VITILIGO IN TANZANIA

A study of the clinical types of the disease, prevalence of autoimmunity and problems of management.

BY

K.J. PALLANGYO, M.D.

A Dissertation in partial fulfilment of the requirement for the degree of Master of Medicine (Internal Medicine).

DEPARTMENT OF MEDICINE

FACULTY OF MEDICINE

UNIVERSITY OF DAR-ES-SALAAM

HEAD: PROFESSOR W.J. MAKENE F.R.C.P

SUPERVISOR: PROFESSOR A.E.J. MASAWE MB CHB M.MED MSC

DAR-ES-SALAAM MAY 1982

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS I

SUMMARY II

PART I: INTRODUCTION AND REVIEW OF LITERATURE 1

(A) MELANOGENESIS..... 1

(B) DECREASED PIGMENTATION OF THE SKIN 5

(C) AETIOLOGY 6

(D) CLINICAL PRESENTATION AND NATURAL HISTORY 10

(E) TREATMENT 12

PART II: THE STUDY 15

PATIENTS AND METHODS..... 16

RESULTS 18

DISCUSSION..... 26

CONCLUSIONS 34

PART III: REFERENCES 35

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Professor A.E.J. Masawe for his invaluable help in all the stages of the study; to Professor K.J. Lindquist of the University of Nairobi and Professor M. Harboe of the University of Oslo who made the antibody studies possible; to Dr. D.H. Mwakyusa and Professor D. McCarty for their suggestions and advice; to my fellow residents for their co-operation in collecting the cases; to the Memphis Company (Cairo) for providing meladinine samples; to Messrs Salim and Muzu of Color Centre for their technical assistance and to Mrs. N. Salim for her good secretarial services.

SUMMARY

67 African vitiligo patients have been studied. Idiopathic vitiligo was the most frequent clinical type encountered. The diesease presents before adulthood in the majority of the victims.

Samples from 40 patients were analysed for autoantibodies. Antinuclear antibody tests were positive in 25 percent of the patients. Gastric parietal cell antibody was weakly positive in one patient. All samples were negative for thyroid antibodies.

Of 30 patients who used meladinine, 16 attained cosmetically acceptable repigmentation.

The results are discussed in relation to what is known about autoimmunity and vitiligo as well as autoimmunity in the African. The problems of managing vitiligo patients in Tanzania are also discussed.

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PART I: INTRODUCTION AND REVIEW OF LITERATURE

Vitiligo is a systemic disease in which pigment cells anywhere in the body are destroyed.[1] It may be an early manifestation of other systemic diseases such as diabetes mellitus, pernicious anaemia and thyroid diseases.[2] The disease occurs in all races and in both sexes.[3] Reported incidences range from 0.14 percent in Switzerland to 3.2 percent in India.[4] In Africa, incidence studies are lacking.[5] Physicians working in the continent have had different impressions about the incidence of the disease in Africans. Browne[6] stated that Vitiligo was extremely common in the African. On the other hand, Soyinka[5] writes that the higher incidence reported among the Africans is apparent rather than real. Incidence studies are therefore, necessary to clarify these two opposing views.

The term vitiligo is derived from the Latin word "Vitellius" which means calf. It was first used by the Roman physician Celsus in the second century AD to refer to the distinguishing white spots of the disease that resemble the white patches of a calf.[7]

A: MELANOGENESIS

The understanding of the disease process in Vitiligo requires knowledge of the process of melanogenesis. Before embarking on Vitiligo, the

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process of melanogenesis will therefore be presented first. The normal human skin color is produced by four skin pigments[8]

a) Exogenously produced carotenoids - Yellow.

b) Endogenously produced melanin-brown in epidermis.

c) Oxygenated hemoglobin - red in capillaries.

d) Reduced hemoglobin - blue in venules.

Melanin is produced in the melanocytes and then transferred into the keratinocytes. Of the four skin pigments listed above, it is the amount of melanin in the keratinocytes that significantly determines the pigmentation of the skin. The keratinocytes, (the cells that make up most of the epidermis), are derived from the lowest cell layer of the epidermis called the basal layer. These basal cells constantly divide and change shape and size. As they are gradually pushed upward to the surface, the other layers of the epidermis (prickle, granular and horny layers) are formed. Other cells found in the basal layer are the melanocytes and the Langerhans cells.

The melanocyte, which embryologically originates from the neural crest, invades the basal layer of the epidermis during the first three months of intrauterine development. The melanocyte and the basal layer keratinocyte are therefore in close proximity. It is in the melanocyte that melanin is synthesized from tyrosine by the enzymatic activity of

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tyrosinase. The different steps in the synthesis of melanin from tyrosine are as shown in figure one.

The enzyme tyrosinase is formed in the endoplasmic reticulum. It is then passed to the Golgi area where it is encapsulated by a lipoprotein material thus forming a vesicle. It is in this vesicle that melanin will be deposited to form a melanosome. The formation of the vesicle, marks the first stage in the production of melanosomes (i.e. melanin particles). In stage two, melanin deposition has not occured but the inner membranous structure of the melanosome has fully developed from the lipoprotein material. The deposition of melanin in the inner membranes of the vesicle marks the third stage of melanosome production. In the last stage (stage 4) the deposited melanin in the vesicle transforms into uniformly dense structures. These particles are then transfered into the keratinocytes.

The mechanism by which melanosomes move inside the melanocytes and their dendritic processes, (from the perinuclear and endoplasmic regions towards the tip of the dendrite) and are transferred into the surrounding epithelial cells is not fully understood.[8] However, several theories have been proposed:

(a) The electrophoresis theory: It is thought that differences in membrane potential between the central and peripheral part of

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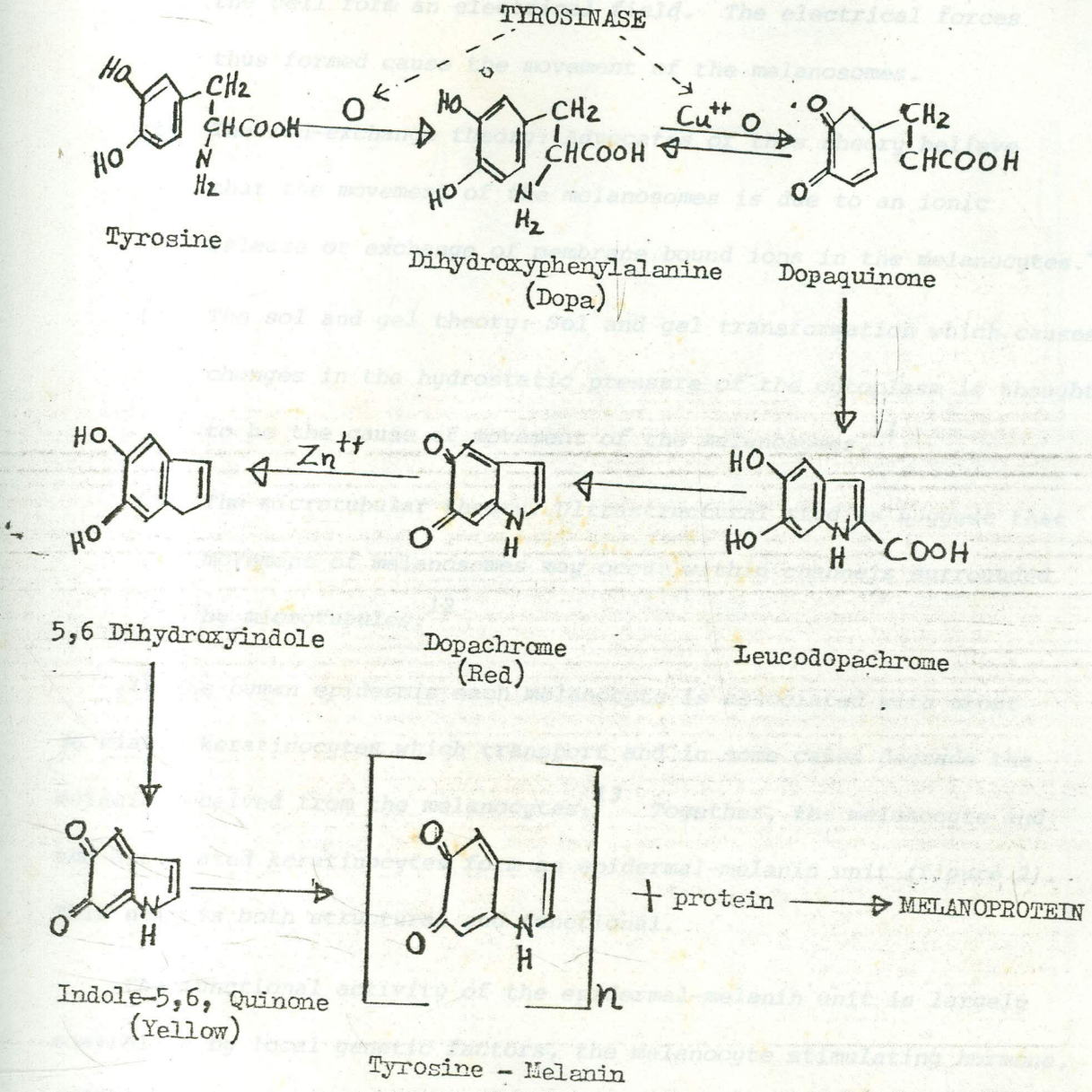


Figure I: A scheme of metabolic pathway of tyrosine to melanin

the cell form an electrical field. The electrical forces thus formed cause the movement of the melanosomes.

(b) The ion-exchange theory: Advocates of this theory believe that the movement of the melanosomes is due to an ionic release or exchange of membrane bound ions in the melanocytes.[10]

(c) The sol and gel theory: Sol and gel transformation which causes changes in the hydrostatic pressure of the cytoplasm is thought to be the cause of movement of the melanosomes.[11]

(d) The microtubular theory: Ultrastructural studies suggest that movement of melanosomes may occur within channels surrounded by microtubules.[12]

In the human epidermis each melanocyte is associated with about 36 viable keratinocytes which transport and in some cases degrade the melanin received from the melanocytes.[13] Together, the melanocyte and the associated keratinocytes form an epidermal-melanin unit (figure 2). This unit is both structural and functional.

The functional activity of the epidermal-melanin unit is largely controlled by local genetic factors, the melanocyte stimulating hormone, (MSH) androgens and adrenocortico-trophin hormone (ACTH), local temperature, and ultraviolet irradiation. Increased amounts of MSH,

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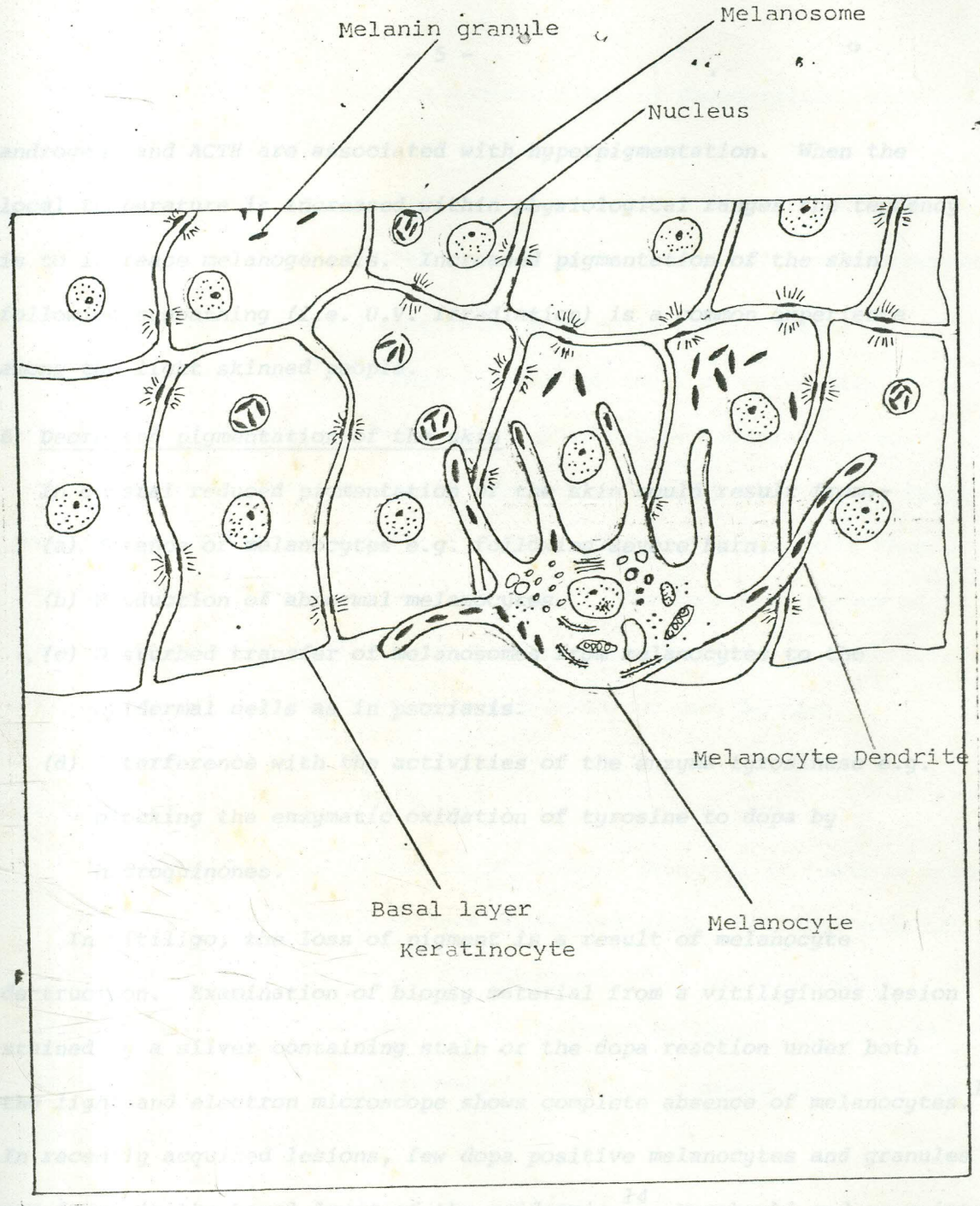


Fig. 2: The Epidermal - Melanin Unit

androgens and ACTH are associated with hyperpigmentation. When the local temperature is increased within physiological ranges the tendency is to increase melanogenesis. Increased pigmentation of the skin following sunbathing (i.e. U.V. Irradiation) is a common experience among the light skinned people.

B) Decreased pigmentation of the skin

In general reduced pigmentation of the skin could result from:-

(a) Absence of melanocytes e.g. following severe burn.

(b) Production of abnormal melanocytes.

(c) Disturbed transfer of melanosomes from melanocytes to the epidermal cells as in psoriasis.

(d) Interference with the activities of the enzyme tyrosinase e.g. blocking the enzymatic oxidation of tyrosine to dopa by hydroquinones.

In vitiligo, the loss of pigment is a result of melanocyte de-truction. Examination of biopsy material from a vitiliginous lesion stained by a silver containing stain or the dopa reaction under both the light and electron microscope shows complete absence of melanocytes.[1.2] In recently acquired lesions, few dopa positive melanocytes and granules are found in the basal layer of the epidermis.[14] Morohashi and associates[15] studied the melanocytes at the periphery of vitiliginous lesions and

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reported that many melanocytes contain signs of degeneration, such as vacuolation of cytoplasm and or fatty degeneration. These investigators also showed that there was direct continuity between the Schwann cell basal laminae and the basal laminae of the melanocytes.

It has been reported that Langerhans cells are increased in vitiliginous lesions.[1,16] Inga Silberg[1] of New York University found that Langerhans cells adsorb or phagocytose antigens and or immune complexes which penetrate the skin and; carry them to the lymph nodes where immune sensitization occurs. The sensitized cells then return to the epidermis as effector cells. The increased number of Langerhans cells in vitiliginous lesions may, therefore, be a reflection of the immunological activities taking place in such lesions.

C: AETIOLOGY

The aetiology of vitiligo is not known. However, it tends to occur in families and may show a pattern consistent with a dominant mode of inheritance.[17] In large series the frequency of a positive family history of vitiligo among patients is reported to range from 35 - 38 percent.[3,17] Therefore, there must be modifying factors affecting the expression of the trait.

The aetiological mechanism(s) in vitiligo are currently considered under the following headings:[2]

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(a) Autoimmune vitiligo or idiopathic vitiligo.

(b) Chemical vitiligo.

(c) Neurogenic or dermatomal vitiligo.

(a) Autoimmune Vitiligo:

The evidence for autoimmune pathogenesis is mainly circumstantial. Goudie and associates[18] have reported patients with anatomical distribution of the skin lesions resembling those of internal lesions in some of the classical autoimmune diseases. Although approximately one percent of the general population has vitiligo, the incidence is 8% - 20% in people with disorders such as thyroid disease,[19,20] pernicious anaemia[21-24] diabetes mellitus[2,20,22,25] alopecia areata[20,26] idiopathic hyperparathyroidism[27] uveitis[28] and sympathetic ophtalmia.[29] The increased prevalence of organ specific autoantibodies reported in several but not all large series of patients with vitiligo provides further support for the autoimmune hypothesis.[23,30-33]

Demonstration of antibodies directed to the melanocytes in patients with vitiligo will provide direct evidence for the autoimmune hypothesis. Langhof, Feustein and Schabinski[34] demonstrated "precipitating" antimelanin antibody in the majority of their twenty six vitiligo patients. However, inspite of attempts by several other workers the findings of Langhof et al have not been reproduced.[33] Recently, antibodies to the melanocyte have

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been demonstrated in patients with multiple endocrine abnormalities.[27,32] These antibodies however, were found to bind to intracellular antigens rather than cell surface. It is therefore quite likely that they were a result rather than the cause of the melanocytic injury. Todate, there is no convincing direct evidence for the autoimmune hypothesis.

(b) Contact or Chemical Vitiligo

As early as 1940, Oliver and associates[34] described under the heading of occupational leucoderma cases of loss of pigment in the dorsum of hands of workers in a factory who wore protective rubber gloves. These gloves had been treated with hydroquinone in the finishing process. The leucoderma was followed by the appearance of vitiliginous macules scattered symetrically in the non-gloved areas (clinically indistinguishable from idiopathic vitiligo). Leucoderma, morphologically indistinguishable from true vitiligo was detected in 54 of 198 men exposed to p - tert - butylphenol (PTBP) during its manufacture.[36] Other chemicals known to produce depigmentation in man include thiols, phenolic compounds, catechol, derivates of cathechol mercaptopurine and several quinones.[37] The pigment loss in chemical vitiligo results from inhibition of tyrosinase and from a direct cytotoxic effect on the melanocyte. The phenomenon of depigmentation distant from the site of exposure has not been fully explained. In the reported event with PTBP it was found that not only

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was the occurence of vitiligo related to the duration of exposure but to the intensity of exposure as well. The authors suggested a systemic absorption of PTBP as a possible explanation for the widespread lesions. Immunological response, resulting from sensitization of lymphocytes after exposure to melanocytic antigens following melanocyte death has also been proposed to explain the appearance of lesions far from the site of exposure.[37,38] A detailed clinical and occupational history is therefore of paramount importance if the correct diagnosis is to be made.

(c) Neurogenic or dermatomal vitiligo

Unlike autoimmune vitiligo, neurogenic vitiligo is not associated with autoimmune disease and cannot be explained on immunologic basis.[2] Response to premelanosome antigens positive in autoimmune vitiligo is negative in neurogenic vitiligo.[39] Because melanocytes arise from the neural crest it is logical to claim that neural factors may play a role in vitiligo. Cases in which vitiligo occur in dermatomal distribution lend support to the hypothesis that neural factors play an important role in the pathogenesis of the disease.

Many authors have reported data suggesting distrubance of the autonomic nervous system. Breathnach, Bor and Wyllie[40] using the electron microscope found degenerative changes in the terminal portion

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of peripheral nerves in vitiliginous lesions. Local injection of physostigmine showed dysfunctioning adrenergic sympathetic pathway in dermatomally distributed vitiligo lesions.[41] Repigmentation occured in 50 percent of patients with dermatomally distributed lesions following oral nialamidine (a monoamine oxidase inhibitor).[41]

Lerner of Yale University, has suggested that the melanocyte is destroyed by a cytotoxic agent released close to or within the cell. This agent could be nor-epinephrine or some catecholamine released in increased amounts at the peripheral nerve endings or more slowly inactivated.[37]

In conclusion, occumulated evidence suggests that sympathetic nerves play a major role in the depigmentation that occurs in dermatomal vitiligo.

D. CLINICAL PRESENTATION AND NATURAL HISTORY

The clinical presentation and natural history of vitiligo is quite variable.[4] The disease may occur at any age.[4] Congenital vitiligo has been reported.[3]

In autoimmune vitiligo, initially there may be one or several areas of depigmentation. The loss of pigment may first occur around a nevus. With time, the disease may spread to involve other parts of the body.

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The time interval between the appearance of the first lesion and the widespread disease varies between days and a few years. The size of the depigmented area(s) is quite variable. On the one hand there may be a single macule and on the other extreme the whole body may be depigmented with only small patches of normal skin.

In some patients, for reasons not known, spontaneous repigmentation occurs. Often times there are periods of activity when new lesions occur followed by prolonged intervals of quiescence.

Neurogenic vitiligo is rare. Out of 821 cases of vitiligo reported by El-Mofty,[2] only 41 (i.e. 5%) had this clinical type.[2] Usually, neurogenic vitiligo presents as a single lesion of depigmentation with a dermatomal distribution. Rarely, similar lesions may occur elsewhere.

Vitiligo may occur several months following exposure to a potential chemical. The areas maximally exposed show depigmentation first. Subsequently lesions may occur distant from the area of contact. Once this has occured, it becomes clinically impossible to differentiate this type of disease from autoimmune vitiligo. The value of a thorough and detailed history of the patients' occupation and activities is therefore, obvious.

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E. TREATMENT

Various modalities of treatment have been tried. A review of the published data indicate that good results have been obtained with psoralens,[3,41,42] steroids[43,44] and surgery.[45]

(i) Psoralens

Fucocoumarine containing plants have been used for centuaries in India and Egypt in the treatment of vitiligo.[3,46] In 1947, El-Mofty introduced methoxsalen (i.e. 8 methoxsalen) for the treatment of vitiligo.[3]

The increased melanogenesis with psoralens appears to result from cellular injury, due to UV irradiation in the presence of psoralens, that directly stimulates mitosis and other biochemical changes.[1,46] The skin that has been photosensitized by psoralens shows increased melanocyte population, an increased size of the melanocyte and their dendrites, increased tyrosinase activity and increased turnover of melanin granules.[46] The intracellular manifestation of psoralen photosensitization of the skin (e.g. erythema and melanogenesis) appear to be directly related to biophysical changes in the psoralen molecules. The role of these molecules in the photosensitizing process is to absorb the quanta of light of specific wavelengths and to dessipate this absorbed energy in such a way as to induce the biochemical changes that

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are presumed to initiate melanogenesis.[46] The response is related to both the drug and solar or UV-irradiation. Neither psoralens alone nor UV irradiation are effective in producing repigmentation. The best results are obtained for lesions on the face and trunk.[42]

The onset and duration of repigmentation varies widely from one patient to another.[3] In some cases repigmentation begin to appear within two to three weeks. On the other hand it may appear after one year of uninterrupted treatment. In the majority of favourable cases repigmentation appear within six to twelve weeks of uninterrupted treatment. Once repigmentation has been acquired it may last for upto 20 years without further treatment.[42] Psoralens are available for topical application and oral administration. The dosage varies with body weight. El Mofty[39] has recommended oral meladinine (methoxsalen) in a single dose of 0.7mg/kg body weight (40-60mg) followed 2-3 hours later by solar or UVA irradiation. In man over 95% of orally administered methoxsalen is absorbed from the gastrointestinal tract and peak blood levels are reached in 1 ½- 3 hours. About 90% of psoralens are excreted in urine within 12 hours.

(b) Steroids:

Steroids have been used in vitiligo on the basis that it is an autoimmune disease. Corticosteroids given orally produced satisfactory

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results in 6 out of 22 patients with vitiligo within six months.[43] Lijama and Mishima[47] in a well controlled double blind study reported that fluoctinomide cream was more effective than a placebo. On the other hand, oral corticosteroids alone or with ultraviolet irradiation for 3 months failed to produce any pigmentary response.[39]

Long acting cortico trophin hormone (ACTH), given on a twice weekly dose of 25 - 40 I.U. I.M. depending on the age of the patient produced 80 percent repigmentation in 16 out of 27 patients.[44] Although there are potential hazards to such treatment, no side effects were observed in this series.

Todate there is no clear information regarding the use of steroids in treating vitiligo.

(c) Surgery

Skin grafting has been done in the treatment of resistant patches (to other forms of therapy) in quiescent vitiligo.[45] However, the observation that depigmentation commonly occur over scar tissue in patients with vitiligo and the fact that vitiliginous lesions are usually multiple speaks much against surgery as a means of treatment. Surgery is therefore, of doubtful value in the treatment of this disease.

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PART II: THE STUDY

The above cited literature show that studies from the west have associated vitiligo with diseases believed to be of autoimmune aetiology.[19-] Other reports have shown increased formation of antibodies to the thyroid, gastric and adrenal tissue in vitiligo patients.[31,32] Although these reports have shown an association between vitiligo and autoimmunity, it should be pointed out that these observations are not true for all patients.

Taking these observations into consideration workers in this field have classified the disease into:[2,37]

(a) Autoimmune or idiopathic vitiligo

(b) Neurogenic vitiligo

(c) Chemical vitiligo

Diseases thought to be of autoimmune aetiology as well as autoimmunity per se, are said to be rare in the African.[50-52] The relevance of the foregoing information to the African vitiligo patient need to be determined.

The aims of the present study are:

(a) To determine the clinical types of vitiligo in the African patients.

(b) To find out the prevalence of

(i) Autoimmune diseases associated with vitiligo

(ii) Autoimmunity in the African with vitiligo

(c) To look into the problems of management of vitiligo in Tanzania.

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PATIENTS AND METHODS

The study was conducted at the Skin Clinic, Muhimbili Medical Centre from 1st April 1980 to 30th October 1981.

Patients

A detailed history and thorough clinical examination was performed on all patients with leucoderma attending the clinic during the period of study. Personal and family history of Vitiligo, diabetes mellitus, pernicious anaemia & thyroid disease were elicted in all patients. Patients with localized leucoderma due to known causes were excluded from the study. Those with vitiligo had a detailed description of the lesions as regards site, number and size. Investigations included urinalysis, stool examination, full-blood count, erythrocyte sedimentation rate, blood grouping and rhesus factor determination. Fasting blood sugar was determined in all patients. Glucose tolerance test was done whenever the fasting blood sugar was 140 mg percent or more. Other appropriate laboratory tests were done where indicated to exclude known causes of leucoderma.

Serological Studies

Serum samples from all patients seen by mid - June 1981 were sent to Norway for analysis of autoantibodies to the gastric parietal cell, thyroid microsomes & thyroglobulin as well as antinuclear antibody and rheumatoid factor. Standard indirect immunoelectrophoretic techniques

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were used to detect anti-nuclear antibody[57] antithyroglobulin antibody[58] thyroid microsomal antibody[59] and gastric parietal cell antibody.[60] Screening for rheumatoid factor was done by both latex slide agglutination test & Rose-Wealer test.

A control group, matched for age (±5 yrs) and sex was selected from patients attending the clinic with conditions not known to be associated with autoimmunity.

Treatment

Adult patients were put on 3 tablets of meladinine at eight o'clock and one tablet at 11 o'clock (1 tablet contains 10mg of 8 - methoxsalen) Children between 10 - 15 years were put on two tablets at 8 am and one tablet at 11 am. Those children in the age group 5 - 10 years of age were given two tablets daily.

Patients were advised to get solar exposure to the vitiliginous lesions 2 - 3 hours after the bigger dose of meladinine. The initial duration of exposure recommended was up to five minutes. The duration of exposure was then gradually increased if no unwanted reaction developed.

Often times meladinine was not available from the hospital pharmacy where drugs are dispenced without fee. In such occasions patients were advised to purchase the drugs from the pharmacies in the city.

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The response to meladinine was graded as good when more than 60 percent repigmentation occured, fair when repigmentation was between 40 and 60 percent, poor when less than 40 percent and nil when no repigmentation occured at all. All case notes were retained to facilitate smooth record keeping.

RESULTS

A total of 67 patients with vitiligo were seen during the period of study. Thirty three (49.2%) patients were males and 34 (50.8%) females- giving sex ration of approximately one to one.

The age distribution of the study population is as shown in figure 3.

From figure 3, it can be seen that over 86% of the patients are 40 years or less.

The mean age is 24.2 years and the mode is in the age range 20 - 30 years.

Figure 4 shows the age at the times of onset of vitiligo. It can be seen that the disease appeared before the tenth birthday in 20 (30 per cent) patients, and before the 30th birthday in 58 (over 86 percent) patients. Vitiligo, therefore manifests first during childhood, adolescence or early adulthood in the majority of the victims.

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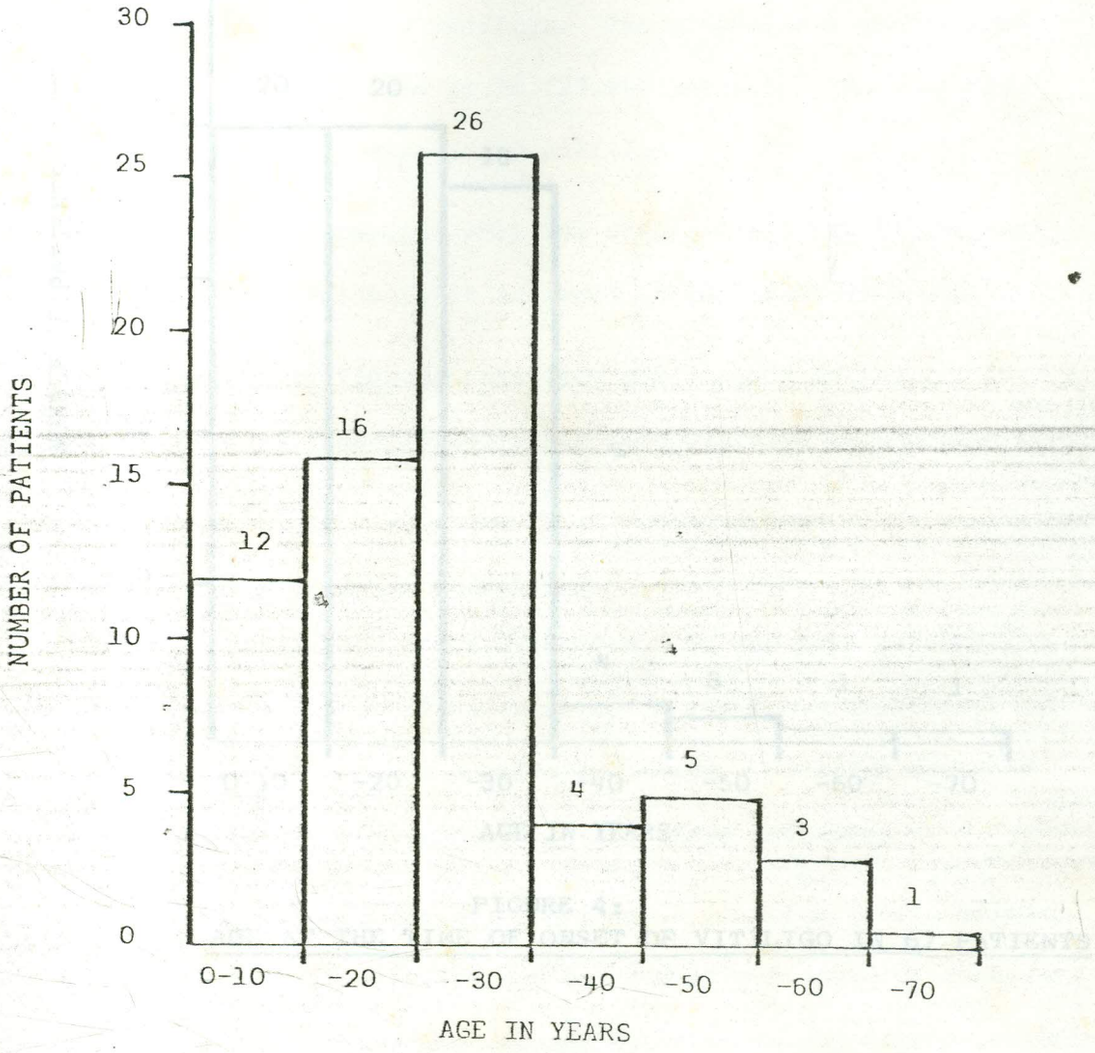


FIGURE 3: AGE DISTRIBUTION OF 67 VITILIGO PATIENTS

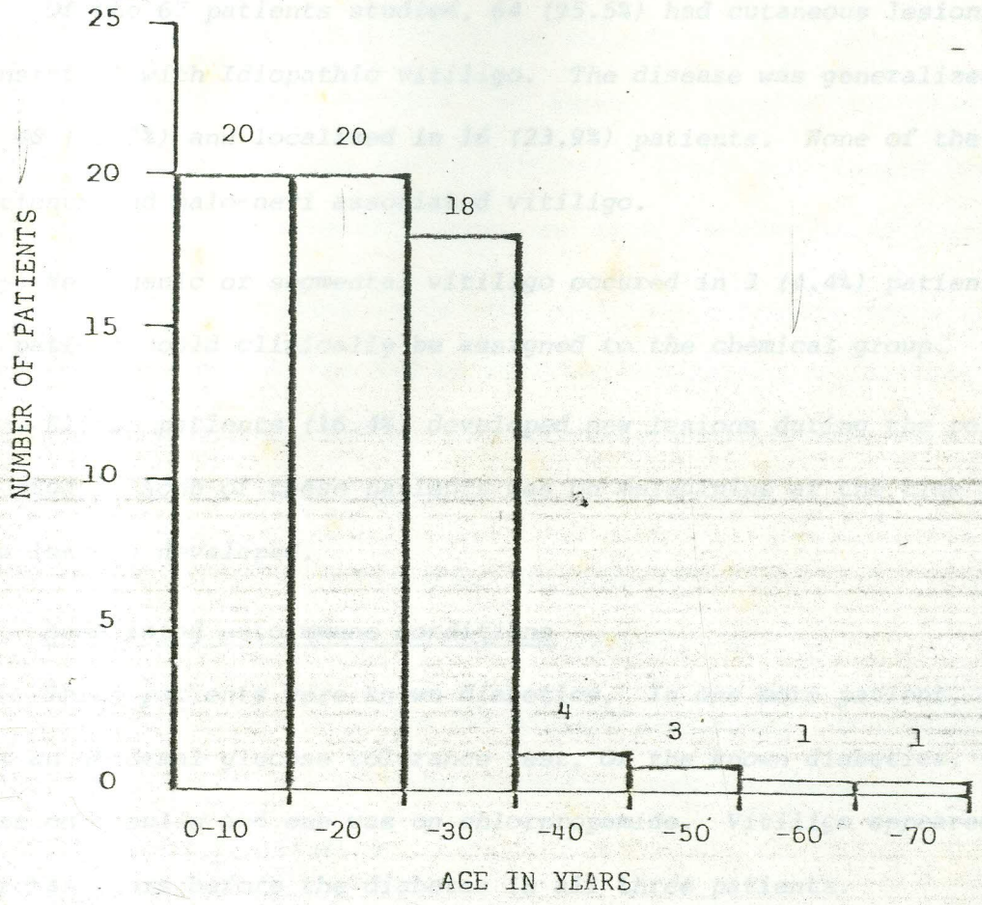


FIGURE 4:
AGE AT THE TIME OF ONSET OF VITILIGO IN 67 PATIENTS

Clinical types

Of the 67 patients studied, 64 (95.5%) had cutaneous lesions consistent with Idiopathic vitiligo. The disease was generalized in 48 (71.7%) and localized in 16 (23.9%) patients. None of the patients had halo-nevi associated vitiligo.

Neurogenic or segmental vitiligo occured in 3 (4.4%) patients. No patient could clinically be assigned to the chemical group.

Eleven patients (16.4%) developed new lesions during the period of study. None of these patients was on meladinine at the time the new lesions developed.

Associated autoimmune conditions

Three patients were known diabetics. In one more patient, there was an abnormal glucose tolerance test. Of the known diabetics, two were on insulin and one was on chlorpropamide. Vitiligo appeared several years before the diabetes in all three patients.

In eleven patients (16.4%) there was a positive family history of vitiligo. Five (7.4%) patients had a family history of diabetes mellitus. Macrocytic anaemia was not detected in any of the patients.

Autoantibodies

Forty three blood samples from vitiligo patients and 35 from a control group were sent to Oslo, Norway for immunological studies.

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However due to technical difficulties only 40 samples, all from vitiligo patients were analysed. Of these, 22 samples were from male patients and 18 from female patients. Their ages ranged from 5 to 47 years. Duration of disease was from 2 months to 18 years.

Antinuclear antibody tests were positive in ten specimens (25%). Of these ten patients one had in addition a weakly positive test for gastric parietal cell. Another patient had a positive test for rheumatoid factor (with a titre of 1:32).

One sample had an antinuclear antibody titre of 1:100. In the rest of the samples the titres did not exceed 1:50.

All samples were negative for thyroid microsomal and thyroglobulin antibodies. There were no relationship between the autoantibody status and duration of the disease.

Published results of autoantibody studies in patients with vitiligo are compared with those of the present study in table I.

Blood groups

There was no relationship between vitiligo and blood group or rhesus factor.

.../21.

TABLE I. COMPARATIVE RESULTS OF AUTOANTIBODY STUDIES IN VITILIGO

	BROSTOFF et al 1969		BOR et al 1969		HOWITZ & SCHWARTZ 1971		WOOLFSON et al 1975		BETTERLE et al 1976		PRESENT STUDY 1981	
	A	B	A	B	A	B	A	B	A	B	A	B
Number of patients	80	80	62	62	102	102	42	42	100		40	-
Thyroglobulin Antibody	8.7	0	-	-	-	-	7.1	0	-	-	0	-
Thyroglobulin Microsomal Antibody	27.5	7.5	-	-	-	-	11.9	4.7	20*	-	0	-
Gastric parietal cell Antibody	21.2	1.2	25.5	8.0	20.0	6	14.2	19.0	13.7*	-	2.5	-
Antinuclear Antibody	3.7	2.5	-	-	-	-	14.2	16.6	-	-	25	-
Rheumatoid Factor	-	-	-	-	-	-	19.0	7.1	-	-	2.5	

A - patients

B - Controls

(-) - Not done

*Significant at $p<0.01$

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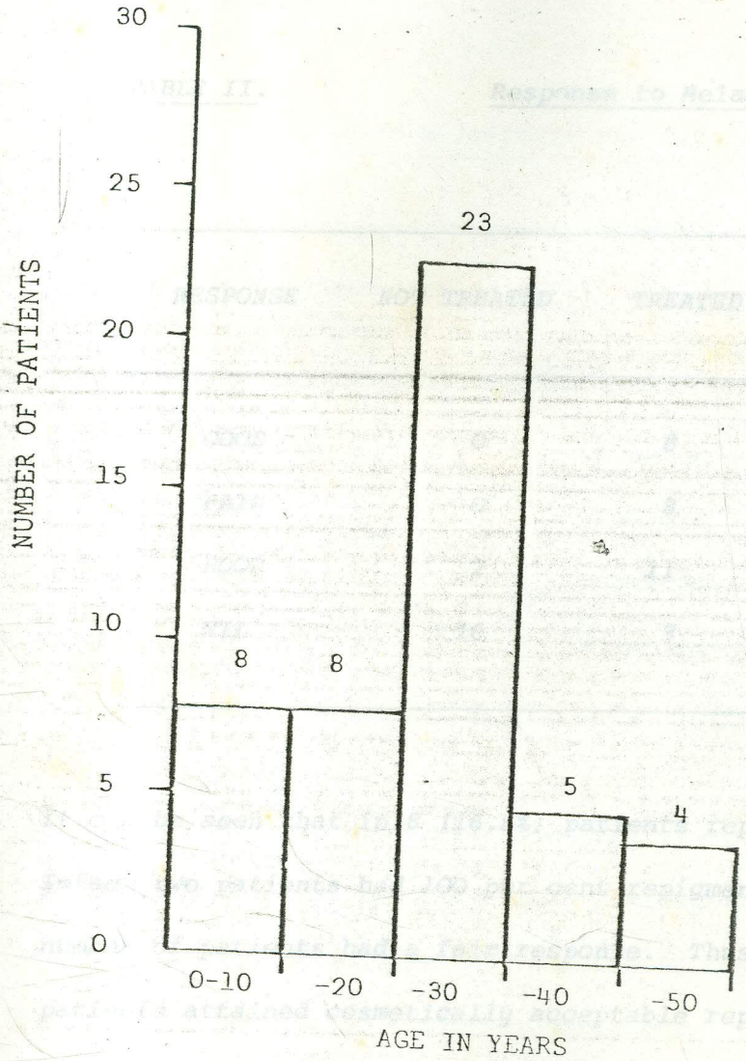


FIGURE 5:
AGE DISTRIBUTION AMONG 48 VITILIGO PATIENTS WHO HAD REGULAR ATTENDANCE TO THE CLINIC

The response to meladinine is shown in table II below.

TABLE II. Response to Meladinine

RESPONSE	NOT TREATED	TREATED	TOTALS
GOOD	0	8	8
FAIR	0	8	8
POOR	2	11	13
NIL	16	3	19

It can be seen that in 8 (16.6%) patients repigmentation was good. Infact two patients had 100 per cent repigmentation. A similar number of patients had a fair response. Thus sixteen (53.3%) patients attained cosmetically acceptable repigmentation compared to none in the untreated group. The results are significant ($p < 0.01$).

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Table III compares the response to meladinine with the duration of the disease.

TABLE III: Response to meladinine viz duration of disease

Response to Meladinine	Number of Patients	Duration of Disease	
		Range	Mean (Years)
GOOD	8	2 months - 10 years	3.9
FAIR	8	2 months - 23 years	4.5
POOR	11	2 months - 35 years	7.0
NIL	3	6 months - 14 years	7.0

From table III it can be seen that there is no clear relationship between the duration of the illness and response to meladinine. However, the results imply that chances of repigmentation are higher when the disease is of a shorter duration.

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Repigmentation in the different age groups is shown in table IV.

TABLE IV: Patients' age viz response to meladinine

Response to Meladinine	Number of Patients	Age in Years		Sex ratio
		Range	Mean	M:F
GOOD	8	5 - 34	17	3:5
FAIR	8	8 - 28	24	3:1
POOR	11	4 - 40	27	3:4
NIL	3	20 - 42	27	2:1

The smaller mean age for patients with good repigmentation (table IV) indicate that younger patients respond better to meladinine than older patients. (The age distribution in this group was 6, 6, 7, 13, 17, 23, 31, 34 years). However, other factors (in addition to the age) are likely to influence repigmentation. That this is true is suggested by the fact that not all children attained repigmentation. On the other hand, some adults had good repigmentation.

Repigmentation was faster and better for lesions on the head and neck. On the contrary genital lesions and those on bony prominences had poor repigmentation.

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DISCUSSION

This study was conducted at the Muhimbili Medical Centre's skin clinic. The clinic receives patients from different parts of the country. Some patients came from as far away as Arusha to the north, Lindi and Songea to the south and Tabora to the west of the country. However, the majority of the patients came from Dar es Salaam. No effort was made to encourage doctors working in these areas or other parts of the country to refer patients with leucoderma to our clinic.

During the course of the study two major problems were encountered.

(a) The supply of the drug (meladinine) came to a stop in the hospital pharmacy and subsequently in the city drug stores. All attempts to get the supply restored failed. However, some patients managed to get drugs from outside the country but the supplies were irregular.

(b) Analysis for auto-antibodies could not be done locally. It was therefore arranged to have the tests done in Oslo, Norway. As the specimens were being shipped to Norway, some specimens were mislaid and were subsequently rendered unsuitable for analysis. The samples affected were those from the control group and few from vitiligo patients.

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Not withstanding the foregoing problems the study provides very useful information about vitiligo in Tanzania. In the first place, over 30 percent of the patients developed vitiligo before their 10th birthday, and the disease had clinically manifested itself before the age of 30 years in more than 88 percent of the patients.

The mean age was 24.2 years and the mode was in the age range 20 - 30 years. The predominantly young population in this study could be due to several factors. Firstly it could be simply a reflection of the age structure of the population since the Tanzania population is comprised mainly of young people.[48] Secondly it could be that the older patients did not turn up to the clinic. This is particularly likely bearing in mind the fact that vitiligo per se does not portend shortened life expectancy of its victims.[29] The older patients may have thus lost hope of getting cured and saw no reason of going to the hospital. However, other studies, done in populations with different age structures, have shown that the disease manifests itself before or during early adulthood in the majority of the victims.[3,41] It is, therefore, quite likely that the population age structure has had no significant influence on the results of the present study.

The sex ration was about one to one. This concurs with what has been reported in larger series by Kugelman and Lerner[4] and by El-Mofty.[3]

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Fitzpatric and associates,[13] reported a sex ratio in favour of females, however they ascribed the female preponderance in their series to the "skin conciousness" of women. The available evidence to date, therefore, suggests that vitiligo has no sex predilection.

The majority (95.5 per cent) of the patients had idiopathic vitiligo. The disease was generalized in 71.6 per cent of the total patients. Considering that this is a hospital based study, it is quite likely that patients with more severe disease sought medical help and were referred to the skin clinic. Patients with small, localized lesions, especially in the covered areas were less likely to go to hospital and even more less likely to have been referred to the skin clinic.

During the period of study, eleven (16.4%) patients developed new lesions. This was not unexpected since the natural history of the disease is characterized by periods of exacebations amd remissions.

History of vitiligo in the family was positive in 11 (16.4%) patients and negative in 56 (83.6%) patients. These results indicate that in the majority of cases the disease was sporadic.

Lerner[16] working in the United States reported that 38 per cent of his patients gave a family history of vitiligo. In Egypt, the frequency was reported to be 35 per cent. Genetic or environmental factors (or a combination of the two) are likely to be the major factors to account for the difference between these reports and my findings.

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Five (7.4%) patients had a family history of diabetes mellitus. In the three patients with clinical diabetes, vitiligo appeared several years before diabetes was detected. Two patients were on insulin and one was on chlorpropamide. Two of the patients had clinical diabetes mellitus before the age of 20. One patient, a 22 years old female had abnormal glucose tolerance test. Since the incidence of diabetes mellitus in Tanzania is unknown, it is difficult to interpret these observations.

The prevalence of antinuclear antibody for the patients was 25 per cent. Except in one sample (with a titre of 1:100) the antinuclear antibody (ANA) titres were low (1:50 or less). Lorincz, Soltani and Bernstein,[49] in a review article stated that only titres of 1:160 or more were of diagnostic significance. Titres of ANA in the range 1:60 - 1:160 were of doubtful significance, and those below 1:60 were of no diagnostic significance. Using this criteria, the ANA titres in this study are insignificant in 9 patients and of doubtful significance in one patient.

Thyroid antibodies were not detected in any of the 40 samples analysed. One sample gave a weakly positive test for gastric parietal cell antibody. These results indicate that vitiligo in the African is not associated with autoantibodies and probably not to autoimmune disease of the thyroid or the gastric parietal cell.

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Serum level of antibodies fluctuate considerably depending on the activity of the disease at the time of taking the blood samples. Estimations of antibody levels while the disease is active (as evidenced by appearance on new lesions) could provide useful information.

My results of autoantibody analysis differ from those reported for caucacian vitiligo patients[23,31,32] and concur with reports that autoimmunity as well as autoimmune diseases are rare in the African.[50,51,52] The explanation for the rare occurence of autoimmunity in the African is not known. It has been said to be related to altered immunological state produced by multiple parasitic infections since childhood.[50] However, the manner in which parasitic infections would interfere with autoimmunity remains entirely speculative. Reduction of the sensitivity of the immune system, to the factors responsible for the production of autoimmune disease, by massive antigenic stimulus of multiple heavy parasitic infections has been suggested to explain the inverse relationship between parasitic infections and autoimmune disease.[50] Taylor,[52] suggested that genetic factors protect the African from autoimmunity. The absence of organ specific antibodies in the patients studied is, therefore, likely to be due to both genetic and environmental factors.

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Concerning the association between ABO blood groups and vitiligo, none could be demonstrated in the present study. The studies of Srivastava and Shukla[53] and those of Sehgal and Dube reported a higher risk of vitiligo in patients with blood groups B and A and B respectively. However, these reports have been disputed on the ground that the control groups were not properly selected. In a study of 1000 patients Kareemullah and associates[56] could not find any association between vitiligo and blood groups. Todate, there is no convincing evidence to suggest that the ABO blood groups and vitiligo are related.

Turning to treatment, lesions on the head and neck responded better to therapy than lesions elsewhere. Conversely genital lesions and those on bony prominences had the poorest response. These observations could be accounted for by histological or biochemical differences of the lesions or differences in the duration and frequency of solar exposure or a combination of these factors.

Histological or biochemical factors are however, unlikely to account for the noted differences as the biochemistry and anatomy of vitiligo lesions in the skin are the same irrespective of the anatomical site. In the tropics, he head and neck frequently and unintentionally get solar exposure. On the contrary lesions on the genitalia are covered and don't get direct solar exposure. Though

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adviced to expose all the lesions to the sun, patients admitted, on questioning, that they did not expose the genital lesion(s). Lack of privacy was the major explanation. It is therefore, likely that genital lesions had poor repigmentation because they never had ultraviolet light which is essential for inducing repigmentation.

As regards the duration of illness and response to therapy no concrete deductions could be made from this study. However, the tendency was for newer lesions to repigment faster and better than older lesions. This could have been due to reactivation by psoralen and U.V. light of few melanocytes that may have been present in such lesions to increase production of melanin which in turn led to repigmentation.

Six of the 8 patients with good repigmentation were children or adolescents. It may be interesting to note that the highest success rate with psoralens has been reported to occur in children. There is no known explanation to account for the observed better response for children. However, it could be that lesions in children have some melanocytes which are reactivated by the psoralens. It is noteworthy that once repigmentation has been acquired, it may last for 20 years after treatment has been stopped.

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Optimal response to psoralens occur after six to twelve weeks of continuous treatment.[3] In only four of my patients was treatment continuous for over six weeks. Two of these patients had complete (100%) repigmentation. It is, therefore, quite likely that other patients would have had better repigmentation had treatment been uninterrupted and for longer duration.

With over 30 per cent of the vitiligo population in the present study, being children, it is expected that treatment with psoralens and ultraviolet light may bring happiness to many miserable patients and their families.

CONCLUSIONS

Like in other racial groups, idiopathic vitiligo was the predominant clinical type of the disease encountered in the African. However, the association of autoimmunity and vitiligo reported in the caucacians was not observed in the present study.

Since psoralens combined with solar exposure (or UVA) can induce complete repigmentation in some patients, it is recommended that vitiligo patients should be given psoralens continuously for a substancial duration of time (preferably six months).

Psoralens should therefore be available in a few selected centres where proper instructions and follow up can be offered.

PART III: REFERENCES

1. Nordlund J.J., Lerner A.B., Miller L.H. Kenney J.A. (1978). Proceedings of the First International Workshop on Vitiligo. J. Invest. Dermatol 71:165 - 166.

2. El-Mofty, A.M., El-Mofty, M. (1980). Vitiligo: A symptom complex. Int. J. Dermatol 19:237 - 344

3. El-Mofty, A.M. (1968). Vitiligo and Psoralens. Oxford, England, Pergamon Press, 1968.

4. Kugelman, T.P., Lerner, A.B. (1961). Albinism, Partial albinism and Vitiligo. Yale J. Bio. Med. 33:407 - 414.

5. Soyinka, F. (1975). Current topics in Dermatology:Vitiligo. Niger. Med. J. 5:82 - 84

6. Browne, S.G. (1972). Common causes of depigmentation of the skin in the tropics. Tropical Doctor 2:59 - 64

7. Fitzpatric, T.B. (1964). Hypomelanosis J. Sth. Med. Ass. 57:995.

8. Jimbow, K., Quevedo, W.C., Fitzpatric, T.B. et al (1976). Some aspects of melanin biology 1950 - 1975. J. Invest. Dermatol. 67:72 - 89.

.../36.

9. Konisita, H. (1963). Electrophoretic theory of pigment migration in the fish melanophore.
Ann N.Y. Acad. Sci. 100:992 - 1004.

10. Novales, R.R., Novales, B.J. (1965). The effects of osmotic pressure and calcium ion deficiency on the response of tissue cultured melanophores to Melanin stimulating hormone.
Gen. Comp. Endocrinol 5:568 - 576.

11. Marsland, D. and Meisuer, D. (1967). Effects of D_2O on the mechanism of pigment dispersal in the melanocytes of Funculus heteroclitus. A pressure temperature analysis.
J. cell Physiol. 70:209 - 215.

12. Green, L. (1968). Mechanism of movement of granules in melanocytes in Fundulus heterolyticus.
Pro. Natl. Acad. Sci. USA 59:1179 - 1186.

13. Fitzpatric, T.B., Arndt, K.A., Clark, W.H. et al (1971). Dermatology in General Medicine: New York, McGraw-Hill Company. A Blankiston publication.

14. Lever, W.F., and Schaumburg-Lever G: Histopathology of the skin. Philadelphia, J.B. ed 5 Lippincott Co. pp 420 - 421.

15. Morohashi, M., Hashimoto, K., Goodman T.F. Jr. et al (1977). Ultrastructual studies of Vitiligo, Vogt-Koyanagi syndrome and incontinentia pigment achromias.
Arch. Dermatol. 113:755 - 766

.../37

16. Riley, P.A. (1967). A study of the distribution of epidermal dendric cells in pigmented and unpigmented skin.
J. Invest. Dermatol. 48:28 - 38.

17. Lerner, A.B. (1959): Vitiligo
J. Invest. Derm. 32:285.

18. Goudie, R.B., Spence, J.C., Mackie, R. (1979): Vitiligo patterns simulating autoimmune and reheumatic diseases.
Lancet; ii:393 - 395.

19. Ochi, Y., DeGroot, L.J. (1969): Vitiligo in Graves' Disease.
Ann. Int. Med. 71:935 - 940.

20. McGrevor, B.C., Katz, H.I., Doe, R.P. (1972): Vitiligo and Multiple glandular Insufficiencies.
JAMA 219:724 - 725.

21. Allison, J.R., Cutis, A.C. and Abor, A. (1955): Vitiligo and pernicious anaemia.
Arch. Dermatol 72:407 - 408.

22. Forcier, J.R., McIntyre, O.R.., Frey, W.G. et al (1972): Autoimmunity and multiple endocrine abnormalities.
Arch Int. Med 129:638 - 41.

23. Howitz, J., Schwatz, M. (1971): Vitiligo, achlohydria and pernicious anaemia.
Lancet 1:1331 - 1335.

24. Grunnet, I. Howitz, J., Reyman, F. et al 1970. Vitiligo and pernicious anaemia.
Arch. Dermatol 101:82 - 85.

.../38.

25. Dawber, R.P.R. (1970): Vitiligo inmature onset diabetes mellitus

Br. J. Dermatol. 80:275 - 278.

26. Burns-Cox and Pearson, J.E.G., (1972): Addisons Disease, Vitiligo & alopecia areata.

Postgrd. Med. J. 48:115 - 117.

27. Hertz, K.C., Gazze, L.A., Kirkipatric, C.H., et al (1977): Autoimmune Vitiligo: Detection of autoantibodies in melanin producing cells.

NEJM 297:634 - 637.

28. Lerner, a.b., nordlund, J.J., Albert, D.M. (1977): Pigment cells in the eyes in people with Vitiligo.

N.E.J.M 296:232.

29. Lerner, A.B., Nordlund, J.J. (1978): Vitiligo, what is it? Is it important.

JAMA. 239:1183 - 1187.

30. Cunliffe, W.J., Hall, R., Newel, D.J. et al (1968): Vitiligo, thyroid disease and autoimmunity.

Br. J. Derm. 80:135.

31. Brostoff, J., Bor, S., Feiwel, M: (1969). Autoantibodies in patients with vitiligo.

Lancet ii:177 - 178.

32. Betterlle, C., Del-Prete, G.F., Peserico, A et al (1976): Autoantibodies in Vitiligo.

Arch. Dermatol 112:1328.

.../39.

33. Woolfson, H., Finn, O.A., Mackie, R.M. et al (1975): Serum antitumor and autoantibodies in Vitiligo.
Br. J. Dermatol 92:395 - 400.

34. Langhof, H., Feuestein, M. and Schabinski, G. (1965): Melaninatikoperbeldung bei Vitiligo. Hautarzt, 5:209. quoted by Woolfson et al (33) (1975).

35. Oliver, E.A., Schwartz, L., Warren, L.H.: (1940) Occupational leucoderma
Arch. Dermatol 42:993 - 995.

36. James, O., Mayers, R.W., Stevenson, C.J., (1977): Occupational Vitiligo induced by p-tertbutyl phenol: A systemic disease.
Lancet 2:1217 - 1219.

37. Lerner, A.B. (1971): Editorial. On actiology of Vitiligo and Gray hair.
AM. J. MED. 51:141 - 147.

38. Kahn, G. (1970): Depigmentation caused by phenolic detergent germicides.
Arch. Dermatol 102:177 - 187.

39. El-Mofty, A and El-Mofty, M. (1981): Vitiligo: Aetiology and treatment. Paper read at the First Pan-African Congress of Dermatology at Arusha. October 1981.

.../40.

40. Breathnach, A.S., Bor. S and Wyllie, L.M.A., (1966): Electron Microscopy of peripheral nerve terminals and marginal melanocyte in Vitiligo.
J. Invest. Dermatol 47:125 - 140.

41. Lerner, A.B., Denton, C.R., Fitzpatric, T.B. (1953): Clinical and experimental studies with 8-Methoxypsoralen in vitiligo.
J. Invest. Dermatol, 20:299 - 314.

42. Kenney, J.A. (1971): Vitiligo treated with psoralens: Long term follow up study of the permanency of repigmentation.
Arch. Dermatol 103:475 - 80.

43. Imamura, S. (1976): Treatment of Vitiligo with oral corticosteroids.
Dermatologica 153:179 - 185.

44. Gokhale, B.B., Gokhake, T.B. (1976): Corticotrophin and Vitiligo.
Br. J. Dermatol, 95:329.

45. Behl, P.N. and Bhatia (1973): Treatment of Vitiligo with autologous this Thierschsgrafts.
Int. J. Dermatol 12:329 - 331.

46. Fitzpatric, T.B. Arndt, K.A., El-Mofty, M. et al (1961). Hydroquinone and Psoralens in therapy of hypermelanosis and Vitiligo Arch. Dermatol 93:589 - 591.

47. Mishima, Y (1978) Histopathology of functional pigmentary disorders.
Cutis 21:225 - 230.

.../41.

48. *1978 Population census: Bureau of statistics. Ministry of Finance and Planning, Dar es Salaam, Tanzania (1981).*

49. *Lorincz, L.L., Soltani, K. and Bernstein, J.E. (1981) Antinuclear antibodies.*

Int. J. Dermatol 20(6):401 - 410.

50. *Greenwood, B.M. (1968): Autoimmune diseases and parasitic infections in Nigerians.*

Lancet 2:380 - 382.

51. *Olurin, E.O., Itayemi, S.O., Oluwasanmi J.O. et al (1973): The pattern of thyroid gland disease in Ibadan.*

Niger Med. J. 3(2):58 - 65

52. *McGill, P.E. (1971): Thyrotoxicosis in the African: A clinical immunological observation.*

B.M.J. 2:679 - 681.

53. *Taylor, J.R. (1968): The Thyroid in Western Nigeria.*

EAMJ 45:390 - 397.

54. *Srivastava, G.N., Shukla, R.C. (1965): ABO blood groups in Vitiligo.*

Ind. J. Med. Res. 53:221 - 225.

55. Sehgal, V.N. and Dube, B, (1968): *Secretion of blood group specific substances in Saliva of Vitiligo patients. A preliminary Report:*

Br. J. Derm. 79:704 - 705.

.../42.

56. Kareemullah, L., Taneja, V., Begum, S. et al (1977): Association of blood groups and Vitiligo. J. Med. Genetics 14(3):211 - 213.

57. Beck, J.S. (1961): Variations in the morphological patterns of autoimmune nuclear flourescence. Lamcet, i:1203 - 1205.

58. Fulthrope, A.J., Roitt, J.M., Doniach, D. and Couchman, K. (1961): A stable sheep cell preparation for detecting thyroglobulin antibodies and its clinical applications. Journal of clinical Pathology, 14:654 - 660.

59. Holborow, E.J., Brown, P.C., Roitt, I.M., Doniach, D. (1959): Cytoplasmic localization of "complement fixing" autoantigen in human thyroid epithelium. British Journal of Exp. Pathology 40:583.

60. Adams, J.F., Glen, A.I.M., Kennedy, E.H., Mackenzie, I.L. et (1964): The histological and secretory changes in the stomach in patients with autoimmunity to gastric parietal cells. Lancet, i:401 - 403.