Disorders of pigmentation of the skin – hypotheses underlying interventions by multiple systems of medicine: is there a role for integrated medicine?

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Biomedicine has not provided a complete explanation with fully effective therapies for disorders of pigmentation. Biomedicine emphasizes the role of melanocyte for protection from UV rays and as a determinant of skin colour. These important properties acquired a genetic basis much later than other functions, many relating to cell contact as in the keratinocyte – melanocyte unit, or as with the synapses of the neurological system. There are other roles, biochemical and mechanical, of melanocyte. Management that is inclusive of a maximally holistic approach justifies the use of diverse herbals, yoga and concern for cultural awareness provided by integrated medicine. Vitiligo provides a model which demonstrates that Ayurveda has a richer view of its presentations, possibly a stronger line on its pathogenesis, and a huge range of herbals, many now backed by studies from ethnobotanical laboratories, awaiting research into the many possible mechanisms by which they may act in the wide and complex field of melanocyte biochemistry.

Keywords: Albinism, defensins, melanaocyte, melanin.

Introduction

THE colour of the skin depends on pigments. The two most significant pigments are melanin and haemoglobin. Colours attributed to human skin and hair are 'red', 'ginger', 'blond', 'black',' brown', 'white', 'red', 'yellow', 'pink' or 'blue'. There are also clinical terms associated with colour such as jaundice, bronzed diabetes and cyanosis.

In this article, we discuss only melanin and ignore pigmented naevi and melanoma, except where they inform us about the properties of melanin. Since melanin is found in many internal organs and this may indicate its function, we will not confine ourselves to the skin alone.

The genetics underlying race is the most important determinant of colour. There are diseases such as that those described by Addison and Cushing which stimulate pigmentation. The most important environmental cause of skin darkening, also known as tanning, is UV exposure either from the Sun or from the artificial sunlight of the 'tanning bed'. Skin lightening from topical depigmenting agents is also discussed here.

Complementary, alternative and traditional medicine lack the evidence of effectiveness and the understanding of mechanisms that biomedicine can provide. Together with homoeopathy they collate answers to questions about beliefs, cultural practices and the environment in which a patient lives.

As the cause of disorders of pigmentation is often largely unknown, integrated medicine has a valued place as an intervention. In the case of vitiligo or melasma, there is no certainty about causation. Neither the favoured hypotheses, nor the leading biomedical therapies are convincingly supported by proof of aetiology or freedom from adverse reactions.

Disorders of pigmentation

Fundamental to understanding the major disorders presenting as hyper- or hypo-pigmentation, is the relationship between keratinocyte and melanocyte. The disorders and relationship are discussed in detail in several contemporary textbooks[1–5]. Our concern, which led us to put forward a hypothesis[6,7], is that too much attention is given to the influence of sunlight, which in evolutionary terms became well used when man became hairless and more exposed. Whereas millions of years earlier primitive organisms found uses for melanin unrelated to sunlight such as the role of tyrosinase in the production of dopamine, acting to safeguard contact between unicellular organisms, many millions of years earlier[8]. There has also been the recent observation of the presence of melanin as a virulence factor in *Vibrio cholera*[9]. Melanocyte manufactures melanin and transfers it to keratinocyte, and in hyperproliferative states in which the keratinocyte is exfoliated taking melanin with it. Loss of melanin in this way is one cause of depigmentation, as in pityriasis alba or psoriasis. We suggest that these may provide a useful point of intervention in

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important diseases such as albinism, piebaldism, vitiligo and melasma.

Albinism is a disease where the relationship between melanocyte and keratinocyte is intact, but pigment production is impaired. Consequently, a person affected by albinism can live a full lifespan without major skin defects. Of course, there is the well-known high prevalence of skin cancer but with protection against the Sun, this is not inevitable. In piebaldism, the skin is deprived of the entry of melanocytes from the neural crest, but like albinism this is only because of Sun sensitivity. Vitiligo is an acquired loss of melanocytes in which the relationship between the keratinocyte and melanocyte is defective.

'Hypomelanosis' is a term used to describe skin in which there is lack of pigment and which therefore appears lighter than the normal skin colour, while amelanosis describes skin with total lack of melanin. Depigmentation, however, is a more specific term that implies loss of pre-existing pigment from the skin. An example of this distinction is albinism, which is a condition of absent melanosis, but not one of depigmentation.

Arianayagam and Ryan[6,7] hypothesized that the attachment processes of melanocyte to keratinocyte and the affinity to elastin as a pathway through the upper dermis, are key to a role originating as a neural crest cell required for the control of tissue shape and size. They emphasized the role of grip and stick and the importance of an inhibitor of plasminogen activator produced by keratinocyte to the affinity of the protease-producing melanocyte for keratinocyte and for affinity to elastin, and for the relationship with the basement lamina. Chung *et al.*[10] found that production of laminin-332 by keratinocyte is essential for the adhesion of both keratinocyte and melanocyte to the basement lamina. McClenic *et al.*[11] showed that both fibronectin and laminin have a role for grip and stick, but the various contributors were sufficiently different to give each cell some independent behaviour. It is a concept that increasingly fits current views of diseases such as vitiligo. Hirobe[12] reviewed just how complex and numerous are the co-factors by which keratinocyte interacts with melanocyte. Moretti *et al.*[13] showed that keratinocytes in vitiligo manufacture more mRNA for tumour necrosis factor (TNF)-alpha and interleukin-6 (IL-6) and it is this that contributes to loss of melanocyte affinity for keratinocyte. The opportunity for proteases to play a role is obvious. It is discussed by Lee[14], while exploring another influence, PI3K/AKT and E-cadherin-catenin complex.

The ratio of keratinocyte melanocyte has long been of interest, since a single melanocyte can attach to many keratinocytes. In culture, the ratio determining effective grip and stick and their role in the wound-healing processes appears to be at least five keratinocytes to one melanocyte and, the more the better. Healing is initiated by keratinocyte followed later by melanocyte[15].

According to Arianayagam and Ryan[6,7], skin temperature should not be ignored as cooling clearly plays a role in determining loss of pigment. As will be discussed below, pH and transepidermal water loss are also determined in part by the melanocyte/keratinocyte interaction.

Vitiligo

Vitiligo is one of the most well-known conditions of skin depigmentation. It is estimated to occur in up to 2% of the world's population[16]. The incidence of the disease is higher in those with racially pigmented skin, where the social and psychological impact is also greater. Genetic factors are involved, and between 30% and 40% of patients have a family history of the condition[16]. It is thought that the inheritance is either polygenic or autosomal dominant with variable penetrance of the gene. Histologically, there is absence of melanocyte in the epidermal layer of the skin[17]. Early studies by electron microscopy suggested that the melanocytes appear to be replaced by Langerhans cells[18–20]. The skin of vitiligo has more mast cells and according to Schallreuter's[21] long-standing explanations of vitiligo, it has higher levels of norepinephrine, presumably derived from dopamine with an influence on grip and stick, as discussed by Arianayagam and Ryan[6]. It has gradually become a contemporary hypothesis that the skin is a neuroendocrine organ[22].

Vitiligo melanocytes do not grow well in culture, have ultra structural defects and, according to Jimbow *et al.*[23], have stubby dendrites. Kumar *et al.*[24] correlate this with impaired expression of matrix metalloproteinase-2, needed for detachment and degradation of denatured collagen and collagen types IV, V, VII, IX and X. It plays a role in migration through laminin. They also postulate that the transcription factor Ets-1 is involved and that it is absent in vitiligo skin samples[24].

There are three main biomedical theories for the aetiology of vitiligo: the autoimmune hypothesis, the neurogenic hypothesis and Lerner's self-destruct hypothesis. Indian and Chinese systems of medicine add other theories to back both diagnosis and intervention for the conditions of vitiligo and melasma. They identify imbalance, reactions to injury, impaired immunuosurveillance, poor general health, heat or cold and stagnation, environmental factors such as sunburn and any factors contributing to unhappiness. They use emesis, purgation and blood letting as interventions.

The autoimmune hypothesis

Although vitiligo can develop at any age, around half of cases occur before 20 years of age, unlike most other autoimmune diseases and age-related pathologies in general. The condition progresses over time and may rapidly extend and then become quiescent for many years.

However a number of observations support the theory that vitiligo is an autoimmune disease. First, it has a

strong association with other autoimmune conditions such as pernicious anaemia, Addison's disease and type-1 diabetes mellitus, and auto antibodies to thyroid, gastric parietal cells and adrenal tissue are found in the serum of patients with vitiligo more often than in the general population[25,26]. A feature of autoimmune disease is DNA methylation, which can be observed in peripheral blood mononuclear cells. This has been shown to occur in vitiligo too[27]. Vitiligo is also associated with the major histocompatibility antigens typically seen in autoimmune diseases. T-cell profiles have been shown to be abnormal in patients with vitiligo. There are increased TNF-alpha and IFN-gamma levels, with a reduction in T-helper cells[28–30]. More recently, the promising response to the macrolide immunosuppressant tacrolimus, has given support to the immune theory[31]. Tacrolimus suppresses Th1, which is believed to effect melanocyte damage, and this suppression may be mediated by IL-10, which is raised in the skin after the repigmentation seen with tacrolimus therapy[32]. The interaction between melanocytes and keratinocytes may also play a part. The supernatant of keratinocytes treated with tacrolimus stimulates melanocyte growth[33]. Since this theory depends on the release of antigen, some interventions might be focused on protection. The various ways, in which the Sun can be used both to initiate vitiligo, since exposed areas are most often affected, as well as to treat it, adds to the difficulty in rationalizing an approach to the use of this intervention. Repigmentation first occurs from the pigmented melanocytes in the hair follicle, and later from amelanotic cells therein. In vitiligo, it is the pigmented cells that are destroyed first while amelanotic cells are destroyed last. However, it is believed that once these are damaged, there can be no recovery[34].

The story of an immune response to pigmentation was strengthened when antibodies shared with melanoma and vitiligo were detected to play a role in halo naevi. It has been recently claimed that segmental vitiligo is capable of converting to segmental mixed vitiligo when associated with halo naevi or depigmented hair[35]. The autoimmune hypothesis has to be discussed in the context of the Sun and immunity. Longwave UVA, including PUVA and climatotherapy at the Dead Sea, both used to treat vitiligo, are believed to be immunosuppressive. Chronic immunosuppression is linked with non-Hodgkin lymphoma. There is also a hypothesis that solar radiation increases the risk of non-Hodgkin lymphoma[36]. Why then is there a suspicion that non-Hodgkin lymphoma is rare in albinism?

No one doubts that melanocyte is destroyed in vitiligo. Damage initiates an immune response. The doubt must be that autoimmunity is not primary but inevitable once melanocyte is injured. Whether primary or secondary, it offers a point of entry for interventions aimed at immunity. The extent to which integrated medicine acts by adding controls to immunity is a topic for debate.

The neurogenic hypothesis

This theory suggests that a substance released by peripheral nerve endings in the skin could inhibit melanogenesis and have toxic effects on melanocytes. There is not a great of deal of support for this hypothesis despite the fact that vitiligo lesions are usually symmetrically distributed, but may be unilateral or in a dermatomal distribution, or not appear below a transverse myelitis[37]. However, there is more recent evidence that neuropeptide Y may have a role in the aetiology of vitiligo[38]. Dopamine may also be a candidate, as emphasized by Arianayagam and Ryan, for it shares a tyrosine pathway with melanin and also plays a role in mechanisms of grip and stick and synapse formation, allowing contact between cells without consequent phagocytosis.

Lerner's theory of self-destruction

Lerner[16] suggested that melanocytes destroy themselves as a protective measure to remove toxic melanin precursors. He based this theory on studies of skin depigmentation by chemical compounds that have a lethal effect on functional melanocytes[39]. Levels of superoxide dismutase, glutathione peroxidase and malondialdehyde are significantly increased in vitiligo skin[40], thus strengthening the concept of free-radical damage. Hazneci *et al.*[41] also found evidence in support of oxidative stress in vitiligo.

However, known low catalase levels in vitiligo have not resulted in effective catalase creams. Vitiligo and autoimmunity may be influenced by vitamin D and a recent Chinese study documents low levels of 25-hydroxy vitamin D in vitiligo[42]. Treatment with calcipotriol is a reminder of the role of vitamin D precursors $1,25(OH)_2D$, which even 500 million years ago protected primitive cellular organisms from environmental hazards, including ionizing and UV-irradiation, microbial infections and oxidative stress[43]. Melanocyte is one of the many cells capable of vitamin D precursor production, a phenomenon activated by sunlight and known to inhibit the maturation and differentiation of dendritic cells.

When comparing the response of skin affected by vitiligo to contra lateral unaffected skin using tape stripping, Liu *et al.*[44] found that barrier recovery was delayed in vitiligo as measured by transepidermal water loss. This would be a failure of the main function of keratinocytes and supports the view that for vitiligo, we must examine the keratinocyte.

A role for damage by free radicals allows an explanation as to why in integrated medicine herbals such turmeric and other antioxidants are so popular.

Clinical features[16,45]

The most prevalent hypopigmented skin disorder is Vitiligo. Its clinical features have been well described in

major texts[16,45]. Surprisingly, regions that are typical sites for amelanotic macules are those that are usually hyperpigmented such as axillae, groins, areolae and genitalia. These are normally protected from the Sun. They are also at a temperature nearest 37°C. It is therefore surprising that the first presentation of this condition is usually as hypomelanotic macules in Sun-exposed skin such as the back of the hands or the face. These areas are at a reduced temperature of around 30°C. Due to loss of melanin, these areas are particularly prone to sunburn. Puzzlingly, induction of mild sunburn is also a therapy. Skin sites exposed to the Sun are also exposed and suffer from repeated friction and trauma, which are also known to initiate vitiligo. Sometimes itching may occur in these areas, without sunburn. This is regarded as an indication of 'heat' in Asian systems of medicine and requires different therapies to other patterns of vitiligo. There is a need for more studies of linkage and especially to other pathologies less frequent in such sites, such as leprosy and melanoma. The involvement of the electromagnetic spectrum is discussed in Arianayagam and Ryan[7]. The macules enlarge and coalesce to form complex patterns. It is often the case that the hairs within the patches retain their pigment, but they too can become amelanotic in older lesions. It is sometimes the case that the margins of the lesion become hyperpigmented.

Spontaneous repigmentation is seen in between 10% and 20% of patients, and is most frequently seen in Sun-exposed areas. This repigmentation is mainly perifollicular and is usually not of great clinical significance. Evidence is provided that repigmentation comes from surviving melanocytes in the hair follicle or dermis, and in adjacent normal skin, but when the rare case of generalized vitiligo repigments, this is less easily explained. The major symptom of vitiligo is cosmetic disability, but sunburn in the amelanotic areas may also be a presenting feature. Unlike albinism, malignancy is very rare. Patients with vitiligo have poor body image, low self-esteem and social isolation caused by feelings of embarrassment.

Treatment

In general, treatment is aimed at speeding up melanin production in an even distribution, and reducing loss. Treatment is largely unsatisfactory and most patients are advised to use cosmetic camouflage for lesions on Sun-exposed skin. Those who attend for camouflage are frequently desperate and in despair that no cure is on offer. Giving them the tool of camouflage which is time-consuming and tedious to do well, often dissolves their anger and they learn to live with their condition knowing they have camouflage in reserve. Sunscreens are of use in sunny climates.

A public health approach must examine stigmatization in vitiligo more thoroughly compared to other stigmatizing disease. Thompson *et al.*[46] see a need in the UK for remedying, especially in Asian women, spoiled identity and being shame-prone with more attention to cultural sensitivity and intergenerational beliefs.

There is a significant and long history of the use of psoralens from several herbals used in Indian and Chinese systems of medicine. Systemic psoralens in combination with sunlight or ultraviolet light sources are effective in some cases[47,48]. These therapies are usually continued for at least six months and are sometimes used for several years. In most patients, the lesions retain pigment long after the psoralen treatment is stopped. The compound khellin, a less toxic photosensitizer than psoralen, can be used with UV[49].

Narrow-band UVB phototherapy has been used, and is safe and effective for vitiligo[50]. Removing the epidermis by laser dermabrasion significantly improves the repigmentation rate. This is possibly due to greater penetration of the UVB to deeper stem-cell melanocytes[51]. However, it would also remove a significant source of plasminogen activator inhibitor-1 (PA1). Wu *et al.*[52] argue that PUVA acts by being immunosuppressive, while NB-UVB repigments by acting through matrix metallopeptidase-2 effects on migration. Ryan and coworkers argue that control of proteases by plasminogen activator inhibitor, which is released from the epidermis by UVB exposure, is part of the story[53,54].

Climatotherapy at the Dead Sea also reduces UVB and provides substantial UVA, shifting the balance towards protease activation. It is recommended as effective with few side effects[55]. Potent topical corticosteroids, for example, 0.1% betamethasone valerate, are effective in producing repigmentation in areas of vitiligo, but do carry the risks of some skin atrophy[56]. They are also used as skin lightening agents. If the vitiligo is extensive and only a few patches of pigmented skin remain, skin-bleachers such as hydroquinone can be used[57]. Grafting techniques, minigrafts and autologous melanocyte culture have garnered some interest, but these may be limited by the Koebner phenomenon[58–60].

Oculocutaneous albinism

Oculocutaneous albinism (OCA) is a group of genetic disorders in which there is a generalized lightening of the skin and hair. Albinism was the first mammalian trait to be analysed for Mendelian inheritance[61] and contemporary pigmentation genetics is rich in gene discovery literature, including more than 200 concerning albinism. It tells us that genes involved in pigmentation not only play a role in skin colour, but also affect vision and hearing. The genes are also associated with skeletal defects and anaemia. Following the theme that a genetic defect may require environmental factors for manifestation, undoubtedly the Sun is the environmental factor having the most obvious role in the expression of pigmentation. However, the presence of melanin in the inner ear is the clearest example that the Sun is not the whole story. The clarifica-

tion of exactly where the genes of albinism are acting revolves around the absence of the copper-containing tyrosinase. Yet that too is not the whole story, because tyrosinase-positive albinism is also a well-recognized phenomenon and several additional genes have evolved over 500 million years.

In patients with albinism, there is a partial or complete absence of melanin within the melanocytes of the skin, hair follicles, inner ears and eyes, despite the number of melanocytes being normal. In some animals the distribution is 'spotty' or avoids other extremities, which is thought to be a primary defect in the neural crest or in copper transport. A supplement of ophthalmic paediatrics describes several of these rarer syndromes and associated defects[62].

In most populations, the frequency of albinism is estimated to be around 1 : 20,000, although it may be as high as 1 : 1500 in some African tribes. It was 1/3900 in Soweto, South Africa[63]: 'There are two distinct types of albinism, one in which tyrosinase is deficient (the so called tyrosinase-negative (ty.neg) type), and the other in which tyrosinase is present (the tyrosinase-positive (ty.pos) type). The two conditions are complementary, so that if a tyrosinase positive albino marries a tyrosinase negative albino the offspring will be normally pigmented. The two types can be differentiated clinically: the tyrosinase positive albino has darker straw coloured hair, often has many small spidery pigmented patches (ephilides) chiefly on the exposed parts of the body, and brown eyes; the tyrosinase negative albino has lighter hair, blue or light brown irides and no ephilides. The majority of Negro albinos seem to have brown eyes rather than the pale blue eyes found in those with Caucasoid skin'.

It is now evident that the four main types of albinism are: OCA1 which can be clinically subdivided into OCA1A – complete lack of pigment throughout life via albinism vulgarise; OCA1B in which some pigment appears in very early life due to reduced activity of tyrosinase; OCAITS in which hairs of cooler areas, limbs and head are pigmented because the tyrosinase optimal temperature is 37°C, and OCA1 MP in which tyrosinase shows minimal activity until, in later years, pigment can appear in the eyes, hair and in lentigos even after middle age[64]. Most types of OCA are inherited in an autosomal recessive fashion, although some rare types have an autosomal dominant inheritance. The subtypes of OCA are caused by mutations in different genes involved in the pigmentation of skin.

Ocular manifestations of ocular and oculocutaneous albinism result from a decrease in the melanin content of eye structures or from a failure of correct optic innervation during development, perhaps due to a reduction in precursor dopamine of melanin, which has a role in neural synapse formation. Squamous cell carcinoma is a particularly common cause of morbidity and mortality in patients with albinism, especially those who dwell in tropical regions.

It is another mysterious feature that, in spite of the presence of melanocytes, melanomas are rare and have not been detected in most studies of individuals with albinism[65]. Kiprono (Regional Dermatology Training Centre, Tanzania, pers. commun.) in a study of 134 African malignancies in albinism in Kenya found only one melanoma. Inability to produce freckles (ephelides) seems to predispose to cancer. By contrast, melanomas are common in xeroderma pigmentosum, in which there is no shortage of melanin and the defect is one of DNA repair, shown easily *in vitro* in the fibroblast. It raises the question: 'does one need melanin in order to develop a cancer of the skin?' Kromberg and Castk[65], describe the tribal groups Xhosa and Nguni, who did not develop cancer. The variation in the number of cancers and in the age of first manifestation has been widely recognized, but further epidemiological studies are needed.

What is the genetic advantage of albinism heterozygotes having lighter skin that is a cultural advantage[66]? It may explain the high prevalence of albinism in Africa, since marriage is earlier and consequently pregnancies are more numerous. One of the roles of a public health approach will be to seek evidence for linkage, or absence of linkage, in conditions such as different genetic types of albinism in comparison to vitiligo, and to detect associated impairments such as lymphoma or defects in wound healing.

Experience of managing several hundred patients affected by albinism at the Regional Dermatology Training Centre in Tanzania has proved the value of an holistic approach which protects them from the Sun, improves their sight and hearing as well as providing a secure environment free from the influence of witchcraft. In southern Tanzania, where albinism is common, there has been much recent publicity given to the murder of children for body parts to be used for witchcraft. Integrated medicine needs to negotiate and educate the first on call, i.e. the traditional health practitioners[67].

The public health or social aspects of pigmentation mostly relate to there being too little or too much, and especially to there being an uneven distribution of pigment. Similar to its genetic origin, it is found in the organs of communication: eye, ear and skin. There can hardly be a more holistic approach to the biology of melanin than a study of the evolution of communication, which includes social aspects of tanning as well as skin lightening.

One of the questions asked is what is the genetic advantage of having pigment. Why does the African with albinism have such a high incidence of skin cancer but very rare melanoma, leprosy, lymphoma and keloid; sorting that one out requires an epidemiological approach. According to Richard Doll, 'Epidemiology offers the simplest, best and most direct way of elucidating causes of disease that are amenable to public health manipulation'. Each facet of pigmentation needs to be examined for its links and associations with all functions of the skin.

Greying of hair

Between the ages of 45 and 65, 74% of people are affected by grey hair. This is more likely in Caucasians than in Africans or Asians[68]. There is a progressive decline of melanocyte progenitor reservoir of the hair bulb. A decrease in catalase activity with ageing may allow greater oxidative stress.

Acquired hypomelanoses

Models of defects in the process of pigmentation may be studied in some skin naevi and freckles. It is interesting to note that a person with a minimal baseline level of pigmentation, who is unable to tan, has a similar density of melanocytes to a person with dark brown or black skin. It is the activity, both in the basal state and after stimulation, and not solely the number of these melanocytes, that is the main determinant of baseline skin colour. Conditions in which depigmentation may be seen include systemic lupus erythematosus and lichen planus, or post-chickenpox.

Chemical depigmentation

There are a number of chemicals that cause depigmentation when applied to the skin[69]. For example, occupational exposure to some substituted phenols leads to a leukoderma in some patients[70,71]. An occupational leukoderma also occurs in workers in contact with hydroquinone[72]. This is a compound used in the treatment of hypermelanosis, and has been previously used in cosmetic skin-lightening products. It is less commonly used in cosmetics following studies of its cancer induction in mice, although this finding has not been replicated in humans[73]. Occupational leukoderma mainly affects the dorsa of the hands, although other areas not in contact with the chemicals may be affected. Even after contact with the chemicals has ceased, the areas of depigmentation can enlarge and new lesions may appear. This is a phenomenon worthy of more study.

Hydroquinone has been used in skin-bleaching formulations for decades. This property of hydroquinone makes it useful in the treatment of hyper pigmentary conditions, but it has also been used in cosmetics. Kooyers and Westerhof[73] reviewed the literature on the use of hydroquinone as a skin-lightening agent. While there was already convincing and accepted evidence that the substance had adverse mid-term effects such as leukoderma en confetti and exogenous onchronosis, this review also raised the possibility that longer-term use may be carcinogenic, due to the fact that it is a derivative of benzene, which itself is highly carcinogenic. However, another review on the safety of hydroquinone suggested that despite widespread use of the substance, there have been no reports of it causing cancer, although the authors acknowledge that this does not rule out the possibility[74].

4-*n*-Butylresorcinol is now considered the most effective topical depigmenting agent[75]. Unlike vitiligo, the depigmentation caused by chemicals does not usually respond to psoralens with UV rays. Histologically, there is an almost total absence of melanocytes in these lesions and studies suggest a selective lethal effect of phenols on functional melanocytes[70,71].

Infections and defensins

Areas of hypomelanosis can occur in inflammatory diseases of the skin, and these may show a loss of functional melanocytes. It has been stated that black skin is better at fending-off cutaneous fungal disease[76] and candida albicans[77].

Epithelial surfaces and neutrophils produce defensins and cathelicidins against bacteria. This intervention is upregulated by $1,25(OH)_2D$ and calcipotriol. Melanin production from dopamine, optimal at 30°C in studies of insect protective mechanisms against bacteria, reminds one of an important early and perhaps still present function of this pigment[78]. Of relevance is the fact that the skin of albinism in Tanzania has a higher density of common bacteria, especially Gram-negative, compared to their pigmented siblings[79].

Pityriasis versicolor is a superficial fungal infection that is often mistaken for vitiligo, even though its lesions are not as white. Hypopigmented lesions are present due to a depigmenting effect on pigmented skin, but against white skin the fungus itself has some colour and hyperpigmented areas can also occur. It has been suggested that the depigmentation is caused by oxidation products formed by the fungus, which inhibit the activity of tyrosinase in melanocytes[80]; however, other mechanisms have also been suggested. The hypopigmented regions in pityriasis versicolor do not appear to be prone to sunburn. This may be because the fungus produces a substance called pityriacitrin, which absorbs a broad spectrum of ultraviolet radiation[81]. Pityriasis versicolor does not generally affect cold sites such as the legs and face.

There is also a condition of idiopathic macular truncal hypomelanosis affecting the trunk named pseudo versicolor, which is a marker of atopic eczema (Nathan *et al.*, pers. commun.). All of the 40 cases examined at the Nathan Skin and Laser Centre, Singapore, showed a normal number of melanocytes but reduced number of melanosomes. Such studies need mitotic figure counts to establish whether there is a high turnover of keratinocytes and whether melanocytes are not keeping up with feeding the keratinocytes.

Leprosy

Hypopigmentation may also be seen in sarcoidosis and leprosy. The reasons for this are unclear, but much investigated in the case of leprosy. It occurs in tuberculoid

leprosy in which the bacilli are sparse, and not in multibacillary leprosy. Elastin is destroyed by the granuloma, reducing the affinity of the dermis to melanocyte[6]. Hypopigmentation is very unlikely to be induced by the mycobacterium leprae and does not occur unless the inflammatory response is adjacent to the epidermis, as in tuberculoid leprosy. The density of elastin production is highest in the upper dermis. Corcos[82] studied how the depigmentation spread, and concluded that it was not passed from one cell to another but that it is brought about by extra bacillary proliferation of a subcellular, self-replicating agent initially carried by mycobacteria, rather than by the mycobacteria themselves. In leprosy, the lepromatous end of the spectrum is 11 times more likely to be associated with vitiligo than is tuberculoid leprosy[83].

It has been most recently demonstrated that *Mycobacterium leprae* alters the genetics of Schwann cells without even penetrating their nuclei and this activates genes that convert the cell into a neural crest stem cell, shielding the bacteria from destructive elements[84].

It has been questioned whether albinism could protect against leprosy, as they are not recorded together despite the fact that in Africa, both oculocutaneous albinism and, until recently, leprosy have high prevalence. Both leprosy and tuberculosis (TB) share genes with albinism[85]. Cytokeratin 10 is similar to the lepra-soluble antigen heat shock protein[65]. Since ultraviolet radiation decreases the granulomatous response to lepromin in humans[86], *Mycobacterium leprae* may be more effectively destroyed in the dermis when there is no blocking of the effects of sunlight by melanin[79].

Deafness and blindness

Melanin is also found in the striae vascularis of the inner ear and is of importance in its association with deafness in the Waardenburg Syndrome and albinism. In vitiligo, there are audio logical abnormalities too, but they are insufficient to cause deafness[87]. Melanin is an important background to the retina like the black inside a camera, but it also absorbs energy released from the effects of light. There is also a supporting background of elastin, which is subject to age changes and leads to age-related macular degeneration. In contrast to the recent interest, which has been molecular, influenced by cytokines, growth factors and genes, it is timely to review these themes and suggest they should recruit epidemiology to explore associations. The effect of the environment becomes of interest to gene expression and is explored best through a public health approach. However, first one must understand some of the mechanisms through which a physical environment has an influence.

Poikiloderma

Poikiloderma characteristically shows an increase in pigment, with atrophy and telangiectasis. Poikilo dermavascular eatrophicans (PVA) is freely translatable as a mottled hyper- and hypopigmentation of the skin (poikiloderma) with interspersed telangiectases (vasculare) and areas of atrophy (atrophicans)[88]. It may be generalized or localized. It may be an idiopathic disorder or a manifestation of connective tissue diseases (lupus, dermatomyositis or scleroderma), lymphomas (parapsoriasis en plaques or mycosis fungoides) and geno-dermatoses (Rothmund Thomson syndrome, hereditary sclerosingpolkiloderma or dyskeratosiscongenita)[89]. Other causes include physical trauma (radiodermatitis, burns or freezing) and certain ingested substances such as arsenic compounds.

Erythema abigne is also atrophy with pigmentation. It is induced by heat with added pressure, and can predispose to skin cancer. The elongation of the papilla in senile lentigo or in a condition such as Dowling–Degos disease, accompanies a state of low turnover and high retention at the basement lamina. Here the favoured basal location of the melanocyte is also obvious and it spreads its melanin through attached dendrocytes.

Melasma: a model of incontinence

Melasma is a common acquired cause of increased pigmentation in which the melanocyte escapes through a basement lamina disrupted by proteases. It is mostly seen on both cheeks in Sun-exposed and rubbed sites[52]; it fades during the winter months[90]. It can be exacerbated by pregnancy, progesterone and oral contraceptives. Autoimmune thyroid disease, phenytoin and other phototoxic drugs are also potential exacerbating factors.

Hyperfunctioning melanocytes with increased mitochondria, Golgi apparatus and rough endoplasmic reticulum produce increased amounts of melanin in affected skin compared to unaffected skin[54]. Under illumination with Wood's lamp, the pigment may be seen at several levels of epidermis and dermis. However, histological findings do not correlate well with reported Wood's light examination findings[91,92]. In the dermal layer, there is usually an increase in melanin-containing macrophages. There may be an increase in the number of melanocytes which have enlarged dendrites. Epidermal hypermelanosis is more amenable to topical treatments and chemical peels, while dermal pigmentation is difficult to treat[92].

In melasma, the melanocytes appear to migrate into the dermis[56], in part due to protease activity weakening the basement lamina[93]. It is similar to the migration of melanocytes observed by Yasutomi[94] in the metamorphosis of tadpole, when the number of epidermal melanin-containing cells of the skin decreases. Epidermal melanocytes and epidermal cells are initially tightly associated with each other in the young tadpole. 'The association becomes looser at the metamorphic stage at which stage, occasionally, small breaks in the basement membrane are seen. These breaks may encourage the migration. The

migration of epidermal melanophores can be induced by treatment of cultured skin from tadpoles at stage 15 with thyroxine, and this hormone may act directly on epidermal melanophores'. Attachment between melanocytes and keratinocytes determines the expression of proteinase-activator receptor-2, which when activated increases the transfer of melanosomes. It is controlled by the agents that control fibrinolysis[95]. UVB inhibits fibrinolysis in the upper dermis by the release of PA1. UVA, which penetrates deeper, activates fibrinolysis[60]. In porphyria the stimulus to the dermis is UVA, which is characteristically pigmented but white cells are not attracted. In this respect activation of proteases may be a feature as in melasma, in which there is some evidence of hypersensitivity to sunlight, even when tested on the non-melasma sites. However, the pigmentation of melasma is without the inflammatory phase of sunburn. Immediate pigment darkening is a feature. Sun blocks are helpful and sandalwood is commonly used for this purpose in Asia.

Anti-fibrinolytic agents, such as tranexamic acid are therapeutic for melasma[96]. Li *et al.*[97] emphasized that this plasmin inhibitor has a greater effect on the affected melasmic skin than on normal skin and that this was due to the greater amount of vasculature and mast cells in the affected skin. They also pointed out that mast cell tryptase degrades basement lamina collagen type IV. Li *et al.*[98] reported and that another serine protease inhibitor, pigment epithelium derived factor (PEDF), inhibits migration of outer root sheaf cells of the hair follicle and may be an inhibitor of VEGF in the hair follicle. It plays a part in some retinal degenerative diseases.

Topical hydroquinone is used as a bleaching therapy for melasma. It bleaches the skin by competing with tyrosine as a substrate for tyrosinase and by selectively damaging melanosomes and melanocytes[99,100]. Topical tretinoin used as a monotherapy leads to a clinical improvement of melasma over a period of at least 24 weeks[101,102], possibly by encouraging clearance via the lymphatics[103].

In their studies on melasma Lee *et al.*[104] did not find any difference between transepidermal water loss of lesional skin and normal skin, but did find that the skin of melasma is more hydrated and recovers from tape stripping more slowly. The role of keratinocyte in the pathophysiology of melasma has also been attributed to the activation of inducible nitric oxide synthase within keratinocytes and activation of the AKT/NFRB pathway[105].

Seif El Nasr *et al.*[106] reviewed melanocyte control by cytokines manufactured by keratinocytes. Thus β-fibroblast growth factor, granulocyte monocyte colony stimulating factor and endothelins released from the keratinocyte respectively, by UVA and UVB all stimulate pigmentation. Keratinocyte interleukin-1α and IL-6, THF-α and TGF-β all suppress pigmentation.

Black is beautiful: is skin colour of public health significance?

From managing relationships between cells to using skin colour in social relationships, there has always been input from adrenochromes such as dopamine. Attachment and detachment, marriage and divorce, privacy and display or camouflage, call on ancestral explanations for a role of melanocyte. Community dermatology embraces common skin diseases such as vitiligo, melasma, or pityriasis alba and versicolor, and rarer conditions such as albinism. It is inclusive of wounds and lymphoedema, both of which heal with hyper- or hypopigmentation. It has also embraced neglected tropical diseases such as leprosy with its diagnostic hypopigmented lesions. It concerns populations of individuals, rather than individuals in a one-to-one relationship. The migration of epidermal melanocytes to the dermis to help with courting may be a factor which accounts for the increase in their number in the dermis. The camouflage and display phase evolved as the look-good–feel–good factor, and became part of courting behaviour in the animal kingdom.

Skin colour is one of the main characteristics noted at first glance of an unfamiliar person. This makes skin colour important, and a change in skin colour can have a major impact (positive or negative) on the psyche of an individual. It is always fascinating to consider the 'grass is greener' attitude to skin colour that is present in different populations. This is a major public health problem affecting quality of life and influenced by social marketing.

As noted above, it is often the case that people with Caucasian skin tones prefer to be tanned, while those with darker skin prefer to be fair. Taking action to modify one's skin colour can have detrimental effects on the individual's health. This is demonstrated in the increased incidence of skin tumours in those who sunbathe or use tanning beds. Similarly, some people with dark skin tones use cosmetic products in an attempt to lighten their skin; too may have harmful effects. The use of plant derivatives for pigmentary disorders is widespread in the developing world and is in itself a public health problem[107].

Beauty is a subjective characteristic, a point highlighted by the age-old adage 'beauty is in the eye of the beholder'. There is some evidence to suggest that those traits which are regarded as beautiful are evolutionarily determined by characteristics deemed to lead to enhanced survival of the perceiving individual's genes.

The media undoubtedly has a great amount of influence in determining what characteristics are deemed beautiful by society. An example is the predominance of fair-skinned women featured in magazines, which leads to the concept that light skin is more beautiful and induces a feeling of inferiority in women with darker skin tones. Darker-skinned women have often been perceived as agricultural labourers, and poorly paid agriculture workers and consequently not rich enough to stay out of the Sun.

The 'Black is Beautiful' movement was founded in USA in the 1960s by African Americans. This movement aimed to dismiss the notion that the natural features of black people are not inherently ugly. It encouraged men and women to stop trying to eliminate their natural traits by straightening their hair and bleaching their skin.

An article by Marie-Brigitte Kabalira[108] highlighted the problem caused by these ideas. In Rwanda, there are many shops that mix creams and lotions without using any measurements and many lotions contain skin-lightening products even if these are not listed under ingredients. The article emphasizes the 'deep, ingrained scars that have transcended generations', indicating the significance the undesirability of dark skin in society[108].

Kabalira discusses products which can contain mercury or potent steroids, both of which can cause serious, long-term adverse effects, particularly if applied to the whole body, as the potential for large concentrations to be absorbed over prolonged time periods is increased. One such adverse effect is thinning of the skin leading to decreased protection from the Sun and decreased rate of wound healing, strikingly a problem in the consequently severely atrophic skin. A study from Senegal recorded the birth of smaller babies in women using generous amounts of steroid creams for skin lightening and also of a patient with leprosy in which skin lighteners led to delay in diagnosis[109]. Mercury-induced depigmentation can cause nephrosis[110].

Taking into account the potential dangers of using skin-lightening agents, it is important to educate people on the adverse effects of these treatments and help them realize that 'black really is beautiful'. Headings discussed by Thompson *et al.*[46] include 'spoiled identity', being 'hidden away', loss of ethnic identity, appearance shame and disgust, 'intimacy impossible', avoidance and concealment, confronting and explaining, over compensation, denial, wishful thinking and minimizing.

So influential is the life of melanocyte on human function and behaviour, that it is necessary to control its effects in populations rather than in individuals. Such control can be chemical and mechanical by acting through the mechanisms described above, or it can be through social marketing aimed at human behaviour and its concern for skin colour.

Integrated medicine as an intervention

The emphasis in this article is on the multiplicity of factors, chemical and mechanical, that play a part in pigmentation. It is a feature occurring throughout the history of living organisms. Biomedicine that seeks single causes is reductionist in its approach to therapy and often ignores the synergism that characterizes cellular biochemistry. Much of modern medicine is based on herbal extracts and only a small fraction has so far been explored. Integrated medicine not only provides abundant herbal approaches but emphasizes energy, physical and mechanical influences. We suggest that integrated medicine provides a useful background of mechanisms, as in this article, and a generous portfolio of approaches, including aspects covered in other papers of this special section, on which to base reasonable expectations of successful control of disorders of pigmentation.

Narahari *et al.*[111], in a discussion of systemic reviews of Ayurveda treatments, used *Switra* (the Ayurvedic term for vitiligo) and summed up in one paragraph the Ayurvedic view of the skin: 'According to Ayurveda, the skin is an essential sense organ. Basic energy principles like 'mobile natured energy' (*vatha*) and one of the five heat-producing activities similar to metabolism (*bhrajaka pitta*) reside in the skin (called *twak* in *Sanskrit*). As the skin covers the whole body *bhrajaka pitta* should be maintained in a proper state and it needs continuous care. Therefore, Ayurveda probably has multiple treatments available for skin care and dermatoses'. In their discussion of treatment of vitiligo, they emphasize four herbal approaches – purgation, oil massage, exposure to the Sun and following these an oral herbal decoction. Totally 66 treatments are discussed and the paper with its 156 references should be read in full. They argue that unless the medicine has some beneficial effect, it is unlikely that over 700,000 practitioners are still using it in their private practice, when competitive options are freely available.

In another study, Narahari *et al.*[112] provide a description of how the Institute of applied dermatology applies Ayurveda to a number of diseases, but when describing vitiligo, emphasize that its presentation varies and may well represent more than one pathology even in the same affected person. Some lesions may be developing and others in the same person may be regressing or in a resting stage. Such variants are better recognized by Ayurveda than by biomedicine.

We argue that if the role of melanocyte were better understood and its biochemistry matched to the many ethnobotanical studies now active in the laboratory, these pigmentary diseases would not remain an unsolved enigma.

We have previously discussed how melanocyte is a stabilizing influence on cell contact and how after cell division in the basal layer, one keratinocyte is jostled to the surface while the other remains in the basal cell layer stabilized by melanocyte[6,7]. The influence of sunlight and the role of camouflage came late in evolution, and one should look for fundamental biological influences to explain the role of cells derived from the neural crest. Diseases affecting pigmentation may be explained by a failure of these influences. One of the latest to be investigated is pH. Thus, it has been observed that proton pump inhibitors, used mainly to control gastric hyperacidity, may aggravate vitiligo[113,114]. Anbar *et al.*[115] proposed that H_2-receptor blockers can inhibit melanization and melanosome transfer from melanocyte to keratinocyte. Namazi[116] suggested that the intramelanocyte pH gradient is

a factor in augmenting oxidative stress in vitiligo melanocytes. In an earlier study[7], we have emphasized that both melanocyte and serine proteases have a role to play in the pH of the surface and may be a determinant of pigmentation. The acid mantle is not as popular a topic as now almost 100 years ago, but darker skins are the more acidic. Asian systems of medicine have many herbal remedies to control gastric reflux and hyperacidity. These are obviously worthy of study concerning the prevalence of vitiligo.

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