [Mosher DB, Fitzpatrick TB et al (1987)].

Melanocytes are derived from the neural crest and migrate to peripheral sites, viz the dermis, mucous membranes, leptomeninges, retina, uveal tract, cochlea, vestibular bodies and the labyrinth of the ear. Melanocytes in the skin are evenly distributed over the body and their numbers are the same

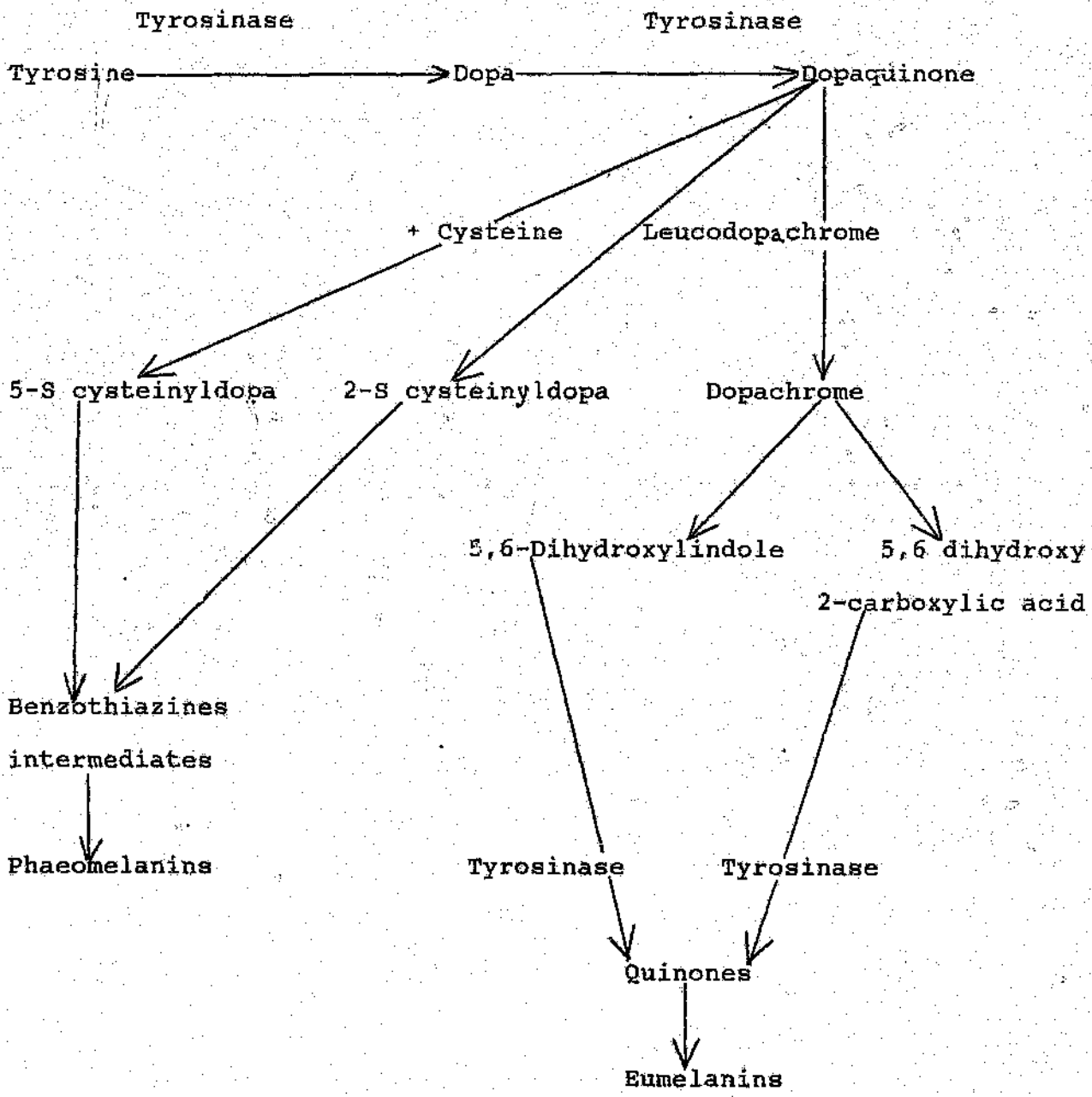
in different racial groups [Bolognia & Pawelek (1988)]. They may be dendritic or non-dendritic. Cells containing melanosomes are first seen at 8 to 10 weeks of gestation and by birth the melanin system is mature and functioning [Rosdahl & Szabo (1976)]. However, the potential amount of melanin in the skin is not fully developed until a person is 10 years old [Walsh (1971)].

MELANOGENESIS

Melanin is formed as a result of a series of biochemical reactions using dopa or tyrosine as substrates (See Table 1 p. 5). The pathway is dependent on the enzyme tyrosinase [King et al (1985), Körner & Pawelek (1980), Kugelman & van Scott (1960)]. Two types of melanin can be formed, eumelanin, which gives rise to brown and black pigmentation and phaeomelanin which gives rise to yellow and red pigmentation. Melanogenesis involves melanosome formation, melanisation, secretion and degradation of the melanosome and is staged according to functional and structural phases in a melanosome's life span [Friedman & Thody (1986), Mosher et al (1987)].

Table 1

THE MELANIN PATHWAY



Adapted from Witkop et al (1983)

1. Melanosome Formation

A melanosome is formed when tyrosinase, a glycoprotein manufactured on the ribosomes of the endoplasmic reticulum, is transferred to membrane bound vesicles, the Golgi bodies. A stage I melanosome is a round microvesicle containing no melanin and is identical whether eumelanin or phaeomelanin ultimately is formed.

2. Melanisation

Melanin formation results from an interaction between the enzyme tyrosinase and the substrate, dopa or tyrosine. As melanosomes become more melanised they move from the perinuclear area in the melanocyte to the dendrites [Jimbow & Kukita (1970), Jimbow et al (1976)].

3. Secretion of Melanin into Keratinocytes

Only dendritic melanocytes are capable of secreting their melanosomes into other cells. A portion of the dendrite containing melanosomes is phagocytosed into the keratinocytes. One melanocyte supplies 36 keratinocytes with melanin which constitutes an 'epidermal melanin unit' [Jimbow et al (1976), Klaus (1969), Mosher et al (1987)].

4. Transport and Degradation of Melanosomes

The melanosomes found in the keratinocytes are usually well

melanised and may remain single or aggregate into organelles which are known as 'melanosome complexes'. Gradually these degrade and fragment into small dense particles [Jimbow et al (1976), Mosher et al (1987)].

The way in which the melanosomes are aggregated depends on the racial group of the individual. In Negroids and Australian aborigines, the melanosomes are large and non-aggregated [Friedman & Thody (1986), Quevedo et al (1986), Rosdahl & Szabo (1976)]. In Caucasoids, Mongoloids and American Indians, melanosomes are aggregated into groups bound by lysosomal membranes [Friedman & Thody (1986), Hori et al (1980), Rosdahl & Szabo (1976)].

In Negroids, melanosomes are large compared to Caucasoids (0.5 - 0.8 μm compared to 0.3 - 0.5 μm), more melanised and usually single. They are distributed from the basal cells to the stratum corneum. In contrast, in Caucasoids the melanosomes are smaller, less well melanised, invariably form complexes and remain in the basal layers of the epidermis [Mosher et al (1987)]. These variations among racial groups are accounted for by a difference in the number of functional melanocytes which melanise, package and distribute melanosomes differently [Quevedo et al (1986), Quevedo & Fleischmann (1980)].

The amount of melanin can be measured by reflectance studies where the light reflected is inversely proportional to the amount of melanin in the skin [Weiner (1951)].

CONTROL OF PIGMENT FORMATION

The greatest influence on pigment formation is genetic ie. a person's constitutive colour. This is the colour seen on sun-shielded areas. The amount of melanin formed may alter according to other stimuli eg. ultraviolet light, hormones and chemicals. The facultative or inducible colour ref . that person's genetic capacity for darkening in response to ultraviolet light. The pigmentation that develops subsequently is the facultative or inducible colour [Bolognia & Pawelek (1988), Mosher et al (1987)].

After UV light stimulation, a Caucasoid skin becomes more pigmented and histologically adopts the features of darker races, but these changes will revert without continued UV light stimulation [Quevedo et al (1986), Rosdahl & Szabo (1976)]. The response of the skin has to UV light can be immediate or delayed.

1. Effects of Ultraviolet Light

i. Immediate Tanning Response

The immediate darkening effect of UV light exposure (i.e. within minutes) is due to the photo-oxidation and activation of enzymes which increase the melanisation of melanosomes. These melanosomes then migrate peripherally and are transferred to the

keratinocytes [Jimbow & Fitzpatrick (1975), Quevedo et al (1986)]. This immediate darkening appears within minutes andfades after 48 to 72 hours [Lavker & Kaidbey (1982), Quevedo et al (1986)]. This type of tanning is induced by UVA radiation (320-380 nm) and visible light (400-700 nm).

ii. Delayed Tanning

Forty eight to 72 hours after sun exposure, previously inactive melanocytes become functional and hypertrophic. Activated tyrosinase increases the melanisation of melanosomes which subsequently are transferred from melanocytes to keratinocytes where they enlarge and lie singly in the keratinocytes [Quevedo et al (1986)]. At a cellular level UV light acts on the thioredoxin-thioredoxin reductase system to activate tyrosinase [Schallreuter et al (1988)]. This type of reaction is stimulated mainly by UVB (290-320 nm).

2. Effect of Hormones

Many hormones stimulate melanogenesis including MSH, ACTH, oestrogen and progesterone [Lerner (1980), Lerner & McGuire (1964)]. MSH is derived from a precursor peptide, pro-opiomelanocortin, the same peptide which gives rise to ACTH (corticotropin), beta-lipotropin and melanotropin [Krieger & Martin (1981), Nakarishi et al (1979)]. The final hormone produced depends on the tissue in which the precursor peptide is

processed. Since all the above hormones contain similar peptide sequences, they all can cause hyperpigmentation [Lerner & McGuire (1964)].

3. Other Factors

Other substances which can cause hyperpigmentation by increasing melanogenesis include nitrogen mustard and prostaglandins C2 and D2 [Flaxman et al (1973), Snell & Bischitz (1960)].

Trauma to the skin and inflammation can also alter normal pigmentation by increasing melanin formation [Quevedo et al (1986)].

EUMELANIN AND PHAEOMELANIN

Two types of melanin may be synthesized :

1. Eumelanin which gives rise to brown and black pigmentation.
2. Phaeomelanin which gives rise to yellow and red pigmentation.

Biochemically they share the initial tyrosinase-dependent pathway but ultimately form different chemical substances. When eumelanin is deposited on a melanosome it is called a eumelanosome, and when phaeomelanin is deposited, a

phaeomelanosome. Both types of melanosome evolve through 4 stages of melanisation with different ultrastructural appearances.

The first stage in the melanisation of both types of melanosome is identical consisting of round, hollow vacuoles formed from enlargement and fusion of Golgi vesicles which are surrounded by a limiting membrane.

1. Eumelanin

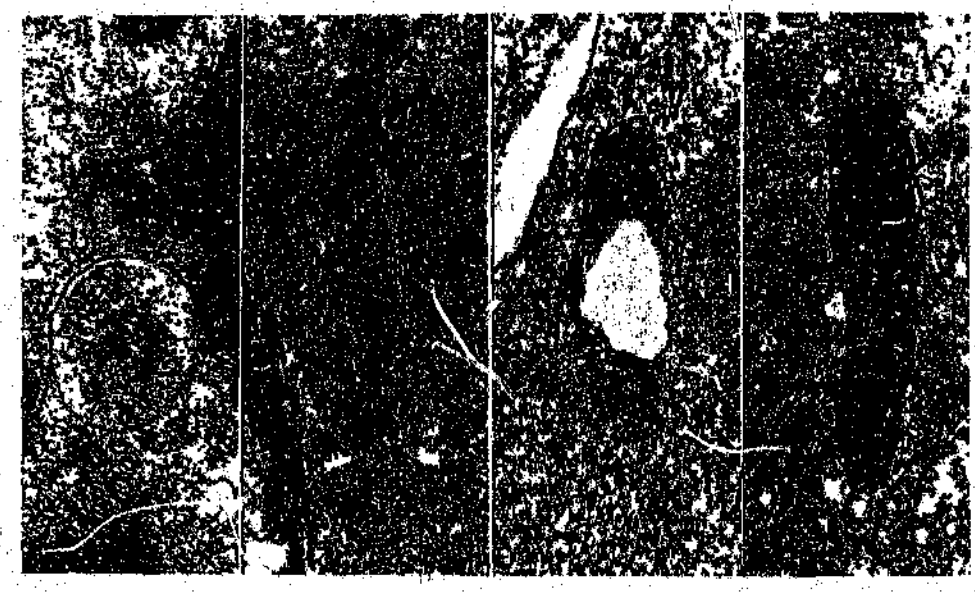
In stage II the round melanosome elongates to form an oval body containing a matrix consisting of proteinaceous material and lamellae (filaments) with regular striations. As the structure matures, it becomes more ellipsoidal. The inner structures arrange themselves more regularly with filaments aligning themselves parallel to each other and becoming most prominent at the periphery. The filaments join together at the poles of the organelle. Tightly coiled helices composed of protein molecules make up the filaments. One of the proteins found in the filaments is tyrosinase, which when activated, causes the inner structures to condense and fuse [Jimbow & Kukita (1970)].

In stage III melanin is deposited. Initially fine osmiophilic grains appear in the central zone. They enlarge to form granules which align on the filaments and migrate peripherally..

In stage IV sufficient melanin has been laid down to cause homogeneous darkening of the melanosome which ultrastructurally is electron dense [Jimbow & Kukita (1970)] (fig. 1, p. 13). Only the vesiculoglobular bodies remain electron-lucent. These consist of microvesicles which attach to the outer layer of the cortex and protrude into the cortical shell. The function of these bodies may be to incorporate tyrosinase into the developing melanosome [Jimbow et al (1979), Mosher et al (1987)]. Ultrastructurally they give melanosomes a moth-eaten appearance which is particularly marked in dark brown hair [Granholm et al (1990)]. Vesiculoglobular bodies are found in both eumelanosomes and phaeomelanosomes and are visible in all stages of melanisation [Jimbow et al (1979)].

Figure 1

Stages in the development of a eumelanosome [From Witkop et al (1983)].



2. Phaeomelanin

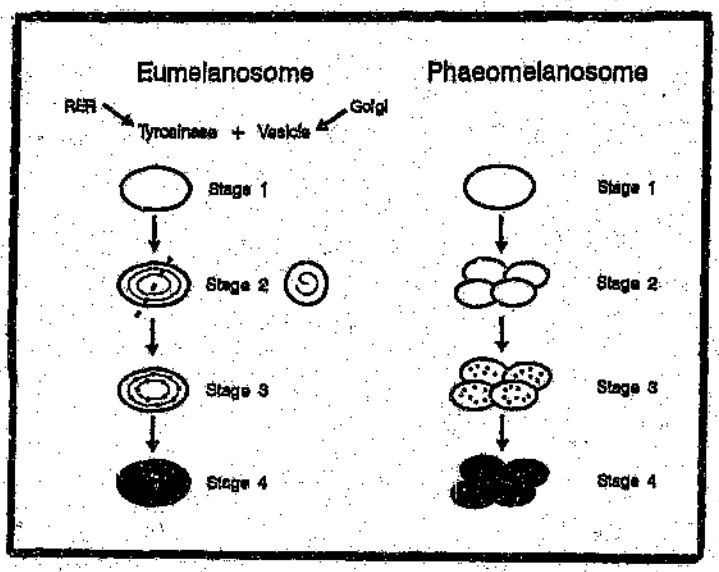
A stage I phaeomelanosome is identical to a eumelanosome i.e. a round microvesicle. In stage II there are more numerous microvesicles containing an amorphous matrix of proteinaceous material and partially formed lamellae. In stage III, the melanin is deposited with a granular configuration. The phaeomelanosome is distinguished from a eumelanosome by the irregular deposition of pigment, the absence of an underlying structure and the scalloped edge. In stage IV there is darker, more uniform pigmentation forming an electron dense structure with an irregular contour (fig. 2, p. 15).

Phaeomelanin is formed faster than eumelanin [Granholm et al (1990), Mosher et al (1987)]. In red-haired people there is a variable proportion of both phaeomelanin and eumelanin [Jimbow et al (1983), Jimbow et al (1979)]. Other pigments found in red-haired individuals are trichochromes B and C [Jimbow et al (1976)].

In addition to eumelanosomes and phaeomelanosomes, so-called mosaic melanosomes may be found in the keratinocytes. They lack a lamellar structure and regular striations, melanise in a spotty fashion, and in stage IV are spherical without electron-lucent vesiculoglobular bodies [Jimbow et al (1983)]. Their significance is not known.

Figure 2

Schematic representation of melanisation of vesicles in the formation of eumelanosomes and phaeomelanosomes.



3. Biochemical features

Biochemical methods can be used to distinguish between phaeomelanin and eumelanin. Whereas phaeomelanin is soluble in dilute alkali, eumelanin is not [Mosher et al (1987)]. The breakdown product of eumelanin is 6-hydroxy, 5-methoxy-indole-carboxylic acid which can be demonstrated in the urine and is found in greater concentrations in Negroids and other dark-skinned populations. The breakdown product of phaeomelanin is 5-sulphur cysteinyldopa. It can be found in the urine even when the hair colour is not red. The amount does not increase with an individual's pigmentation. The amount of 5-sulphur cysteinyldopa in the urine is lower in albinos, but this cannot be used to differentiate between the different albino types [Hansson (1988)]. This compound also can be formed in the absence of tyrosinase by an oxidation technique using the enzyme hydroxylase [Nimmo et al (1985)].

The production of phaeomelanin is not confined to phaeomelanin-producing melanocytes. When conditions for the formation of eumelanin are unfavourable, cysteine or glutathione can form dopaquinone and subsequently phaeomelanin. Cysteinyldopa is a detoxification product of dopaquinone [Jimbow et al (1983)].

When melanin is isolated from human tissue, both eumelanin and phaeomelanin are usually found on biochemical testing, suggesting that a mixed type of melanin may be the usual product of the melanin pathway [Jimbow et al (1983)]. This may be the same as the mosaic melanosome seen ultrastructurally.

CHAPTER 2

TYPES OF ALBINISM

Albinism comprises a heterogeneous group of inherited conditions where there is decreased formation of melanin [Mosher et al (1987), Witkop et al (1983)]. The pigment dilution affects the skin, hair and eyes. In the skin this results in sun damage; in the eyes, the decreased melanin in the iris and retina and abnormal optic tracts cause nystagmus, photophobia and reduced visual acuity [Bolognia & Pawelek (1988), Witkop (1989)].

In the so-called 'albinoid' conditions, decreased pigmentation is found but there is no nystagmus, photophobia or decreased visual acuity and the optic tracts are normal [Witkop et al (1983)]. Examples of this include Menkes syndrome and Waardenburg-like conditions.

Two groups of albinism exist which vary in their genetic, clinical, histological and biochemical features. They are:

1. Oculocutaneous albinism
2. Ocular albinism

OCULOCUTANEOUS ALBINSIM

In this form of albinism, there is hypopigmentation of the skin, hair and eyes with defects of the optic tracts. Ten types of this form of albinism have bee described [Witkop (1989)]. They are all inherited in an autosomal recessive manner except for autosomal dominant type VII albinism.

The types of oculocutaneous albinism are :

1. Tyrosinase negative albinism Type I A
2. Yellow mutant albinism Type I B
3. Platinum albinism Type IC
4. Tyrosinase positive albinism Type II
5. Minimal pigment albinism Type III
6. Brown albinism Type IV
7. Rufous albinism Type V
8. Hermansky-Pudlak Syndrome Type VI A
9. Chediak-Higashi Syndrome Type VI B
10. Autosomal dominant albinism Type VII [King & Summers (1988)].

The types are derived from their allelic grouping. For example, tyrosinase negative, yellow mutant and platinum albinism result from allelic mutations at the tyrosinase locus. Platinum and minimal pigment albinism may be the same condition [King et al (1986)].

In order to distinguish between tyrosinase positive and tyrosinase negative oculocutaneous albinism, the tyrosinase test is done [Kugelman & van Scott (1960)](figs. 3 & 4, p. 21 & 22). Anagen hair bulbs are plucked and incubated in tyrosine and L-dopa. If functional tyrosinase is present, pigment is produced. Tyrosinase positive albinos are an example of this i.e. the tyrosinase functions normally in vitro, but not in vivo. It is not certain why tyrosinase does not function in vivo when the enzyme is kinetically normal and active in vitro [Boissy et al (1987), King et al (1978), King et al (1979), Kugelman & van Scott (1960)]. Theories put forward to account for its malfunction include defective transport of the enzyme, an inhibitor or a defect in the activation of the enzyme [Mosher et al (1987)].

Figure 3

A. Freshly epilated hair bulbs from a tyrosinase negative albino.

B. The same hair bulb after incubation in L-tyrosine.

C. Freshly epilated hair bulbs from a tyrosinase positive albino.

D. Pigmentation in this hair bulb after incubation in L-tyrosine [Witkop et al (1983)].

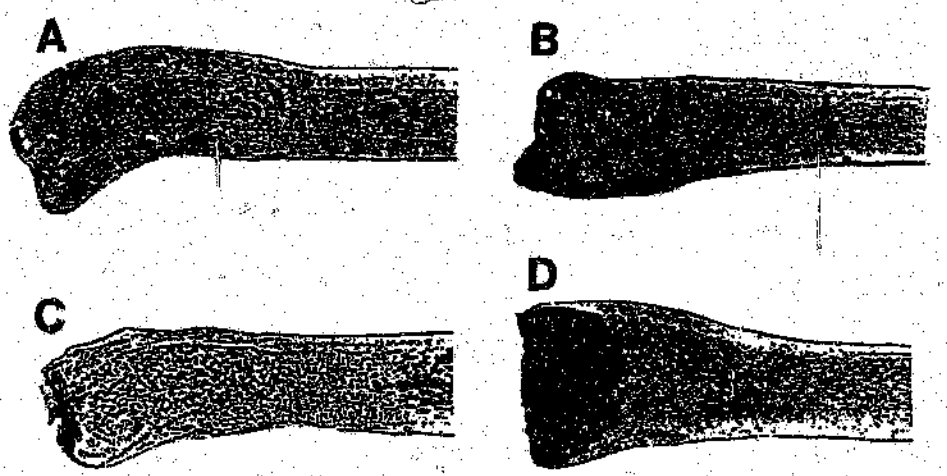


Figure 4

Microscopic view of an anagen hair bulb from a tyrosinase positive albino before and after incubation in L-tyrosine.



OCULAR ALBINISM

In this form of albinism, the major clinical manifestations involve the eye, although abnormalities in pigment formation of the skin may also be found [Witkop et al (1983)]. There are four types :

1. X-linked of Nettleship-Falls (XOAN)
2. X-linked with deafness (XOAD)
3. Autosomal recessive ocular albinism (AROA)
4. Autosomal dominant form with lentigines and deafness (ADOA) [King & Summers (1988)]

The frequency of the autosomal recessive trait is the same as that of the X-linked trait. The X-linked form of Nettleship-Falls (XOAN) and the X-linked form of ocular albinism with deafness (XOAD) both demonstrate melanin macroglobules in the melanocytes of the skin. Melanin macroglobules are also found in the lentigines of ADOA. In heterozygotes with XOAN or XOAD, there is a mosaic pattern of pigment distribution in the eye [Witkop et al (1983)].

CLINICAL FEATURES

1. Ocular Changes

i. Iris translucency

The decrease or complete absence of pigment results in diaphanous slits and translucence on transillumination of the iris [Witkop (1971)].

ii. Photophobia

The hypopigmented fundus causes the photophobia.

iii. Decreased visual acuity

The hypoplastic fovea decreases visual acuity.

iv. Nystagmus

Foveal hypoplasia and abnormal development of the abducens nucleus result in poor visual resolution and therefore compensatory nystagmus [O'Donnel et al (1976, Witkop et al (1982)].

v. Mononuclear vision

For normal binocular vision to occur, there should be fibres going from the temporal retina to the ipsilateral side of the brain. Thus, impulses from the right temporal and left nasal sides of the retina should project to the same part of the brain [Lund (1965), Creel & Giolli (1972), Witkop et al (1982)]. In an albino decreased or no homolateral fibres are found.

Normally pigment in the optic stalk is responsible for directing the optic pathway and therefore in albinos these pathways are abnormal. In order to compensate for the defect in the optic chiasm, other abnormalities develop in the organization of the lateral geniculate body and the geniculocortical tracts [Witkop et al (1983)].

vi. Strabismus, enotropia and exotropia

Misdirected oculomotor reflexes and blunted macular reflexes cause these abnormalities [Drager (1986)].

vii.Visual evoked potentials (VEP's)

In normal people they are symmetrical, whereas in albinos they are asymmetrical [Witkop et al (1983)].

2. Hearing

Decreased melanin in the ear results in increased noise trauma. Abnormal auditory pathways can also be found which may result in poor hearing. Hearing is especially poor in X-linked ocular albinism and autosomal recessive ocular albinism because, in addition to decreased melanin, they demonstrate a defect in the brainstem [Witkop et al (1983)].

3. Skin

The skin is lighter than in unaffected siblings and affected

individuals can not tan normally. Since melanin is one of the major absorbers of UV light, the hypopigmented skin of albinos is susceptible to sun damage, viz. solar elastosis, keratoses and skin carcinomas (See chapt. 4, p. 47).

Intellectual function in the albino is normal [Manganyi et al (1973)].

Details of each type of albinism are described in Table 2, p.27.

Table 2 FINDINGS IN OCULOCUTANEOUS ALBINISM

Type of albinism	Tyrosinase negative	Yellow mutant	Platinum	Tyrosinase positive	Minimal pigment	Brown	Rufous	Hermansky-Pudlak	Chediak-Higashi	Autosom: dominant
Allelic grouping	IA	IB	IC	II	III	IV	V	VIA	VIB	VII
Inheritance	AR.	AR.	AR.	AR.	AR.	AR.	AR.	AR.	AR.	AD.
Clinical Hair colour	white throughout li	white at birth yellow-red by 6 months	white at birth metallic off-white later	white - yellow darkens with age	white - light yellow	beige - light brown	mahogany-red - deep red	white, red, brown	blond - dark brown steel-gray tint	white - cream with reddish tint
Skin colour	pink - red	white at birth, cream, tans slightly	pink - red	pink-white - cream	pink-white	cream, tans slightly	red-brown.	cream - normal	pink - pink-white	white - cream
Pigmented lesions	0	+	+	+	0	+/0	+/0	+	+	+/0 be
Susceptibility to neoplasia	++++	+	++++	+++	?	+(like fair Caucasians)	low	+++	++	?
Eye colour	gray - blue	blue in infancy, age dependant	gray - blue	blue, yellow, brown, age dependent	gray - blue	hazel - brown	red-brown - brown	blue-gray - brown, race age dependent	blue - dark brown	gray blue
Transillumination	no pigment	adults - cartwheel	adults - cartwheel	cartwheel	translucent pigment	cartwheel	translucent	no pigment - cartwheel	cartwheel - N	transiu cent-car wheel
Red reflex	+	+	+	+/0	+	+/0				
Fundal pigment	0	0 - +\	0	0 - +	0	+ - ++	+ - ++	0 - +	+ - ++	0 - +
Nystagmus	++++	+ - +++	++++	++ - +++	++++	+ - ++	0 - ++	+ - ++++	0 - ++	++ - ++
Photo phobia	++++	+ - ++	++++	++ - +++	++++	+ - ++	0 - ++	+ - ++++	0 - ++	++ - ++
Visual acuity	blind	20/200 - 20/90 - 20/400	20/200 - 20/400	20/60 - 20/400	20/160 - 20/200	20/30 - 20/150	N - 20/100	20/70 - 20/400	N - I	20/70 - 20/200
Incorporation of hair bulb in tyrosine	no pigment	? no pigment	slight	pigment ++	no pigment	+/- pigment	pigment	pigment	pigment	pigment
Melanosomes in hair bulb	I + II eu	I - III phaeo	I - III round & eliptical	I -III eu-	I - late II eu	I - III eu early IV	?	I - III phaeo + eu-	I - IV macromel-anosomes	I - III eu

Adapted from Witkop et al (1983)

1. Tyrosinase Negative Albinism

Clinically tyrosinase negative albinos have no visible pigment. Their phenotype does not vary in different racial groups. Their skin is pink to red and their hair white. Since there is a direct correlation between the lightness of the skin and the degree of sun damage, they are very susceptible to carcinomas of the skin. They do not have pigmented lesions but may develop reddish macules where unpigmented naevus cells accumulate [Witkop et al (1983)]. Their eyes are gray to blue with no pigment on transillumination of the iris, and show a red reflex. There is no fundal pigmentation and hypoplasia of the fovea is present. As a result, there is marked nystagmus, photophobia and very poor visual acuity. Most cases are legally blind [Witkop et al (1983)].

Although a tyrosinase negative albino may resemble a tyrosinase positive albino at birth, with time more pigment will develop in the tyrosinase positive whereas a tyrosinase negative albino's colour remains unchanged. A tyrosinase positive albino's visual acuity may improve, whereas in the tyrosinase negative albino it can worsen with time [Witkop et al (1983)].

The tyrosinase test (p. 20) serves to differentiate between these two types of albinos. Tyrosinase activity is low in homozygous tyrosinase negative albinos and below normal in heterozygotes [King & Olds (1984), King & Witkop (1979)].

The defect in tyrosinase negative albinism is a mutation at the tyrosinase locus. Mutations at the same locus are found in yellow mutant and platinum oculocutaneous albinism [Witkop (1989)].

2. Yellow Mutant Albinism (YM, Xanthous)

At birth this group have white skin and hair and resemble tyrosinase negative albinos. However, by six months, the skin is darker and the hair is a yellow-red colour. The skin can tan slightly and may show pigmented lesions. It is darker in Negroids. Their eyes are blue in infancy, but darken with age. Older yellow mutant albinos can resemble tyrosinase positive albinos, but there is less photophobia and nystagmus. The hair colour of yellow mutants may resemble redheads or blonds [Witkop et al (1983)].

To differentiate YM albinism from tyrosinase positive albinism, the hair bulb test can be done. When the hair bulb is incubated in cysteine and tyrosine or L-dopa, the bulb becomes yellow in yellow mutants and black in tyrosinase positive albinos. Ultrastructurally partially melanised eumelanosomes and phaeomelanosomes are seen in yellow mutants [Hu et al (1980)].

3. Platinum albinism

This group develops small amounts of pigment in their hair and eyes in late childhood. Their skin remains pink to red and cannot tan, but may show pigmented lesions. Their hair is initially white, but becomes a metallic colour with time. Their eyes are gray to blue and with time more pigment develops around the pupillary limbus and in cartwheel-like spokes radiating from the centre of the iris.

This condition may be the same genetic entity as minimal pigment albinism and is allelic with tyrosinase negative albinism [King et al (1986)].

4. Tyrosinase Positive Albinism

This is the commonest form of albinism and is found widely throughout the world. Clinically tyrosinase positive albinos are a heterogeneous group, appearing darker in Negroids and older individuals than in Caucasoids and the young [Bolognia & Pawelek (1988)]. Negroids have cream-coloured skin which can develop pigmented naevi, lentigines and freckles. Their hair initially is white, but becomes straw-coloured or brownish with age (fig. 5, p. 32). Their eyes can be blue, brown, gray or hazel and the pigment is most prominent at the pupillary limbus in a 'cartwheel configuration' (fig. 6, p. 32). Although the

red reflex is prominent in the lighter races, it may be absent in darker races or adults [Witkop et al (1983)]. The nystagmus and poor visual acuity are less severe in tyrosinase positive than in tyrosinase negative albinos and improve with time.

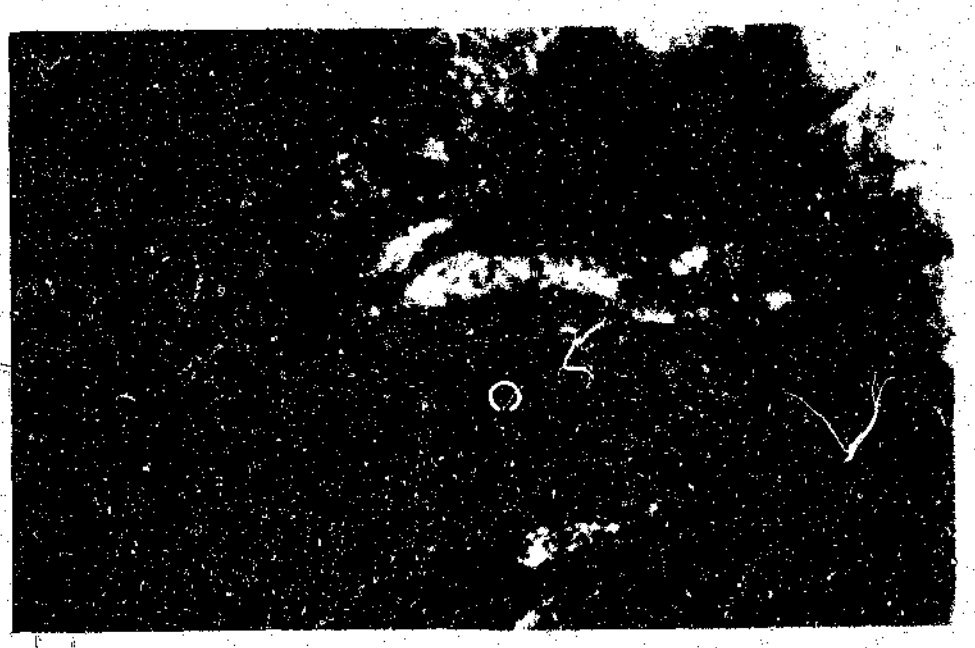
The pathway for melanin production is blocked at the distal site of tyrosinase activity [Barber et al (1984), King & Olds (1984)] possibly because of an intrinsic defect in the tyrosinase-melanin pathway distal to dopachrome [Witkop (1989)].

Figure 5
Tyrosinase positive albino with pinkish-cream skin, straw-coloured hair and brown eyes. Dendritic freckles are also present.



Figure 6

Eye of a tyrosinase positive albino showing the cartwheel effect ie. the pigment is most prominent at the pupillary limbus and projects from the centre like the spokes of a wheel.



5. Minimal Pigment Albinism

These albinos have no pigment in skin, hair or eyes at birth. The skin is pink or white without pigmented lesions and the hair is white, becoming yellowish with time. The eyes are gray or blue with clumping of pigment at the limbus. However, since the pigment is minimal, nystagmus and photophobia are marked and visual acuity very poor.

The hair bulb test shows a minimal increase in Golgi-associated melanin after incubation in tyrosinase and L-dopa [Kugelman & van Scott (1960)]. This group may be a genetic compound or the same genetic entity as platinum albinos [Witkop (1989)].

6. Brown Oculocutaneous Albinism

This form of albinism occurs in Nigeria, New Guinea and in American Negroids of South and Central America. No Caucasoids have been described with the condition which may be difficult to identify in this population.

Clinically there is only moderate pigment dilution in the skin, hair and eyes and the optic system is a more reliable site for making the diagnosis. The skin is light brown, tans, and may develop pigmented lesions. It is uncommon for them to develop sun-related damage. Their hair is light

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brown and their eyes hazel to brown (fig. 7, p 35). A car wheel effect may be seen. Although a red reflex can occur in children, it disappears in adulthood. Nystagmus and photophobia may occur and visual acuity is variable. The foveal reflex and retinal pigmentation are decreased [King et al (1985)].

Hair bulb tyrosinase activity is within the normal range. Biochemically the block in melanin production is probably more distal than the dopaquinone to phaeomelanin step, and there may be a defect in melanosome maturation [Witkop (1989)].

7. Rufous Albinism

Rufous albinism is found in the natives of New Guinea and in African and American Negroids [Loewenthal (1944), Barnicot (1952), Walsh (1971), Witkop et al (1983), Kromberg et al (1990)]. According to Witkop, in most cases the skin is mahogany brown and the hair mahogany to sandy red [Witkop et al (1983)]. Pigmented lentigines [Loewenthal (1944)], naevi and freckles [Barnicot (1953), Witkop et al (1983)] may develop. The rufous albinos in New Guinea are described as having light brown hair and red-tinged skin [Walsh (1971)]. In Nigeria, Barnicot described them with brownish red hair and copper coloured skin [Barnicot (1953)] The hair of the New Guineans is redder than in Africans in whom it is ginger

Figure 7

A South African brown albino with coffee-coloured hair and light brown skin.



and may be lighter or darker than the skin [Barnicot (1953), Walsh (1971), Witkop et al (1983), Kromberg et al (1990)]. In Nigeria, in South African rufous albinos the skin is reddish-tan, the hair ginger-blonde and the eyes hazel and characteristically the hair is lighter than the skin [Kromberg et al (1990)]. The skin colour is similar to that found in a heterozygote for the tyrosinase positive gene (fig. 8, p. 37).

Young rufous albinos are more red than older individuals who develop more brown pigmentation. The relative amount of red and brown pigmentation varies in different sites of the body. The palms, soles and axillae are least red [Walsh (1971)].

Nystagmus, photophobia and visual acuity are normal or slightly decreased. When tested after lateral gaze with dark adaption, 80% of cases demonstrate nystagmus. There is no foveal hypoplasia and fundoscopy shows a red-tinged retina. Slight transillumination of the iris may be found and photophobia is rare [Witkop (1989)].

The hair bulb tyrosinase test is positive with normal or greater than normal tyrosinase levels [Kromberg et al (1990)]. The defect possibly is at the phaeomelanin switch point [Witkop (1989)].

Figure 8

A South African rufous albino with reddish-tan skin and brown eyes.



8. The Hermansky-Pudlak Syndrome

This group clinically resembles tyrosinase positive or ocular albinos. In addition, a mild haemorrhagic diathesis and a ceroid storage disorder are found. The haemorrhagic diathesis results from a deficiency in the storage pool of platelets which lack non-metabolic adenine nucleotides, calcium and serotonin [Witkop et al (1983)]. They do not aggregate normally in response to epinephrine or collagen [Logan et al (1971)]. Lipid and ceroid accumulate in the reticuloendothelial system. The lipid resembles that found in neuronal ceroid-lipofuscinosis. Deposits are also found in the oral and intestinal mucosae, the pulmonary epithelial cells, the kidneys, heart and leucocytes. As a result of these deposits, affected individuals can develop gingivitis, granulomatous colitis resembling ulcerative colitis, interstitial fibrosis, restrictive lung disease, kidney failure and cardiomyopathy [Witkop et al (1983)].

A feature of the syndrome are the giant melanosomes found in the melanocytes and keratinocytes. They probably result from a defect in the synthesizing microvesicles. The matrix fibres run at various angles and do not show the normal ordered, lamellar pattern. Partially melanised eumelanosomes are found in the keratinocytes of the skin either singly, coupled or in groups. Hair bulbs demonstrate poorly pigmented phaeomelanosomes and eumelanosomes in stages II and III, as in redheads [Witkop et al (1983)].

9. Chediak-Higashi Syndrome (CHS)

In this condition there is abnormal fusion of organelles resulting in giant pigment granules in melanocytes and keratinocytes, giant lysosomal granules in leucocytes and other abnormally large cytoplasmic organelles [Blume & Wolff (1977)]. The basic defect is in the processing of lysosomal membranes [Blume & Wolff (1977), White & Clawson (1980)]. Melanosomes are normally melanised. However, individuals with CHS are hypopigmented as a result of abnormal packaging and a reduced number of melanosomes [Zelickson et al (1967)]. Giant melanosomes are degraded in melanocytes by lysosomal hydrolases within the cell. Normal sized melanosomes are transported to keratinocytes where they form unusually large phagolysosomes.

The giant granules in leucocytes are malfunctional, causing a susceptibility to infections which often are fatal before the age of 20 years. The defect lies in the membrane of the granules which cannot discharge their contents normally. As a result peroxidase which is bactericidal, is not released [Clark & Kimball (1971), Clark et al (1972)]. Abnormal microtubule assembly or abnormal cyclic nucleotides may cause malfunction of the membrane. Ascorbic acid improves leucocyte function by increasing the number of centrioles associated with the microtubules [Witkop et al (1989)].

A similar defect in microtubules is found in platelets and fibroblasts [Witkop et al (1989)]. This results in a bleeding diathesis. As the disease progresses, pancytopenia may develop.

Other problems found in the CHS include a lymphohistiocytic infiltrate in the reticuloendothelial system, lymphoreticular malignancies, peripheral neuropathies, defects in cell mediated immunity and antibody dependent cytolysis [Blume & Wolff (1977)]. Biochemical findings patients with CHS show a high level of ceroid and dolichol (constituents of lysosomal membranes) in the urine [Blume & Wolff (1977)]. The site of the gene defect, as in HPS, is extrinsic to the tyrosinase-melanin pathway [Witkop (1989)].

10. Autosomal Dominant Oculocutaneous Albinism

This condition was first described in the Swiss [Witkop et al (1983)]. Clinically the dilution of pigment is similar to tyrosinase positive albinos, but the inheritance is autosomal dominant.

ALBINO-LIKE SYNDROMES

In the following 2 conditions (BADS syndrome and CROSS syndrome) there is a clinical resemblance to an albino, but because melanocytes are absent or reduced, they can neither be classified with the other types of albinism nor with the albinoid conditions since their eyes are abnormal.

1. BADS syndrome (Black Locks Oculocutaneous Albinism and Deafness of the Sensorineural Type)

Clinically this group have predominantly white hair and skin with locks black hair and round black macules on the skin. Their eyes monstrate the characteristic changes of oculocutaneous albinism. Associated with these abnormalities, there is congenital sensorineural deafness. The combination of poor hearing and vision lead to social retardation.

Ultrastructurally, melanocytes are absent in the white areas and present in the black areas [Witkop (1979), Witkop (1985)]. The sites where no melanocytes are found may represent either a defect in migration or survival of the melanocytes [Witkop et al (1983)].

2. Cross Syndrome

Subjects with this syndrome demonstrate hypopigmentation of the skin and hair plus microophthalmia, oligophrenia, spasticity and athetoid movements [Witkop et al (1983), Witkop et al (1989)]. At birth they have a hypopigmented skin and small eyes with cloudy corneas. By 3 months they develop writhing movements of the limbs, retain sucking reflexes and develop high pitched cries. They are never able to sit unaided. There is severe mental and physical retardation. Other clinical features include high arched palates, constriction in the pre-molar area, gingival enlargement, scoliosis, hallux valgus and underdeveloped sexual organs.

OCULAR ALBINISM

There are four types of ocular albinism :-

1. X linked ocular albinism (XOAN)
2. X linked occular albinism with deafness (XOAD)
3. Autosomal recessive ocular albinism (AROA)
4. Autosomal dominant ocular albinism with lentigines and deafness ADOA)

Details about each type of ocular albinism are listed in Table 3 p. 43.

Table 3

FEATURES OF OCULAR ALBINISM +

Type of albinism	X-linked ocular albinism (XOAN)	X-linked ocular albinism with deafness (XOAD)	Autosomal recessive ocular albinism (AROA)	Autosomal dominant ocular albinism with deafness and lentigines (ADOA)
Hair colour	normal - slight lightening	normal - slight lightening	normal	normal
Skin colour	normal to mottled	normal	normal	normal
Pigmented legions	present	present	present	present + lentigines
Susceptibility to skin neoplasia	0	0	0	?
Eye colour	normal	normal	normal	normal
Transillumination of iris	cartwheel - males diaphanous females	cartwheel - males diaphanous-females males + females	cartwheel - diaphanous	cartwheel - diaphanous
Red reflex	present - males	present - males	present - males + females	present
Fundal pigment	males - 0 females mosaic	males - 0 females mosaic	males + females 0 to +	0 0
Nystagmus	++ to ++++	++ to ++++	++ to +++	+++
Photophobia	++ to +++	++ to ++++	++ to +++	+++
Visual acuity	moderate to severe (20/50 - 20/400)	moderate - severe (20/50 - 20/400)	moderate to severe (20/100) to 20/400	20/200
Incubation of hair bulb in tyrosine	pigment	pigment	pigment	?
Melanosomes in hair bulbs	macromelanosomes	macromelanosomes	normal	macromelanosomes in lentigines

Adapted from Witkop et al (1983)

CHAPTER 3

PREVALENCE OF ALBINISM

The prevalence of albinism varies in different countries (Table 4, p. 46). The South African prevalence of 1 in 3900 in Negroids with tyrosinase positive albinism is high compared to that in other parts of the world. The carrier rate in the Negroid population in South Africa is 1 in 32 [Kromberg & Jenkins (1982)]. Prevalence differs within the various Negroid population groups because of differences in consanguinity (table 5, p.46). It is commonest in the Southern Sotho i.e. 1 in 2 254, because in 20.5% of this group consanguineous marriages are customary and women marry paternal uncles in order to keep the cattle in the family [Kromberg & Jenkins (1982)]. They are followed by the Swazis and then the Tswana. The lowest rates of albinism are found in the Shangaan, Pedi, Venda, Xhosa, Ndebele and Zulu in whom consanguineous marriages are taboo. There appears to be no difference in the sex ratio in albinos.

The high prevalence of the gene in Negroids (one albino is born every 2 months in Soweto) may be because of an advantage held by the heterozyote. They have paler skin than normal people which may be seen as a social advantage [Kromberg & Jenkins (1982), Oettle (1963), Roberts et al (1986)]. The rate of albinism in

South African Negroids is five times greater than in any reported Caucasoid population [Kromberg (1987)].

Rarer forms of albinism is South Africa are the brown and rufous albinos. Rufous albinism occurs 1 in 8 500 people. Their prevalence is probably underestimated because they are not easily identifiable [Kromberg et al (1990)]. The prevalence of brown albinism is not known.

Table 4

PREVALENCE OF ALBINISM IN VARIOUS COUNTRIES

COUNTRY	TYPE	PREVALENCE
Ireland	all	1/10 000
Nigeria	ty +ve	1/ 1 100
American Caucasians	ty +ve	1/37 000
American Negroes	ty +ve & rufous	1/15 000
Puerto Rico	HPS	1/ 2 000
South African Negroes	ty +ve	1/ 3 900

Witkop (1985)

Table 5

PREVALENCE OF ALBINISM IN DIFFERENT SOUTHERN AFRICAN NEGROIDS

Botswana	ty +ve	1/ 1 300
Swazi	ty +ve	1/ 1 900
Southern Sotho	ty +ve	1/ 2 000
Zulu	ty +ve	1/ 4 500
Xhosa	ty +ve	1/ 4 800
Shangaan	ty +ve	1/28 000

Fromberg et al (1989)

Kromberg & Jenkins (1982)

CHAPTER 4

SKIN CANCERS IN ALBINOS

Since melanin normally provides photoprotection, high numbers of skin cancers develop in albinos [Lund (1965)]. In Caucasoids five times as much UV light reaches the papillary dermis compared to Negroids [Kaidbey et al (1979)]. In albinos who are paler, more UV light penetrates and causes even greater damage. This includes photoaging, solar keratoses and skin carcinomas [Kugelman et al (1979)]. Unfortunately many of the population groups most affected by the gene for albinism, live in the sunny parts of the world [King et al (1979)].

Melanin protects against the adverse effects of ultraviolet radiation by dissipating light energy as heat. Melanin consumes oxygen by a chemical technique which scavenges reactive oxygen, eg. superoxide and singlet oxygen [Witkop et al (1983)]. Phaeomelanin, in addition to its photoprotective function, can exert a toxic effect. In persons with greater concentrations of phaeomelanin, photo-oxidation gives rise to superoxide which damages the cell [Witkop et al (1983)]. This may explain why there is a higher risk of skin cancer in red-haired people than in other groups [Witkop et al (1983)].

Several skin cancers are related to sun exposure viz. squamous and basal cell carcinomas and melanomas. A squamous cell carcinoma is a malignant tumour derived from the epidermis which may show some maturation towards keratin formation. Clinically they are verrucous, tumid or ulcerated lesions with an elevated indurated border which usually develo on sun damaged skin (fig. 10 p. 50). Squamous cell carcinomas which arise on sun damaged skin metastasize in 0.5% of cases, except on the lower lip where the incidence of metastasis is about 11%. Death occurs in about 3% of patients with metastases [Epstein et al (1986), Moller et al (1979)].

Premalignant solar keratoses occur more frequently, often in association with squamous cell carcinomas. Clinically, solar keratoses are erythematous, non-infiltrated lesions with an adherent scale resulting from damage to the epidermal cells by cumulative sun exposure. They arise on sun damaged skin where there is evidence of solar elastosis (figs. 9 & 10, p. 50).

They may later become squamous cell carcinomas.

A basal cell carcinoma is a malignant tumour composed of cells derived from the basal layer of the epidermis. Clinically they are translucent, raised, rounded papules covered by a thin epidermis through which a few dilated, superficial vessels can be seen. The incidence of metastases from basal cell carcinomas is 0.0028% [Paver et al (1973)]. Basal and squamous cell carcinomas are more common in fair-skinned people where the skin is more susceptible to damage by chronic sun exposure.

A melanoma is a malignant tumour arising from epidermal melanocytes or naevus cells. They may arise de novo or in association with a pre-existing naevus. Malignant change should be suspected if a melanocytic lesion shows a change in colour, irregularities of pigmentation, elevation, an inflammatory border, the development of symptoms (itch or pain) or bleeding. Melanomas frequently metastasize and often are lethal. Melanomas also are more common in lightly pigmented individuals, but are related to intermittent exposure to high doses of solar radiation, rather than to chronic exposure. UV light can have a mutagenic effect on naevi [Nicholls (1973)]. Other factors involved in the pathogenesis of melanomas include the presence of dysplastic naevi, heredity and exposure to chemical carcinogens [Houghton & Viola (1981)].

The incidence of skin cancers varies in different parts of the globe and is greatest at the equator. For every 10° latitude towards the equator, the incidence doubles. Most skin cancers develop in places with a high altitude, low latitude and numerous sunny days [Scott et al (1982)]. Additional factors which influence the development of skin cancers include dress, occupation and hereditary factors [Cervenka et al (1987)].

Nigeria, situated near the equator has a very high prevalence of albinism (see p. 46). Okoro found that here all tyrosinase positive albinos over the age of 20 years had malignant or

Figure 9

Solar elastosis on the neck of a 27 year old albino giving a thickened, wrinkled appearance.

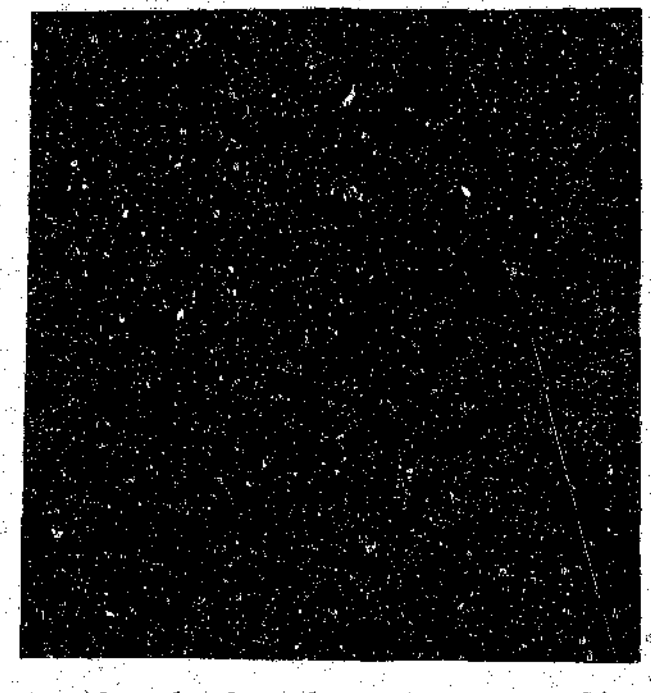
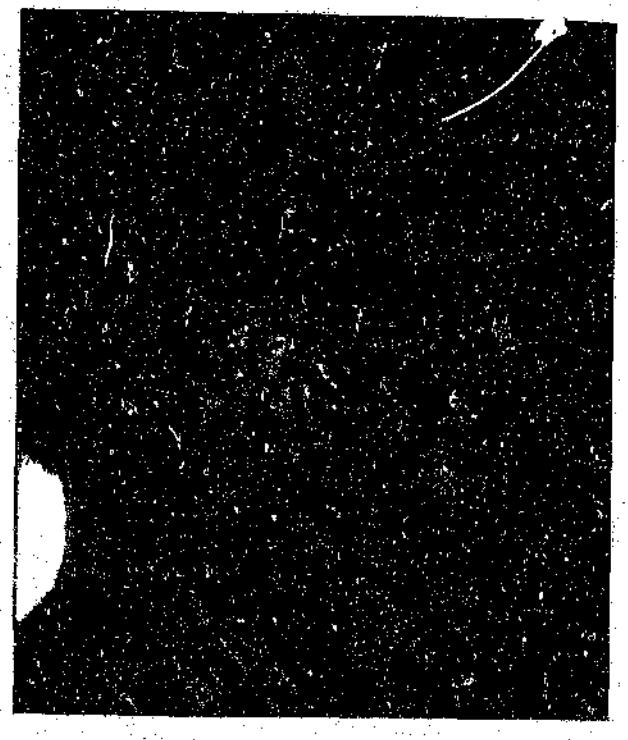


Figure 10

Solar keratoses on the cheek and a squamous cell carcinoma on the neck of a 58 year old albino.



premalignant lesions. By the 3rd decade, they had advanced skin cancers and by the 5th decade 70% had died of their malignancies [Okoro (1975)]. Overall 50 % of the subjects had solar keratoses and unspecified 'superficial ulcers' [Okoro (1975)].

In Tanzania the intensity of sunlight is similar to Nigeria. Here, all albinos were found to have sun damage by the end of the first year of life, by 20 years they had premalignant and malignant change and by the third or fourth decade a large percentage of these tumours had disseminated and caused death. Patients with advanced skin cancer had a median age of 31 years [Luande et al (1985)].

In Johannesburg, which is 26° S, 31% of Negroid tyrosinase positive albinos were found to have skin lesions by the end of the second decade, 42% by the end of the third, and 61% by the fourth decade had some form of skin cancer. Only 32 to 37% lived beyond 30 years [Kromberg et al (1989)].

The Nigerian and Tanzanian experience showed that squamous cell carcinomas are most common although basal cell carcinomas also occur [Ademiluyi & Ijaduoula (1987), Luande et al (1985), Okoro (1975)]. The squamous cell carcinomas tend to be well differentiated and to metastasize late. In South Africa, Kromberg and coworkers showed that 87% of the cancers were squamous cell and 13% basal cell [Kromberg et al (1989)].

Melanomas are rare in comparison to other types of skin cancer and do not develop more frequently in albinos than in normally pig-

mented people [Oettle (1963), Stoll et al (1981), Witkop (1981)]. In places like Nigeria where skin cancers in albinos are common [Okoro (1975)], no melanomas have been reported and in Tanzania the only case reported was in 1985 [Luande (1985)]. In a study by Scott on tyrosinase positive albinos in America, 4 out of 8 reported melanomas developed from naevi and all 8 cases were amelanotic [Scott et al (1982)]. Albinos have the predisposing factors for melanoma development viz. pale skin, exposure to sunlight, naevi, including dysplastic ones [Houghton & Viola (1981)] yet rarely develop this tumour.

Melanomas occur commonly in South African Negroids and form 12.6% of all their skin cancers. The incidence of skin cancer in Negroids in Johannesburg is 1,1/100 000 per year. They are particularly common on the feet where they usually present with large, deeply invasive nodular tumours with a poor prognosis [Rippey & Schmaman (1972)]. Freinkel and Rippey found that about 60% of black South African Negroids develop pigmented macules on the palms and soles. Histologically they show increased melanin production, sometimes in association with proliferation of melanocytes. They suggested that melanomas may arise from these macules [Freinkel & Rippey (1976)]. This suggestion is substantiated by the finding by Lewis in Uganda in 1967 that the number of melanomas on the soles of the feet is proportional to the degree of racially determined palmoplantar pigmentation [Lewis (1967)]. There is no published data about the presence of palmoplantar pigmented macules in albinos. They are known to develop melanomas rarely [Kromberg et al (1989)] despite their pale skin and their racial origins being the same as the Negroids who develop melanomas on their soles.

CHAPTER 5

PIGMENTED LESIONS IN ALBINOS

Various pigmented lesions can be found in albinos viz. naevi, lentigines and ephelides. At these sites, the melanocytes are normal in function and form pigment.

NAEVI

Melanocytic naevi are benign tumours formed by proliferation of melanocytes at the dermo-epidermal junction. The proliferating cells form nests which migrate into the dermis. Clinically, they are brown macules with distorted skin creases [Nicholls (1973), Rhodes (1987)] which can become raised and finally sessile as the naevus cells drop from an epidermal to a dermal position [MacKie (1986)]. Clinically naevi first appear in childhood, their numbers reach a peak in the second or third decade and then decline [Fitzsimmons et al (1984)]. In the seventh or ninth decade, naevi seldom are found.

Ultrastructurally naevus cells are similar to melanocytes except that short, stubby projections called pseudopodia and not long dendritic processes are found. In the upper dermis the naevus cells resemble those in the epidermis, but as they move deeper into the dermis, the Golgi and rough endoplasmic reticulum become less well developed and fewer melanosomes are seen. In albino's, melanocytes the Golgi and rough endoplasmic reticulum are poorly developed, but these organelles are well

developed in naevus cells. The eumelanosomes found in the naevus cells may be fully melanised and arranged in complexes. The melanosomes deeper in the dermis are round and more unmelanised, abortive forms are found. At these sites, the dopa reaction which stains for melanin becomes less positive [Tsuji & Saito (1987)].

Initially pigmented naevi in albinos were thought to be uncommon and individual cases were reported [Hall et al (1976), Ho et al (1956), Martin et al (1975), Roller & Hahn (1977), Stoll et al (1981), Tsuji & Saito (1978)]. When Witkop defined the various types of albinism in 1974, he stated that naevi may occur in albinos [Witkop et al (1983), Witkop et al (1986)]. Witkop stated that in tyrosinase negative albinos, naevi are clinically pinkish in colour and the naevus cells do not contain melanin [Witkop et al (1983)]. In tyrosinase positive albinos, naevi cells contain melanin which increases progressively and clinically the naevi may darken with time [Roller & Hahn (1977), Witkop et al (1983)]. Akiyama and coworkers suggested that the presence of a pigmented naevus implied that an albino was tyrosinase positive since his own and other reported cases of pigmented naevi all were found in tyrosinase positive albinos [Akiyama et al (1987)].

Naevi in albinos can be junctional, compound or intradermal [Perez & Sanchez (1985), Tsuji & Saito (1978)]. A histological study of naevocellular naevi in albinos showed that there is an increase in giant melanocytic cells. These cells are predominantly near the dermo-epidermal junction and look like Touton or foreign body giant cells [Perez & Sanchez (1985)]. They are not unique to albinos and may also be found in Spitz naevi, banal naevi, and malignant melanomas. Their significance is not known. Eosinophilic globules are found in 17% of albinos' naevi, whereas they are less common in normally pigmented subjects.

In albinos a significant number of naevus cells demonstrate intranuclear pseudoinclusions which can also be found in patients with malignancies including leukaemia, lymphoma, leiomyosarcoma and meningioma. Cases of dysplastic naevi in tyrosinase positive albinos have been described [Levin et al (1988), Pehamberger et al (1984)].

LENTIGINES

Two types of lentigines are found in the normal population, simple and solar. Simple lentigines are well defined, flat or slightly raised pigmented lesions which develop on the skin in areas unrelated to sun exposure eg. trunk, mucous membranes and

nail beds. Histologically there is elongation of the rete ridges, an increase in the number of melanocytes and increased melanin production. They first appear in childhood at about 7 years of age, unless they are part of a syndrome of congenital anomalies when they may be present from birth. It is impossible to determine whether a lesion on the skin is a simple lentigo or a junctional naevus on clinical grounds. According to MacKie, simple lentigines represent an earlier stage in the development of a melanocytic naevus [MacKie (1986)].

Solar lentigines are found in sun-exposed areas in over 90% of Caucasoids. They are irregularly shaped brown macules which can become more warty with time. Histologically there is down-budding of the epidermis, an increased number of melanocytes producing more melanin and elastotic degeneration of the collagen. Melanophages and a mild perivascular infiltrate are often found in the upper dermis.

In albinos pigmented macules with an irregular border in sun-exposed areas have been described by some authors as lentigines without describing the lesions or giving reasons for the use of the term [King et al (1985), Witkop (1985)] (See p. 57 & 84).

PALMOPLANTAR PIGMENTATION

About 60% of normal Negroids have racially associated plamoplantar pigmentation which histologically shows increased melanin, sometimes in association with increased melanocytes localized in the epidermis [Freinkel & Rippey (1976), Lewis (1967)]. Their numbers on palms and soles are inversely proportional to the degree of skin pigmentation ie. high in Negroids and low in Caucasoids [Coleman et al (1989)]. These lesions have not been sought, or their presence commented on, in albinos of any race.

FRECKLES (EPHELIDES)

The freckles found in red-haired and fair-skinned people are small, round to oval, often closely aggregated pigmented macules on sun exposed areas. They are caused by increased melanin production by overactive melanocytes under stimulation of UV light. Sun-related pigmented macules have been reported in albinos and variously called freckles [Barnicot (1953), Witkop (1985)], ephelides [Kromberg et al (1982)], lentigines [Kromberg et al (1985), Witkop (1985)] and dendritic freckles [Findlay (1962)]. As they have not always been well described, there is some confusion regarding the nature of these lesions and their significance (See p. 84).

SECTION II

A CLINICAL AND ULTRASTRUCTURAL STUDY OF SOUTH AFRICAN NEGROID TYROSINASE POSITIVE AND RUFOUS ALBINOS

INTRODUCTION

The purpose of the following study was to :-

1. Describe the clinical characteristics of South African Negroid tyrosinase positive and rufous albinos.

2. Determine the prevalence of freckles, naevocellular naevi and lentigines in these tyrosinase positive albinos and, in particular, to define the nature of the so-called freckles.

3. Establish the prevalence of solar elastosis, keratoses and skin cancers and to correlate these with the presence of the pigmented lesions defined in (2). The naevi found in normal Negroids were also examined for comparison with the albinos.

4. Examine the ultrastructure of skin and hair bulbs in tyrosinase positive and rufous albinos. The findings in rufous albinos were compared to those in normal red-haired Caucasoids.

Although the clinical features of South African tyrosinase positive and rufous albinos have previously been described [Kromberg et al (1989), Kromberg et al (1990), Kromberg & Jenkins (1982)] the nature, prevalence and significance of pigmented lesions in albinos has not been clearly defined. The ultrastructural lesions of South African tyrosinase positive and rufous albinos has not been previously descibed.

MATERIALS & METHODS

Sixty one South African Negroid tyrosinase positive albinos were examined. All lived in Johannesburg or the surrounding areas. Their ages ranged from 7 to 65 (mean 23) years. Of these, 28 were males and 33 were females. Twelve rufous albinos from the same area were also examined. Their ages ranged from 16 to 62 (mean 28) years. Sixty two normal South African Negroids were examined as controls.

The albinos were examined for skin, hair and eye colour and the presence and distribution of naevi, lentigines, palmoplantar pigmentation and freckles. Solar elastosis and the presence of solar keratoses and skin cancers were noted. Biopsies of 5 naevi and 10 freckles from different albinos were taken for routine histological light microscopy examination.

Of the 61 tyrosinase positive albinos, the anagen hair bulbs were examined electron microscopically in 28 cases. Of the 12 rufous albinos, the anagen hair bulbs were examined in 5 cases. The findings in a control group of 5 red-haired Caucasoids were used to compare with those in the rufous albinos.

To obtain hair bulbs a small bunch of scalp hair was plucked in a single pull with an artery forceps. If good anagen hair bulbs were visible, they were placed into 3% glutaraldehyde and 4% formaldehyde in Millonig's phosphate buffer [Phillips et al (1986)]. After rinsing in buffer alone, post fixation took place in 1% osmium tetroxide and again buffered in Millonig's buffer for 1 hour. Following further rinsing in buffer, the tissue was dehydrated in graded dilutions of ethanol prior to infiltration with Spurr's resin. Polymerisation took place overnight at 70°C. Thin sections (60 nm) were stained with alcoholic saturated uranyl acetate and alkaline lead citrate at pH 13,5. [Phillips et al (1986)] Sections mounted on copper grids were examined with a Hitichi H-600 transmission electron microscope.

Skin biopsies were taken from the arms of 2 tyrosinase positive albinos, 2 rufous albinos and 2 red-haired Caucasoids. A naevus from a tyrosinase positive albino and a rufous albino

and a freckle from the trunk were examined light microscopically and ultrastructurally. They were placed in 3% glutaraldehyde, prepared by the same method for the ultrastructural examination.

RESULTS

1. Clinical Features of South African Tyrosinase Positive and Rufous Albinos

The tyrosinase positive albinos had white to cream-coloured skin that darkened slightly with age. In some cases pigmented lesions were present (fig. 11, p. 62, fig. 13, p. 64). Their hair was white to cream and also darkened with age. Their eyes often consisted of 2 colours e.g. blue and grey, green and hazel and the pigment was most prominent around the pupillary limbus, radiating from the pupil with the so-called cartwheel appearance.

The rufous albinos had reddish-tan skin, ginger-blonde hair and hazel to brown eyes. The hair was lighter than the skin (fig. 12, p. 62).

Figure 11

An albino boy with dendritic freckles on his face and pigmented naevi on his trunk.



Figure 12

Rufous albino sisters with a normal South African Negroid.



Figure 11

An albino boy with dendritic freckles on his face and pigmented naevi on his trunk.



Figure 12

Rufous albino sisters with a normal South African Negroid.



2. Pigmented Lesions

i. Naevi

Of the 61 tyrosinase positive albinos, 50 (82%) had lesions clinically diagnosed as naevi (fig. 11, p. 62). The naevi consisted of pink to light brown macules and papules, often with irregular skin creases. a greater percentage of naevi were found on the trunk in the albinos than in the controls (Table 6, p. 65). Biopsies in 4 cases confirmed the presence of naevus cells, of which 3 were compound and one was intradermal. None showed the histology of simple lentigines. Ultrastructurally, the naevus cells appeared similar to melanocytes, containing prominent Golgi bodies and endoplasmic reticulum. Eumelanosomes in stages III and IV of development lay in groups in the naevus cells.

The mean number of naevi per person in the albinos was 11.8 (standard deviation 13.7). The mean age at which the naevi were found was 22.9 (standard deviation 13.9). Of the 62 normal controls, naevi were present in 44 (i.e. 70.9%). The mean number of naevi per person was 6.7 (standard deviation 11.3). The mean age at which a person demonstrated naevi was 27.9 (standard deviation 11). A greater percentage of albinos demonstrated naevi than the controls and the albinos had significantly more naevi than the controls ($p=0.05$).

Figure 13

Close-up of pigmented naevi on the trunk of a tyrosinase positive albino ie. well circumcribed pigmented papules.

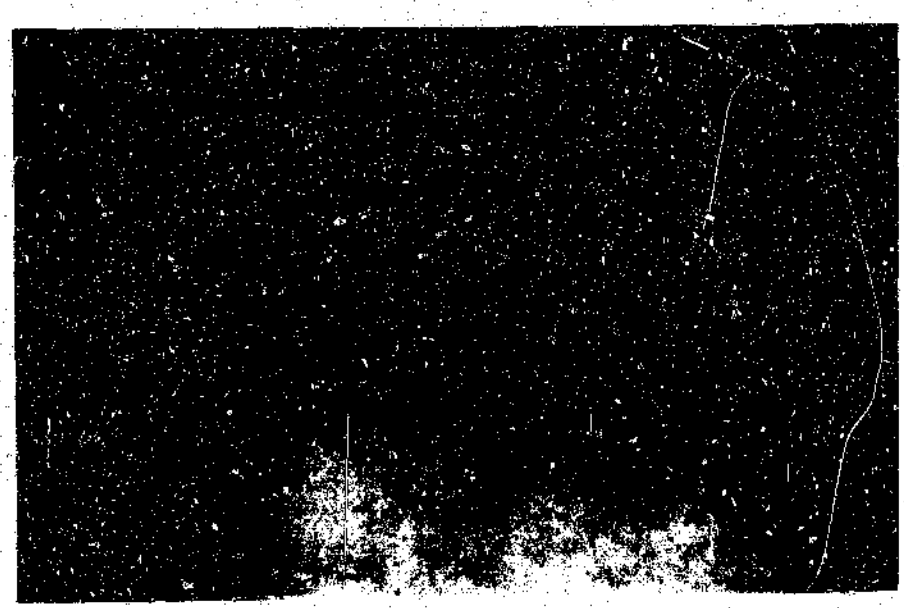


Table 6

NUMBER AND DISTRIBUTION OF NAE"I IN ALBINOS AND CONTROLS

SITE	ALBINOS (61 cases)	CONTROLS (62 cases)
Head and neck	8 (1%)	62 (18%)
Arms and hands	112 (14%)	56 (15%)
Legs and feet	182 (24%)	85 (22%)
Trunk	468 (61%)	172 (45%)
TOTAL NUMBER OF NAEVI	770	382

Whereas the frequency of naevi in the albinos was greatest in the second decade, the frequency of naevi in the controls was greatest in the fourth decade. (Table 7, p. 67).

Of the 12 rufous albinos, 8 had naevi. The average number per person was 5. In the one case that was biopsied, the presence of naevus cells containing pigment was confirmed histologically and ultrastructurally.

ii. Lentigines

No simple lentigines were diagnosed in the albinos. However, it is possible that some of the pigmented lesions counted as naevi were simple lentigines since clinically they can be identical and it is not feasible to biopsy all the lesions.

iii. Palmoplantar pigmentation

Seventy five percent of the controls had palmoplantar pigmentation. It was not seen in any of the albinos.

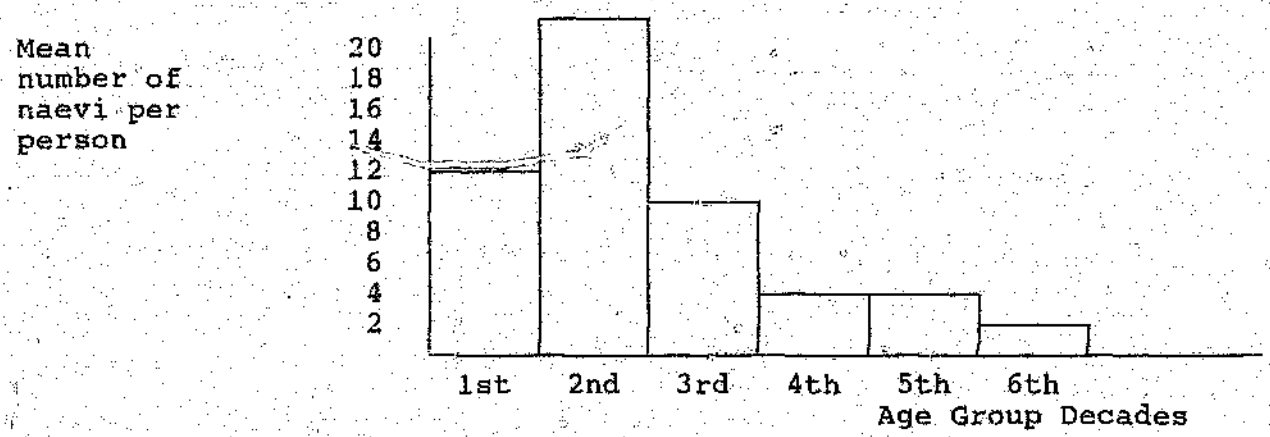
iv. Freckles

The lesions we called 'freckles' were found in sun exposed areas, mainly the face and the arms, and once formed, persisted indefinitely. They consisted of well circumscribed, irregularly shaped lesions varying in size from 0.5 to 3.0 cm. Smaller lesions were angulated, while larger lesions consisted

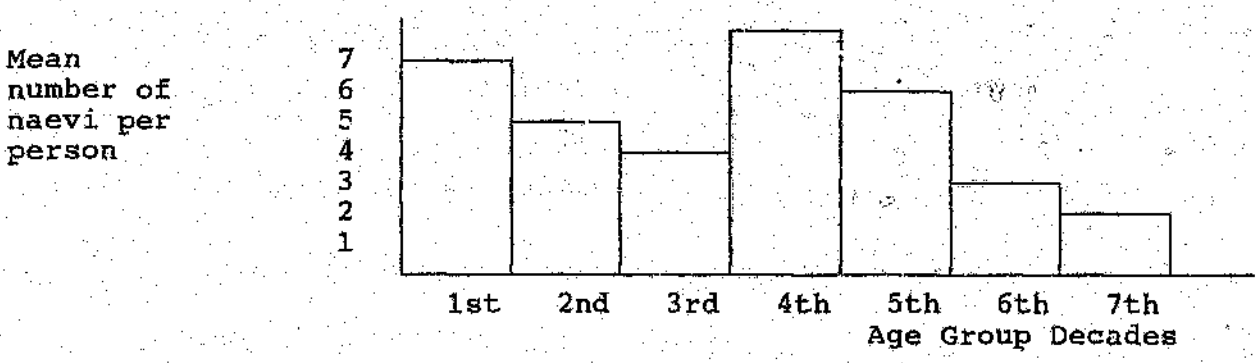
Table 7

MEAN NUMBER OF NAEVI PER PERSON VS AGE GROUP IN ALBINOS AND CONTROLS

ALBINOS



CONTROLS



of a central macule from which dendritic processes projected (fig. 14 & 15, p. 69). The pigmentation was pale to dark and often had a reticulate appearance. No rufous albinos showed these lesions.

Twenty four of the 61 albinos (43%) had freckles. The number of freckles per person varied from 10 to 230 with a mean of 81 per individual. The number of freckles increased with age (Spearman's correlation coefficient = 0.4, p = 0.04).

In the 10 freckles examined, histology showed marked orthokeratosis in all cases. The epidermis, of normal thickness, was flattened in some parts while in others the rete pegs were retained. The number of melanocytes was normal. In the basal layer rows of pigmented cells alternated with rows of unpigmented cells (fig. 16, p. 71). The number of consecutive pigmented cells varied from 20 to 50. The pigment was usually more prominent in the basal cells of the rete pegs than in those of the flattened epidermis (fig. 16, p. 71). The pigment, which formed 'caps' above the nuclei, was sometimes also seen in the overlying cells and the stratum, corneum (as occurs in normal Negroids). The basement membrane of both the epidermis and the vessels was thickened. The capillaries were dilated. The collagen in the dermis showed solar elastosis in the upper and mid-dermis, the elastotic fibres were fine and degraded,

Figure 14

Close-up of dendritic freckles on the cheek ie. irregular, branched, pigmented macules.

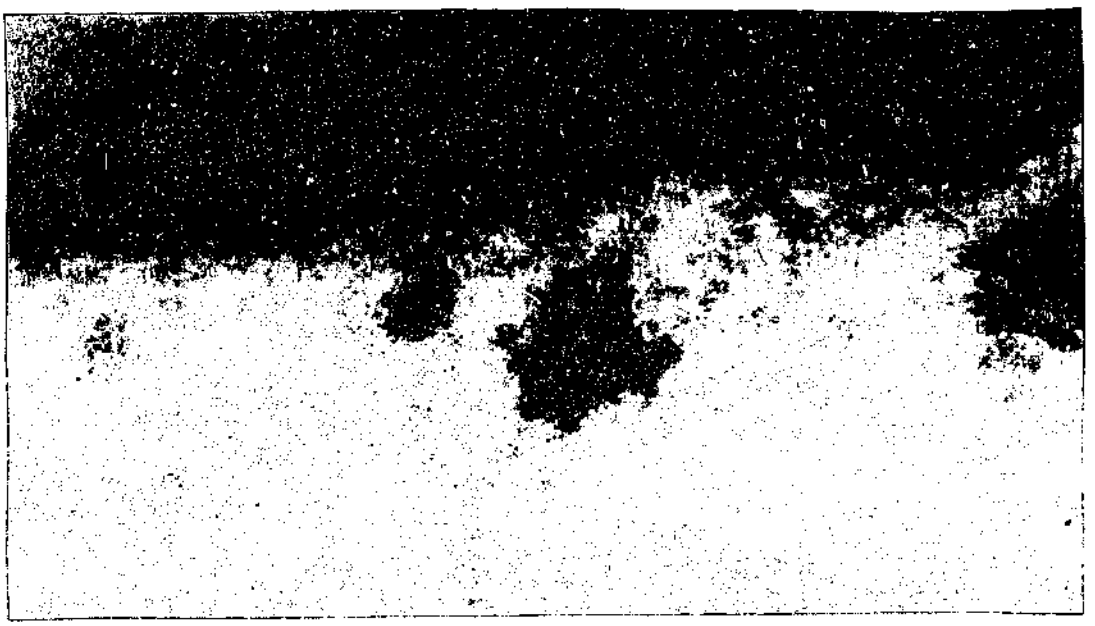


Figure 15

Close-up of dendritic freckles on the arm.



whereas deeper in the dermis they were coarse and thick. Elastic von Gieson staining confirmed the elastotic degeneration (fig. 16, p. 71). In 2 cases, the elastotic material had become homogeneous in parts, resembling colloid milium in one case (fig. 17 and 18, p. 71 & 72).

Electron microscopically the freckle showed eumelanosomes up to stages III and IV of melanisation in both the melanocytes and the keratinocytes. In the melanocytes, the melanosomes lay singly, whereas in the keratinocytes they were single or grouped. The melanocytes showed signs of activity in that they had a prominent Golgi apparatus and en mic reticulum.

3. Sun Damage

Sun damage was evidenced by the presence of solar elastosis, solar keratoses and skin cancers. All albinos showed solar elastosis. Solar keratoses were found in 50% of the freckled and 73% of the non freckled albinos. The keratoses increased with age (Spearman's correlation coefficient = 0.503 p=0.009). Five albinos (8.2%) had squamous cell carcinomas, 3 in non-freckled and 2 in freckled albinos.

There was no correlation between the number of naevi and the number of keratoses, (Spearman's correlation coefficient = 0.27 p = 0.03) nor between the numbers of the freckles and the

Figure 16

Elastic von Gieson stain of a biopsy of a dendritic freckle showing rows of melanised cells, dilated capillaries and degraded elastotic fibres.

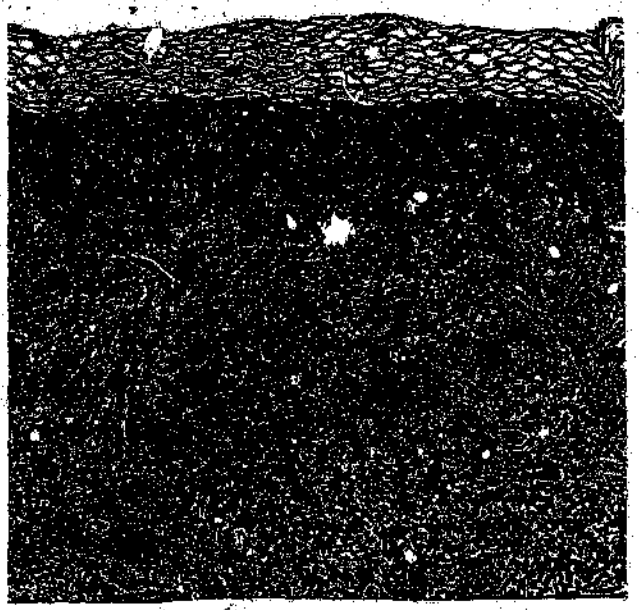


Figure 17

Haematoxylin-eosin stain showing othokeratosis, elastotic collagen and colloid milium-like changes.



Figure 18

Higher power view of elastotic degeneration.



number of naevi (Spearman's correlation coefficient = 0.21, p=0.38). There was no correlation between the number of keratoses and the number of freckles (Spearman's correlation coefficient = 0.06 p=0.84).

4. Ultrastructure of Melanosomes in Albinos

The findings of the present study are summarised in table 7, page 74. Our findings compared to previous studies of melanosomes in normal individuals of different races and in albinos.

In tyrosinase positive albinos stages II and III eumelanosomes were found in the hair bulbs, and stage I eumelanosomes in the skin (figs. 20 & 21 p. 76). The eumelanosomes lay singly in the melanocytes and were both single and in groups in the keratinocytes.

In the rufous albinos eumelanosomes in stages II and III were found in the hair bulbs and in stages III and IV in the skin (figs. 22 & 23, p. 77). They lay singly in the melanocytes and mainly in groups in the keratinocytes. In the red-haired Caucasoid hair bulbs, both eumelanosomes and phaeomelanosomes were found, the former with an internal structure and smooth border, the latter without an internal structure and with a more irregular border (figs. 24, 25 & 26, p. 78 & 79). In the skin only eumelanosomes up to stage II were seen.

Table 8. MELANOSOMES IN NORMAL INDIVIDUALS AND ALBINOS

	SKIN		HAIR	
	MELANOCYTE	KERATINOCYTE	MELANOCYTE	KERATINOCYTE
NORMAL CAUCASOID				
Brown-haired	I - III (a,b,c,)	Eu II - III, some IV aggregates (a,b,c) in basal layers	Eu I - III some IV (e,i)	Eu III - IV single, grouped moth-eaten (e,i)
Blond	Eu I - II (a,b,c) smaller, fewer	Eu II (a,b,c) fewer, aggregate	Eu I - II (e,f)	Eu I - II fewer single or grouped (e,f)
Red-haired	Eu I-II (a,b,c,k) smaller, fewer	Eu II (a,b,c,k) some aggregates	Eu + Ph (d,e,f,j) II - III	Eu + Ph I - III some degraded (d,e,f,k)
NORMAL NEGROID				
	Eu I - III (a,b,c)	Eu III - IV single: extend to stratum corneum (a,b,c)	Eu I - IV (e,i)	Eu III, IV single grouped (e,i)
TYROSINASE POSITIVE ALBINO				
American Negroid	Eu I - III (g,h)	Eu II - late III (g,h,)	Eu I - II (g,h)	Eu II - III Single (g,h)
Japanese		Eu II, III (j)		
S African Negroid	Eu I (k)	Eu II single, scanty (k)	Eu I - III single (k)	Eu II - III single or grouped (k)
YELLOW MUTANT ALBINO				
Japanese	Eu I - III (f)	Eu II - early III (f)	Eu + Ph (f)	Eu (f)
RUFOUS ALBINO				
American Negroid				Ph (g)
S African Negroid	Eu I - III (k)	Eu III, some IV (k) single or grouped	Eu I - III (k)	Eu II - III (k) single or grouped

Sources :

(a) Quevedo et al (1986)
(b) Rosdahl and Szabo (1976)
(c) Szabo et al (1969)
(d) Jimbow et al (1983)
(e) Birbeck and Breathnach (1952)
(f) Hu et al (1980)
(g) Witkop (1989)
(h) Witkop et al (1973)
(i) Jimbow and Kukita (1970)
(j) Akiyama et al (1992)
(k) Bothwell (1992) Present study

Figure 19

Ultrastructure of a normal hair bulb with melanocytes in the matrix.



Figure 20

Stages II and III eumelanosomes in the hair bulb of a tyrosinase positive albino.



Figure 21

Stage I microvesicles in the skin of a tyrosinase positive albino.



Figure 22

Stages II and III eumelanosomes in the hair bulbs of a rufous albino.

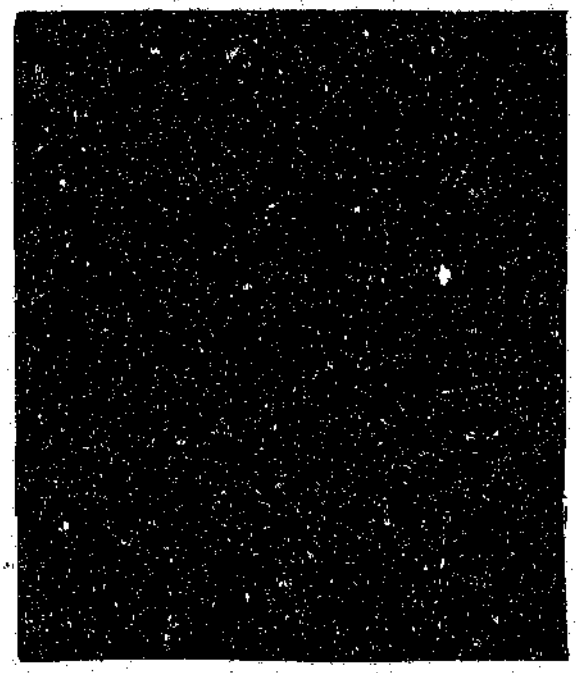


Figure 23

Stages III and IV eumelanosomes in the skin of a rufous albino.

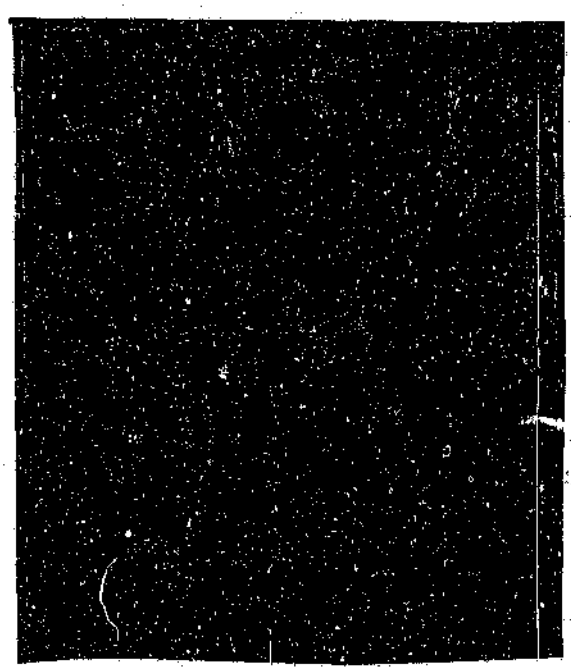


Figure 24

Stage III phaeomelanosomes with an irregular border and no internal structure in the hair bulb of a redhead.



Figure 25

Stages II and III eumelanosomes with a smooth border and internal lamellae in the hair bulb of a redhead.

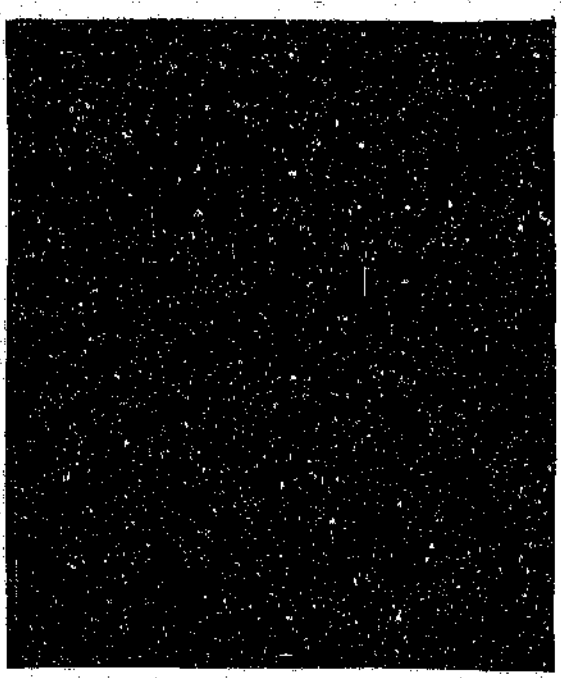
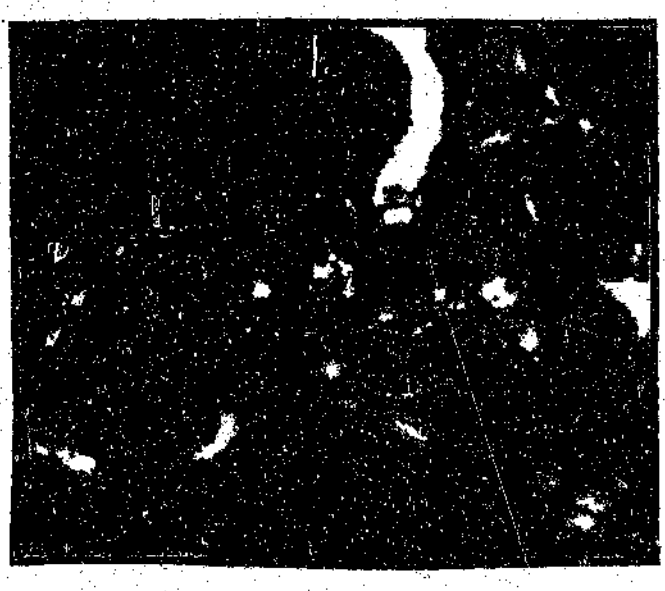


Figure 26

Phaeomelanosomes and eumelanosomes lying next to each other in the hair bulb of a redhead.



DISCUSSION

1. Clinical Features

Tyrosinase positive albinism is the commonest form of albinism with variable clinical features. Although the tyrosinase test [Kugelman & van Scott (1960)] was not done for the purpose of this study, this test had been done previously on most of our cases by Kromberg and coworkers during previous investigations of the same group of albinos [Kromberg et al (1989)]. The clinical features of our South African Negroid tyrosinase positive albinos have been described previously by Kromberg and Jenkins [Kromberg & Jenkins (1982)]. Our tyrosinase positive albinos are similar in appearance to American Negroid tyrosinase positive albinos. In the younger albinos some pigmentation is present in the skin and hair and increases with age, probably in response to exposure to ultraviolet light [Witkop et al (1983)].

Rufous albinism is uncommon and has previously been described in Papua New Guineans, [Walsh (1971)] American Negroids [Witkop (1989), Witkop et al (1973)] and African Negroids. [Barnicot (1952), Kromberg et al (1990), Loewenthal (1944)] In the classification of albinism by Witkop they are described as having mahogany-brown skin and mahogany to sandy-red hair [Witkop et al (1983)]. The rufous albinos in New Guinea have

light brown hair and red-tinged skin. [Walsh (1971)] The skin and hair colour of our rufous albinos resemble those in Africa more closely than those in New Guinea. In our albinos the hair was lighter than the skin whereas in New Guinea the hair varied from light to dark but was always darker than the skin [Walsh (1971)]. Although they have been described as having lentigines, [Loewenthal (1944)] naevi and freckles, [Barnicot (1953), Witkop et al (1983)] our rufous albinos demonstrated only naevi.

2. Pigmented Lesions

i. Naevi

In normally pigmented people, the number of naevi varies according to race, age, degree of sun exposure and skin colour. [Fitzsimmons et al (1984)] The number of naevi per person is fewer in Negroids than Caucasoids. [Nicholls (1973), Rampen & de Wit (1989)] Nicholls found the average mole count in Australian Caucasoids to be 15 per person; [Nicholls (1973)] Fitzsimmons found 15 in British Caucasoids; [Fitzsimmons (1983)] Coleman and coworkers found 2 to 8 moles in American Negroids; [Coleman & Gately (1989)] and Lewis 11 in Ugandan Negroids. [Lewis & Johnson (1986)] Rampen and De Wit found 17 naevi per person in white adults compared to 2.5 in non-whites and that as pigmentation darkens from white races through those of mixed, oriental and Negroid descent, the number of naevi decreases [Rampen & de Wit (1989)].

The albinos examined in this study were racially Negroid, yet clinically pale. [Rampen & de Wit (1989)] It was noted that the number of naevi they demonstrated was high, ie. more like that in fair-skinned races than in dark races. There was also an earlier peak age for naevi in albinos than in the control Negroids ie. the peak age was closer to that in Australian Caucasoids than in our control Negroids. [Fitzsimmons et al (1984)]

It has been postulated that sun exposure induces the formation of naevi. Naevi can develop suddenly after exposure to the sun. Nicholls has proposed that men develop more naevi on the trunk and women on the legs, because most intermittent sun exposure occurs at these sites in the different sexes. [Nicholls (1973)] The effect of the sun on a pale skin might explain the increased numbers of naevi per person in albinos and the earlier peak age for naevi in the albino population.

ii. Lentigines

Simple and solar lentigines have different clinical and histological features. It ma impossible to differentiate simple lentigines from naevi on clinical grounds since naevi initially also present as pigmented macular lesions and neither doctor nor patient willingly submits these lesions to biopsy. The skin creases are irregular in some naevocellular naevi,

[Nicholls (1973), Rhodes (1987)], but this distinction may be unreliable. According to MacKie, simple lentigines are early stages of melanocytic naevi [MacKie (1986)] and we therefore felt justified in classifying all flat, non-infiltrated pigmented macules as naevi. All the biopsies taken from lesions with this clinical appearance in our study were naevi and not simple lentigines.

King and coworkers described the pigmented lesions found in sun-exposed areas of tyrosinase positive albinos as 'freckles and lentigines', the freckles being round, lightly pigmented macules and the lentigines 'irregularly shaped, deeply pigmented macules with a serpiginous border'. [King et al (1985)] Their description fits best with the appearance of a solar lentigo. However, the type of lentigo is not specified and no histology is reported.

The dendritic sun-induced lesions in albinos are obviously not simple lentigines which are never branched and show only an increase in the number of melanocytes on histological examination. The pigmented lesions found in sun-exposed areas in albinos resemble solar lentigines in that both develop on sun-damaged skin and may have a reticulate border. Solar elastosis is present in both and down-budding of the epidermis is occasionally found in albinos' sun induced lesions. In the albinos lesions there is no increase in the number of melanocytes as found in solar lentigines.

We decided that the term 'dendritic freckle' as used by Findlay [Findaly (1960)] describes the sun-induced lesions found in tyrosinase positive albinos best.

iii. Freckles (Ephelides)

In normal fair-skinned individuals freckles or ephelides are small, round to oval pigmented macules which bear no resemblance to the irregularly shaped, filigree lesions in albinos alluded to in many previous reports. Reports in the literature concerning the sun-induced macules in albinos are confusing as they have been referred to as freckles [Barnicot (1953), Witkop (1985)], ephelides [Kromberg et al (1989)] or lentigines [King et al (1979), Witkop (1985)]. (See Section I, p. 3)

In 1952, Barnicot recorded the occurrence of pigmented macules with ragged or concave edges in sun exposed areas in tyrosinase positive Nigerian Negroid albinos [Barnicot (1952)]. He called them 'freckles' and noted that they increased in number with age. Biopsies showed increased pigmentation of the melanoblasts with 'capping' of pigment in the basal epidermal cells.

In 1962 Findlay called the sun-induced pigmented macules found in South African Negroid albinos 'dendritic freckles' [Findlay (1962)]. The term is descriptive of the lesions viz. 'spots' that vary from sparsely distributed lesions of 3mm to large arborizing filigree patterns of 30mm in diameter, varying in colour from yellow to dark brown. Histologically they showed normal numbers of melanocytes, but increased melanin in rows of basal cells alternating with unpigmented cells. The pigment was particularly prominent at the bases of the rete pegs. The epidermis was flattened in parts and showed marked solar elastosis in the upper and reticular layers of the dermis at the edges of the freckle [Findlay (1962)].

Our cases showed identical clinical features to Findlay's dendritic freckles. Histologically our findings were similar to his, the only difference being the hyperkeratosis which was marked in our cases and the down- udding of the epidermis seen in most of our cases. Findlay postulated that the melanocytes of a freckle were more capable of responding to the stimulation of the sun. He showed that grafting or irradiating the skin destroyed the melanocyte's ability to produce melanin [Findlay (1962)].

In 1978 Tsuji and Saito noted 'miliary brown macules in sun exposed areas', which they termed 'ephelides' in Japanese

tyrosinase positive albinos. A large amount of melanin was present in the epidermal basal layer without an increase in melanocytes [Tsuji & Saito (1978)]. In 1985 King et al referred to 'round lightly pigmented macules' in tyrosinase positive albinos, as 'freckles' and described 'lentigines' as 'irregularly shaped, deeply pigmented macules with a serpiginous border' [King et al (1985)]. These 'lentigines' are identical to Findlay's 'dendritic freckles' and the lighter pigmented lesion may correspond to freckles at an earlier stage of development. In 1985 Witkop called the pigmented lesions found in sun exposed areas of tyrosinase positive albinos 'goosefoot lentigines'. He also mentioned 'freckles' without describing them [Witkop (1985)]. In 1989, Kromberg and coworkers described 'pigmented large spidery freckles' in tyrosinase positive albinos which were obviously the same as the 'dendritic freckles'. They called them 'ephelides'. The problem may have been that Findlay's work was published in an obscure South African journal and therefore not read by later authors.

The dendritic freckles are similar to both solar lentigines and freckles but with a unique clinical and histological appearance and therefore are a separate entity.

In 1989 Kromberg found that 61% of Negroid tyrosinase positive albinos in Johannesburg had 'ephelides', which clinically were the same as the dendritic freckles [Kromberg et al (1989)]. In the present study in 1991 we found that 43% of the same population had dendritic freckles. This difference may be explained by the fact that these albinos had been using sunscreens regularly in the interim. Kromberg and coworkers investigated the significance of these lesions and reported that albinos with 'ephelides' developed fewer solar keratoses and unspecified 'chronic superficial ulcers' (73% compared to 33%) [Kromberg et al (1989)]. This was confirmed in our study in which 50% of albinos with dendritic freckles developed solar keratoses compared to 73% of those without them. We conclude that the presence of dendritic freckles is indicative of the ability to develop some pigmentation in sun exposed areas and that this seems to provide some protection against sun damage.

These clinical observations can be correlated to genetic findings in tyrosinase positive albinos with 'dendritic freckles'. Studies by Ramsay and coworkers have shown that the tyrosinase positive oculocutaneous locus was linked to loci DI5S10 and DI5S13. They postulated that the p locus which is reponsible for production of decreased eumelanin may be homologous to the tyrosinase positive locus. One allele, p^{un} produces dilute and intense pigmentation, the latter resulting from somatic reversion to the wild-type form. The appearance of mice with p^{un}/p^{un} resembles tyrosinase positive albinos

with 'dendritic freckles' and a similar allele may exist in these albinos [Ramsay et al (1992)].

iv. Palmoplantar pigmentation

Previous reports showed that 60% of normal South African Negroids have palmoplantar pigmentation [Freinkel & Rippey (1976)]. In our study 75% of the Negroid controls demonstrated this pigmentation, but none of the albinos. It is of interest that although tyrosinase positive albinos are capable of producing pigment in the form of pigmented naevi and dendritic freckles, none showed palmoplantar pigmentation. In 1967 Lewis showed that racial groups with the highest numbers of palmoplantar lesions also had the greatest number of melanomas, mainly confined to the palms and soles. He postulated that the melanomas were derived from these pigmented macules [Lewis (1967)]. If this is true, the absence of palmoplantar pigmentation in the albinos may be one of the reasons for the infrequent development of melanomas in albinos as compared to the normal black population [Rippey & Schmaman (1972)].

3. Sun Damage

The pale skin of the albinos showed an expected increase in sun-related damage increasing with age. All showed marked solar elastosis even the youngest of 8 years. A greater

percentage of solar keratoses was found in non-freckled than in freckled albinos (see p. 66).

4. Ultrastructure

Eumelanosomes are found in all individuals irrespective of colour; phaeomelanosomes are found in addition in redheads and certain types of albinism i.e. yellow mutants, rufous albinos and in the Hermansky Pudlak syndrome. Variations in skin and hair colour depend on the type and size of the melanosomes, the degree of melanisation and state of aggregation of melanosomes [Quevedo et al (1986)]. Our South African Negroid tyrosinase positive albinos who are are similar in clinical appearance to American Negroid tyrosinase positive albinos reported by Witkop show similar electron microscopic findings, differing only in that melanisation in the skin was slightly more advanced in Witkop's series [Witkop et al (1984)].

The reddish tinge seen in rufous albinos has previously been accounted for by the presence of phaeomelanosomes [Witkop (1989)]. Hu and coworkers found incompletely melanised eumelanosomes and phaeomelanosomes in the hair bulbs of Japanese yellow mutants [Hu et al (1980)]. Witkop and

coworkers described the same features in the Hermansky Pudlak syndrome [Witkop et al (1983)]. The melanosomes in all these albinos resemble those found in red-haired Caucasoids.

Our rufous albinos had reddish skin and hair. It was previously reported that phaeomelanosomes occur in South African rufous albinos [Kromberg et al (1990)], but this could not be confirmed in the present study in which re-examination of the same hair bulbs and skin biopsies failed to confirm the presence of phaeomelanosomes. Only eumelanosomes were found in the skin and hair of our rufous albinos. The presence of eumelanin without phaeomelanin does not explain the distinctive reddish tinge seen in our rufous albinos. Perhaps the explanation could lies in the presence of mosaic forms [Jimbow et al (1983)] or alternatively our so-called rufous albinos may form a separate genetic entity in which the reddish colour is due to incomplete melanisation of eumelanosomes.

CONCLUSION

Clinically South African Negroid tyrosinase positive albinos resemble Negroids elsewhere in the world with the same disorder. One of the main purposes of this study was to record the presence of pigmented lesions in our tyrosinase positive albinos.

Pigmented naevi were found in 80% of tyrosinase positive Negroid albinos and 70% of normal blacks and the mean number per person was 12 and 17 respectively. The trunk was the main site involved in both groups. Dendritic freckles were found on sun-exposed parts in 43% of the albinos. These were distinguished by their irregular, branched shape, light to dark brown colour and large size (0.5 to 3cm). Clinically and histologically they are unique. Solar keratoses occurred more frequently in albinos without freckles (73% versus 50% in those without) confirming the sun- protective role of the increased ability to form pigment in this group. Genetically this group may have a p^{un}/p^{un}-type allele at the p locus which could cause a reversion to pigment production. There was no correlation between the number of naevi and the number of keratoses. Racially determined palmoplantar pigmented macules were found in 75% of normal controls and in none of the albinos.

In the skin of tyrosinase positive albinos eumelanosomes were found in stages I to II, singly in the melanocytes and singly or in groups in the keratinocytes. In the hair bulbs these melanosomes were found singly or grouped in stages I to late stage III. The findings in our tyrosinase positive albinos showed that the melanosomes of the hair bulbs were identical to other reports, but those in the skin were slightly less melanised.

South African rufous albinos look more like rufous Nigerians than Papua New Guineans.In the skin of rufous albinos, eumelanosomes were found singly in the melanocytes in stages I to IV and singly or in groups in the keratinocytes in stages III and IV. In the hair bulbs only eumelanosomes in stages I to early stage III were seen singly and in groups. Our rufous albinos may be a distinct genetic entity since they failed to demonstrate the phaeomelanosomes found previously in rufous albinos.

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