# CUTANEOUS MALIGNANT MELANOMA

# IN

# THE NATAL PROVINCE

## AN EPIDEMIOLOGIC STUDY

## REFLECTIONS UPON ITS AETIOLOGY

by

A H FLAMMENT

Submitted in partial fulfilment of
the requirements for the degree of

Doctor of Medicine

in the

Department of Plastic Surgery

University of Natal

1985

Durban
1985

# I N D E X

# PREFACE

The research work described in this thesis was carried out in the Department of Plastic Surgery, University of Natal, Durban, from January 1981 to December 1983, under the supervision of Professor J P Jordaan.

These studies represent original work by the author and have not been submitted in any form to another University. Where use was made of the work of others it has been duly acknowledged in the text.

# ABSTRACT

The purpose of the study has been primarily to draw a profile of malignant melanoma in the different population groups inhabiting the Natal Province and Kwa-Zulu, to compare the presentation and incidence of the disease between these groups as well as with similar racial groups in different countries. The data collected then permitted to estimate which parameters were relevant in predicting the course of the disease, as well as the results of surgical and adjuvant therapy, and was utilized in a search for the aetiology of the tumour.

# TERMINOLOGY AND ABBREVIATIONS

## MELANOMA

Since all melanomas are malignant, the adjective malignant has been deleted in most instances. The plural form, ending with s, has been adopted preferably to the Greek plural form : melanomata.

## CLASSIFICATION

The following description has been used:

Lentigo maligna melanoma (LM)

Superficial spreading melanoma (SS)

Nodular melanoma (Nod)

Acral melanoma (AC)

Amelanotic (Amel)

Staging has been described as:

Stage I - Localized melanoma without metastases to distant or regional lymph nodes.

Stage II - Metastases limited to regional lymph nodes.

IIa - Regional lymph node involvement at the time of surgery.

IIb - Regional lymph node involvement occuring after excision of the primary lesion.

Stage III - Disseminated melanoma (either visceral and/or multiple lymphatic metastases, or multiple cutaneous and/or subcutaneous metastases.)

## ABBREVIATIONS

BCG - Bacillus Calmette Guerin

DTIC - Dacarbazine

CCNU - Lomustine

# INTRODUCTION

In the annals of medical history, Hippocrates is the first to mention melanoma. It is then reported in the literature, along the centuries: Rufus of Ephesus (607 - 1207), Highmore (1651), Bartholin (1677), Bonet (1679). (1)

Laënnec discussed it before the Faculty of Medicine in Paris in 1806 (2). He called it "La melanose" (melanosis). However, the word melanoma, as we understand it nowadays, was first used by Carswell in 1833 to describe pigmented malignant tumours (3). Pemberton in 1858 performed a wide and deep dissection, carrying the level of excision deep to the deep fascia, excising at the same time involved lymph nodes in the groin, a practice still accepted today (4). In 1908, Pringle (5), following Handley's concept of permeation of the lymphatic vessels by malignant melanoma, was the first to adopt the principle of "excision and dissection in continuity," meaning a radical excision of the tumour with skin, fascia and dependant lymph nodes in an "en bloc" excision.

Our ancestors were not immune to the disease : seven pre-Colombian mummies, estimated to be 2400 years old, showed diffuse metastases, mostly of the skull and extremities (6,7). This correlates with modern findings of bone involvement by metastatic melanoma; in the mummies skin, cutaneous tumours could still be recognized. This is indeed a surprising discovery; as far as can be ascertained, only the superior class of these populations qualified for such post-mortem attention; mummies being a rare finding, that so many presented an advanced stage of melanoma leads one to think that the disease must have been rather common then, and this amongst a non-white population.

A comparative study of two vastly different populations living in the same environment is therefore feasible. At the same time, it is of interest to compare the findings resulting from the study of both groups, with American Negroes on one side, and Australian Whites on the other side, bearing in mind, for the latter, that Natal shares with Queensland nearly identical latitudes, the same narrow coastal fringe giving rise to the same escarpment and plateau westward and, lastly, a comparable daily average number of hours of sunshine.

In so far, the surgical treatment of the primary lesion in melanoma has been rather stereotyped and for most surgeons still consists of a tri-dimensional wide excision which includes skin, fat and fascia, often associated with a regional lymph node dissection, whether the nodes appear clinically involved or not. It must be noted that the word "wide" is used in a broad sense; indeed, few have committed themselves in giving numeric values.

As for many concepts in modern surgery, the reference is to be found in the beginning of the century; Handley's observation in 1907 has been the cornerstone in the management of melanoma, and its influence still prevails. Yet, in his observation, Handley was not referring to a primary lesion but the autopsy findings of a disseminated melanoma. Thus, our surgical approach to the problem has been based on inadequate premises and can rightfully be questioned.

If one accepts the concept that malignancy arises when there is a systemic breakdown in the host's resistance, then boosting the immune system would appear to be the logical approach; yet the value of such additional therapy is doubted by many, possibly because the series published have been few, have involved small numbers of patients, and have produced no definitive conclusions.

Natal is shared between four population groups: Black, White, Indian and Coloured, in order of numerical importance. Each presents a different incidence in melanoma, when not a different type; such a set of circumstances leads to reflection in our quest for the aetiological factors governing the occurence of melanoma: is the disease the stereotyped clinical manifestation of entirely different race-related and/or habit-related factors?

# CUTANEOUS MELANOMA IN THE ZULU POPULATION

## EPIDEMIOLOGIC SURVEY IN THE ZULU POPULATION (1977-1982)

The present study was conducted in order to determine the incidence rate of melanoma in the Zulu population group, its variation in incidence over the last six years, and a profile of the affection. This is a hospital epidemiologic study; no field survey was undertaken.

### MATERIALS AND METHOD

All cases of malignant melanoma referred to the combined melanoma clinic, King Edward the VIIIth Hospital, and to the Department of Plastic Surgery, Wentworth Hospital, have been included in the series. All Zulu patients presenting with such tumours, in the Natal Province and Kwa-Zulu, are referred to both Institutions, either for primary treatment or, if treated primarily elsewhere, for further surgery as deemed necessary and/or palliative treatment. The figures obtained are therefore as near a true account as possible of the number of melanoma patients in this population group. Furthermore, since 1977, a register is being kept, in the Oncology Department, of all new cases, and used for follow-up.

Data collected for each case include: sex, age, region of residence, related history, anatomic site of the lesion, size of the lesion, clinical stage, level of invasion (8) and tumour thickness (9) when available, type of surgery performed, medical treatment and survival. Population statistics were obtained from the Department of Statistics, Pretoria (last census). There was no Albino patient in the series. Nine patients refused treatment.

### GENERAL TIME TREND

From the beginning of 1977 to the end of 1982, one hundred and nine(109) patients were referred to either or both Institutions. (Table I) Calculated with the last census figure of 4 756 320 Zulus in the Natal

Province and Kwa-Zulu, the incidence rose from 0,22/100 000 in 1977 to 0,50/100 000 in 1982.

| | 1977 | 1978 | 1979 | 1980 | 1981 | 1982 |
|---|---|---|---|---|---|---|
| Number of Patients | 11 | 14 | 15 | 21 | 22 | 24 |
| Incidence per/100 000 | 0,22 | 0,29 | 0,31 | 0,43 | 0,45 | 0,50 |

TABLE I : YEARLY INCIDENCE

Over the six year period covered in the study the incidence has more than doubled; the curve shows a linear progression with little dispersion. (Fig. I)

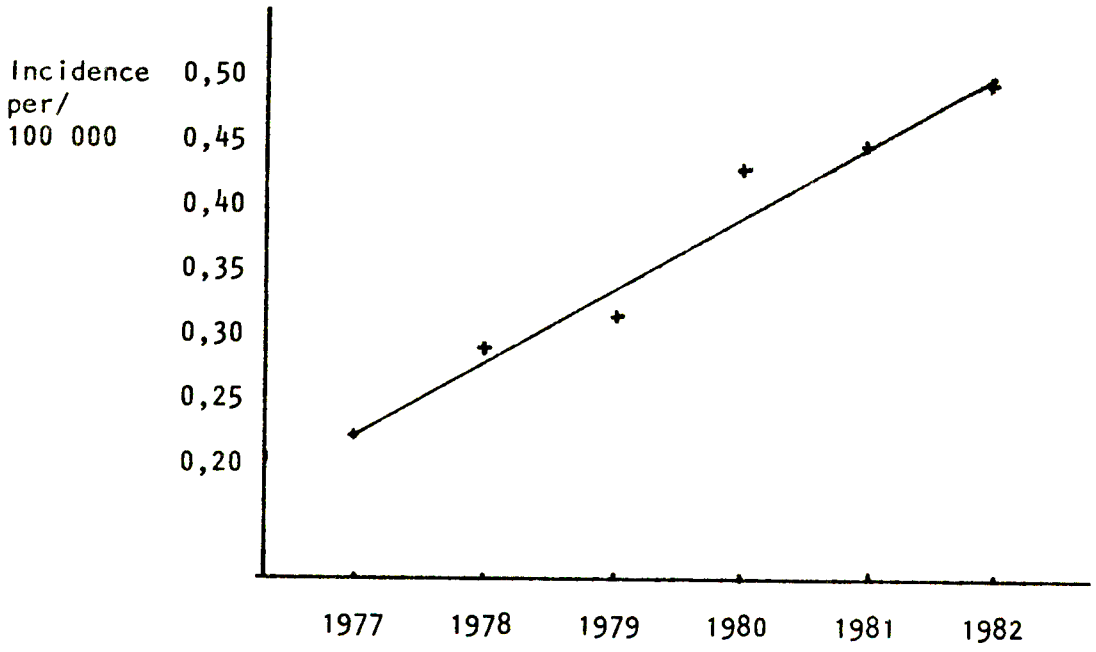



FIG. I CRUDE INCIDENCE (PER 100 000 POPULATION)

GEOGRAPHIC DISTRIBUTION

Only 17,5% of all patients lived in urban areas, the remaining 82,5% in a rural environment. In this subset of rural dwellers, 47% lived in the coastal plain while the others were widely dispersed over the rest of the Province.

SEX TREND

The incidence increase has affected more females than males: over the six year period, the increase has doubled for males, trebled

for females. The female to male ratio was 1,5/1. (fig. II)

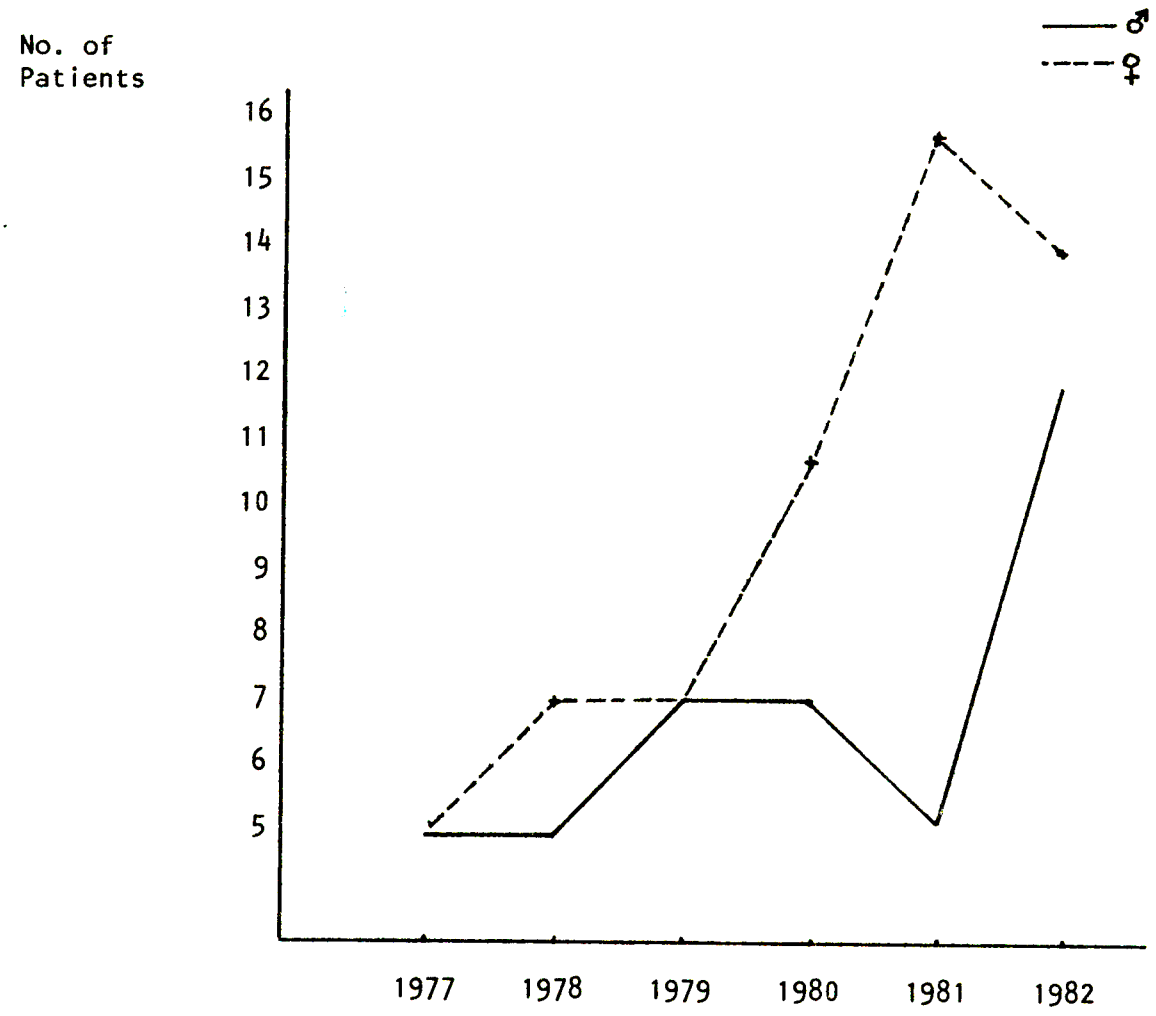



FIG. II SEX RELATED INCIDENCE

## AGE TREND

Incidence according to age has been studied in ten year intervals. The youngest patient in the series was 30, the oldest 89.

A steep rise in age-related incidence appears in the 40-50 year increment, to reach a peak in the 60-70 year group then sharply decrease (fig. III). However, when dissociated according to sex, the distribution presents a different pattern (fig. IV). Where most of the tumours affecting males occur during the 40-50 year period, and then steadily decrease in numbers, most of the female cases appear in the 60-70 increment, after a steady increase; there is a 20 year shift

between the two maximums. The peak of incidence as revealed on the histogram for cumulated figures is therefore artefactual and results from the greater number of females affected by the disease.

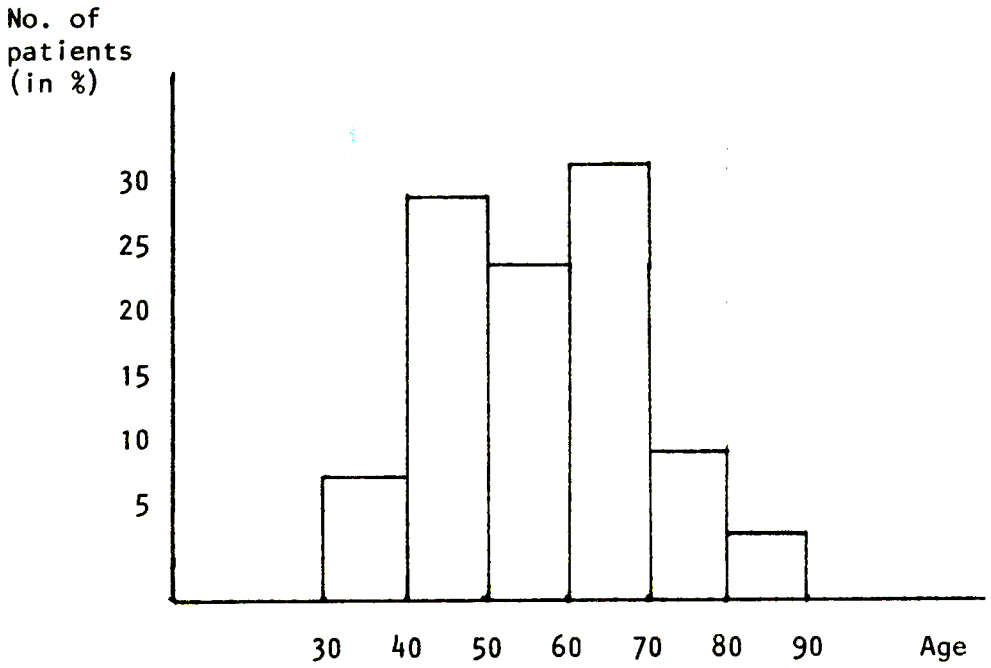



FIG. III AGE RELATED INCIDENCE

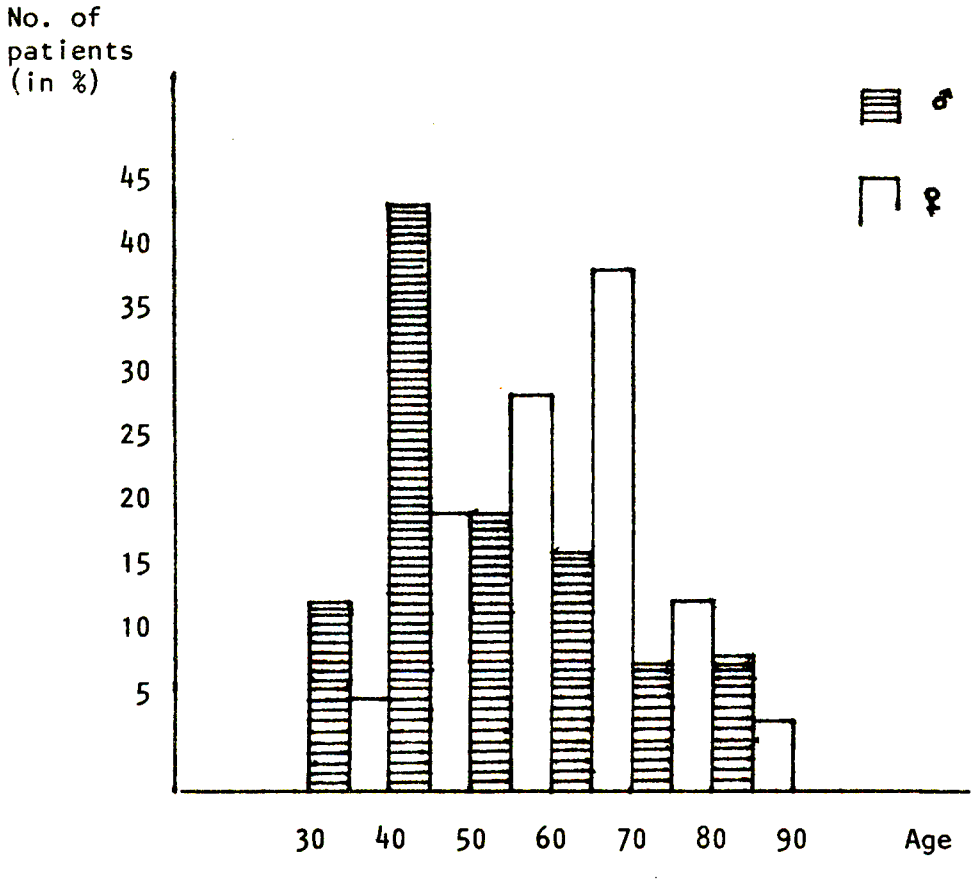



FIG. IV INCIDENCE ACCORDING TO SEX AND AGE

The small number of melanoma patients in the 80-90 year increment is also likely to be artefactual; since the standard death rates in the Zulu population are not available, a standardised mortality ratio could not be calculated, but it is doubtful that the number of melanomas occuring after 70 years of age should show such a decline.

## ANATOMIC DISTRIBUTION AND INCIDENCE

In the data collected, the following sites/subsites have been affected: Lips (lower), Hands (palm), Fingers, Leg, Feet (sole), Toes, Nail beds (parungual lesions). In one patient, the primary lesion could not be found. Three patients presented satellite lesions and all were on the plantar skin.

As intuitively assumed from clinical experience, most lesions affect the sole of the foot. In this series, all cases of melanoma of the foot were involving, even if slightly, the lesser pigmented skin of the sole, although at times the subsite seemed to be more prevalent in pressure areas, namely the region covering the head of the first metatarsal bone, the lateral side of the foot, the heel and the plantar aspect of the first toe. The incidence for each site/subsite is summarized in Table II.

| Site | Lip | Hand | Finger | Leg | Foot | Toe | Parungual | |
|---|---|---|---|---|---|---|---|---|
| No. of Patients | 3 | 1 | 2 | 2 | 73 | 9 | 17 | = 107 |
| Percentage | 3 | 1 | 2 | 2 | 68 | 8 | 16 | = 100% |

TABLE II SITE-RELATED INCIDENCE

Site-related incidence did not vary when considered in relation to sex groups.

## HISTORY OF THE LESION

16% of the patients related the tumour to previous trauma:

thorns, nails penetrating the sole of the foot; one patient reported that the tumour grew soon after the removal of a splinter from a fingernail bed, and another that the lesion appeared a few months after he had inflicted himself a heavy hammer blow on the finger tip.

Only 12% of the patients related the lesion to a pre-existing naevus. The African patient does not usually seek medical attention unless he feels pain or discomfort: because melanomas are to this regard, symptomless at the beginning, the delay between the time the lesion was first noticed and the time of first consultation is unfortunately long (Table III), as much as 24 and 39 months for the two leg lesion patients.

| Site | Duration before diagnosis: mean (in months) |
|---|---|
| Head and neck | 8 |
| Hand - Finger | 4 |
| Leg | 31 |
| Foot - Toe | 12 |
| Parungual | 6 |

TABLE III DURATION BEFORE TREATMENT

All tumours of the foot but one were ulcerated and infected when first seen, as well as all lesions affecting the palmar skin of hand and fingers.

## SIZE OF THE LESIONS

Because of the long delay before reporting for treatment, lesions were extensive with a maximum observed of 28,2$cm^2$ (foot lesion). 54% of all lesions were in the 9$cm^2$ range, 12% averaged 13$cm^2$.

## STAGING

After investigations including chest roentgenogram, lymphangiogram and when deemed necessary CT scan of bones, liver and

spleen, thirty six patients (33%) were classified as Stage I melanomas, 62 as Stage IIa (57%) and 11 as Stage III (10%). No particular site-related incidence could be identified in relation to the different stages, nor was there a sex-related trend. Twenty-seven patients (25%) presented with ulcerated lymph nodes (26 had ulcerated inguinal lymph nodes, one axillary ulcerated nodes). The mean number of clinically involved lymph nodes was 3.

DEPTH OF INVASION - TUMOUR THICKNESS

Histology reports were available for only 98 patients (9 refused treatment, in one the primary lesion could not be found). Measurement of tumour thickness according to Breslow's technique was not introduced before 1980 and was available for only 56 patients. No attempts were made in obtaining tumour thickness measurements for patients treated previously, since it could not be ascertained whether sections made at the time of first examination had intersected the thickest part of the speciment or not.

Levels of invasion according to Clark's classification for each site and subsite and summarized in Table IV.

| Site | Lip | Hand | Finger | Leg | Foot | Toe | Parungual |
|---|---|---|---|---|---|---|---|
| Level of Invasion: | | | | | | | |
| I | | | | | | | |
| II | | | | | 2 | | 1 |
| III | | | | | 7 | 1 | 2 |
| IV | 1 | 1 | 1 | 2 | 30 | 5 | 5 |
| V | 2 | | | | 26 | 3 | 9 |

TABLE IV LEVEL OF INVASION AS FUNCTION OF LOCALIZATION

Tumour thickness measurements varied from 1,3mm - the thinnest lesion in the series - Clark level II level of invasion - to 31mm,

Clark level V. Levels of invasion and tumour thickness did not correlated adequately: there was a wide dispersion of tumour thickness values for each depth of invasion (Fig. V). The explanation to this discrepancy is to be found in the characteristics of the skin involved: eighty six melanomas in the series occured in the skin of the palm of the hand and the sole of the foot: atrichal and weight-bearing skin can be exceedingly thick, even more so when shoe-wearing is occasional.

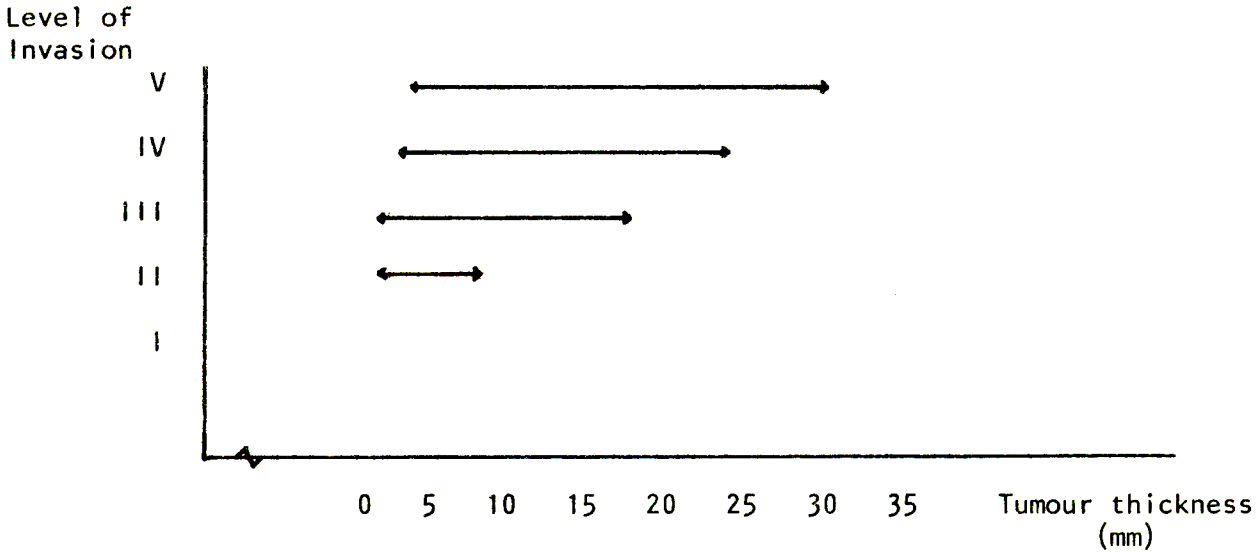



FIG. V LEVEL OF INVASION VERSUS TUMOUR THICKNESS

## DISCUSSION

While there is much research carried out on melanoma amongst diverse White populations, little information is available concerning the epidemiology of melanoma in Negro population groups. I. Kaplan and J. Youngleson (10) reviewed all melanoma cases treated at Baragwanath Hospital, Johannesburg, from 1951 to 1964, 98 patients over a 14 year period; however, they calculated the incidence according to hospital admissions and not population groups. Unlike the present series, there was no increase in incidence rates, but similarly was noted the slightly higher number of females, the same body distribution of the lesions and the length of symptoms. Giraud et al (11) conducted the same survey, in the same Hospital, and recorded a 100 cases from 1959 to 1970 (thus

including patients from Kaplam and Youngleson's study); they concluded that the incidence of melanoma in the Johannesburg Bantu population was 1,2 per 100 000, but gave no time trend. Their incidence figure is much higher than in the present study. John Higginson and A.G. Oettle, in their extensive "Cancer survey in the Transvaal" (12) reported only six cases of melanoma in the Bantu population (from which they had included migrants working in the mines) over a three year period, while Des Ligneris (13) mentioned the occurence of 17 melanomas from Northern Transvaal over twenty years. More recently, Shah and Goldsmith (14) studied the clinical behaviour of 18 cases of melanoma in American Negroes treated during the past twenty years at the Memorial Sloan-Kettering Cancer Center, New York, against 1483 cases of melanoma in White patients who received treatment at the same Institution over the same period; they made no mention of previous trauma as a possible aetiology, but thirteen of their patients had noticed a pre-existing mole at the site of the lesion.

Data are presently being collected by the Medical Research Council Unit in East London, but no results have yet been published.

RACIAL BACKGROUND

The American Negro differs genetically from any African group since there has been admixture of different ethnic genotypes; although most originate from the Western and Central parts of Africa, there has been inter-marriage between Blacks, Indians and Whites. Similarly, the Bantu population of the Johannesburg district is not representative of a specific sub-group since the region attracts workers from the whole sub-continent. On the contrary, the Zulu group appears homogeneous; because of his culture and proud history, the Zulu does not usually loosen ties with his ancestral customs; Zulus commonly marry Zulus, and tribal discrimation is prevalent. The present survey is therefore representative of the Zulu population only.

## ACCURACY OF THE SURVEY

Few Zulus are conversant with either official language of the Republic of South Africa; case histories and informations were obtained with the assistance of an interpreter, usually a nurse. As far as can be ascertained, the translations were adequate.

## CALCULATED RATIOS

Two common sources of error in epidemiologic surveys are: under-estimation of the population at risk and under-evaluation of cases. In the present survey, under-estimation of the population at risk is unlikely since the ratios have been calculated with figures from the most recent census; under-evaluation of cases is possible because of the very primitive conditions in which some members of this population group still live (particularly in Northern Natal), with inherent travelling difficulties.

## INCIDENCE OF MELANOMA

The study has revealed the following aspects: firstly, there is an increase in incidence rates in the Zulu group; secondly, the incidence increase follows a linear pattern: thirdly, there is a marked difference in the sex-related incidence in patients over fifty years of age. Yet, the highest incidence rate of 0,50 per 100 000 in 1982 does not correlate with other figures for other black population groups (Table V).

The rising incidence, however consonant with world-wide findings concerning White population groups, does not seem to have been reported in other Black population groups (but again, information available is scanty and the series published small). This rise could be the result of the following:artefactual errors, cohort effect, true rise in incidence, the reason for which is not apparent.

| BLACKS | Males | Females | Total |
|---|---|---|---|
| Nigeria (1960-1965) | 0,2 | 0,7 | 0,5 |
| U S A (1969-1971) | 0,7 | 0,6 | 0,6 |
| South Africa | | | |
| Cape (1956-1962) | 1,6 | 2,1 | 1,8 |
| Natal (1964-1966) | 0,9 | 1,2 | 1,0 |
| Transvaal (1953-1955) | 0,6 | 0,9 | 0,8 |
| Johannesburg (1959-1970) | 0,4 | 1,7 | 1,1 |

Figures given per 100 000

TABLE V INCIDENCE OF MALIGNANT MELANOMA FROM J J RIPPEY, E RIPPEY(15)

ARTEFACTUAL ERRORS

It is possible that year after year, more patients seek medical treatment for a lesion which was previously let to run its own course (or treated exclusively by the local Inyanga)* Greater awareness by general practitioners may also partially explain the increasing incidence of referrals. Diagnostic errors can be ruled out because the patients present with such advanced lesions that in most instances the diagnosis is clinically unmistakable. Because the rise is linear and affects both sex groups equally, because it is encountered throughout the Province and has more than doubled over the six year period of the survey, it is likely to reflect a true situation, however, difficult it is to exclude artefactual errors completely.

COHORT EFFECT

It is not feasible to exclude a cohort effect+ in a six year period study.

ANATOMIC DISTRIBUTION

The sites affected by the tumour as well as the incidence for each site do not differ markedly from other series.(Table VI)

* - Witch-Doctor

+ - A "Cohort" is defined as a group of individuals identified by a common characteristic, who are studied over a period of time.

The comparatively slightly higher number of melanomas affecting the sole of the foot result from adding to lesions of the sole other lesions of the ankle and sides of the foot, because they originated from non-pigmented skin. There were no lesions of the dorsum of the foot nor the hand; only two patients (1,8%) presented lesions on heavily pigmented skin (leg lesions); it is a striking feature of melanoma in Negroes, whether they live in Africa or in European-type societies, that the highest incidence is to be found in non or lesser pigmented skin, the site of predilection being the sole of the foot. This feature invalidates the aetiological hypothesis, at least in these population groups, of UV radiations being the responsible carcinogen.

| | | |
|---|---|---|
| Lower extremity (foot) | 156 - 76,5% | (80,4%) |
| Upper extremity (palms and fingers) | 19 - 9,3% | (10,7%) |
| Head and neck | 12 | ( 5,9%) |
| Trunk | 6 | ( 3,0%) |
| | 204 | |

TABLE VI SITE OF MELANOMA

(From Giraud R M et al: Malignant melanoma of the skin in Black Africans. South African Med. J. 49, 665 (1975)(11).

## SURGICAL TREATMENT AND SURVIVAL

Surgical treatment was undertaken by different teams, not following a standard pre-determined protocol.

## TREATMENT OF THE PRIMARY LESION

### CLEARANCE MARGINS

The mean clearance margin of excision was 2,5cm ranging from 1 to 8cm. It would seem that in most instances the limiting factor was the localization of the lesion itself, and the surgeon's deep concern of skin grafting a weight-bearing area when the plantar skin was involved.

Amputation as a treatment of the primary lesion was performed for all cases of parungual, finger and toe lesions; in these cases, amputation was performed at the level of the metacarpo/metararso-phalangeal joints (19 cases) or involved the whole ray (8 cases). The patients needed much convincing when this form of surgery was offered.

ADEQUACY OF EXCISION

Removal of the lesion was found incomplete in 12 cases, where the deep line of resection was not free of tumour; six of these cases were referrals from country hospitals; all were re-excised.

No prophylactic lymph node dissections were performed in Stage I melanomas, irrespective of level of invasion or thickness of the tumour. Local recurrence occured in sixteen cases, of which nine had an amputation and presented a tumour arising on the surgical scar.

## TREATMENT IN STAGE II AND III MELANOMAS

RECURRENCE

Despite complete excision of 36 Stage I patients, nineteen presented regional lymph node metastases following treatment of the primary lesion (53%), after a mean delay of eight months, ranging from 1 month to 17 months: likewise five such patients developed visceral metastases (Table VII).

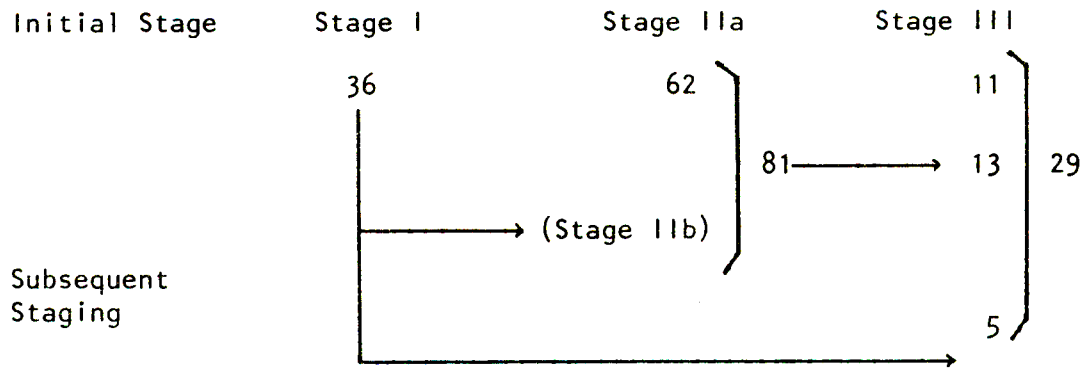



TABLE VII PATIENTS STAGING

In all cases of Stage II melanoma, a radical regional lymph node dissection was proposed; twenty-seven patients refused such treatment and were subsequently lost for follow-up. Stage III melanoma patients

were offered palliative therapy in the form of immuno-therapy (Bacillus Calmette-Guerin injections) and chemotherapy (DTIC- CCNU): no surgery was performed. Regular attendance for treatment was so poor as to render the results meaningless.

SURVIVAL

The difficulties encountered in locating patients or their relatives in order to estimate survival rates cannot be over-emphasised; the problem is compounded even further when it is known that patients often use different first names when registering in Hospitals. Only seventy one case histories could be utilized to estimate crude survivals and the number was estimated too small to draw valid conclusions regarding level of invasion, thickness of the tumour or staging and corresponding survival.

As could be expected from the advanced state of the tumours, survival is extremely poor in this population group. (Table VIII)

| | Males n = 34 | | Females n = 27 | | Percentage of Total (71) - all cases |
|---|---|---|---|---|---|
| Survival | | | | | |
| 1 year | 19/71 | 27% | 18/71 | 25% | 52 |
| 3 years | 10/71 | 14% | 12/71 | 17% | 31 |
| 3 years | 5/71 | 7% | 7/71 | 10% | 17 |

TABLE VIII CRUDE SURVIVAL RATES

DISCUSSION

Malignant melanoma in Negroes presents a monomorphous pathologic pattern, with particular characteristics: the tumour affects non or lesser pigmented skin, is predominant on extremities, is ulcerated and is prevalent in weight-bearing areas. Reed (16) in 1975 introduced the concept of acral lentiginous melanoma (ALM) to characterize those lesions which arise on volar and subungeal skin and histologically present a phase

of radial growth similar to that of mucosal melanomas. Arrington (17) further defined the behaviour of such tumours in a retrospective study of plantar lesions and noted that such melanomas presented a more aggressive behaviour than the superficial spreading or lentigo maligna types. A recent study of plantar lesions in the Black population of Nigeria reported that 66 percent were classified as nodular, 23,8 percent superficial spreading and the remainder were unclassifiable (18). The same doubtful classifications appeared in the present survey. Because these tumours have the same clinical behaviour and affect always the same anatomic sites i.e. the body extremities, they have been regrouped as acral lesions, as a separate entity.

Acral lentiginous melanoma, first described by Sir Jonathan Hutchinson in 1886 as a melanotic whitlow, occurs only in atrichous skin and mucous membranes, as seen in Black patients; its evolution is usually slow and it is not related to actinic damage. The tumour gradually enlarges, causing no pain or physical impairment, and large areas of skin are involved when symptoms call for attention, a clinical behaviour which is encountered in the Black patient; it may thus be assumed that the same type of tumour is being classified under two different names, acral melanoma being the clinical definition of acral lentiginous melanoma, a conclusion similarly reached by Krementz (19) in a review of White patients presenting this type of lesion. These melanomas have been attributed a poor prognosis; when tumour thickness and levels of invasion are considered, they do not seem to behave more aggressively than the other types of melanoma and certainly not the nodular variant. The poor prognosis is rather the result of the lesion being inconspicuous or thought inocuous over a long period. When comes the time of surgery, in-transit metastases have long spread; improvement in survival could certainly be achieved, should the patients seek treatment earlier.

# CUTANEOUS MELANOMA IN THE WHITE POPULATION

## EPIDEMIOLOGIC SURVEY IN THE WHITE POPULATION (1975-1982)

The survey covers the seven year period from the 1st January 1975 to the 31st December 1982.

### MATERIALS AND METHOD

Data was collected from the following sources: Department of Oncology, Addington Hospital; Department of Plastic Surgery, Wentworth Hospital; Doctor Duncan Taylor's Pathology Laboratory, Durban. Messrs J L Cooke, W M M Morris and J Youngleson kindly permitted access to their malignant melanoma patients' files which, besides allowing for cross reference with Doctor Duncan Taylor's register, provided for follow-up and history of a great number of patients.

Both Departments of Oncology and Plastic Surgery work in close relationship as regards the treatment of skin malignancies; moreover, the Oncology Department deals with many patients referred by Plastic and General Surgeons in private practice for the purpose of medical treatment of the disease after surgery, or for palliative treatment when, for various reasons, surgery was not possible.

In the absence of an official Cancer Registry, the figures obtained are thought to be as accurate as possible in the circumstances.

Data collected for each patient include: age, sex, region of residence, occupation, related history, site or subsite of the primary lesion, depth of invasion and tumour thickness when available, type of surgery performed, subsequent treatment and survival. Population statistics were obtained from the Department of Statistics, Pretoria (last census).

### GENERAL TIME TREND

From the beginning of 1975 to the end of 1982, 545 patients presented with a malignant melanoma. However, although this figure could be used to determine the population incidence, in 37 cases full data could not be obtained as regards the other parameters to be studied:

in three cases "shave-biopsies" had been performed, which did not allow for full histological reports: one case presented with disseminated melanoma after the primary lesion had been cauterized three years previously, no histology report was available. The following figures for each year are as follows:- (Table I)

| | 1975 | 1976 | 1977 | 1978 | 1979 | 1980 | 1981 | 1982 |
|---|---|---|---|---|---|---|---|---|
| No. of Patients (Total 545) | 44 | 37 | 47 | 74 | 71 | 85 | 93 | 94 |
| Incidence (per/100 000) | 7,4 | 6,2 | 7,9 | 12,4 | 11,9 | 14,3 | 15,6 | 15,8 |

TABLE I YEARLY INCIDENCE

The mean interval between time of occurence of the tumour and/or onset of changes in a pre-existing lesion and time of first consultation was 19,3 months, with extremes ranging from 3 months to 48 months.

With a White population in Natal and Kwa-Zulu of 595 820, the incidence has risen from 7,4 to 16 per 100 000 population. Over the 8 year period of the study, the incidence has more than doubled, (Fig. I) equally affecting men and women with a female to male ration of 1,2/1 (Fig. II). The years 1977 and 1978 showed a considerable increase, to be followed by more stability.

AGE TREND

Age incidence rates were determined for each ten year groups; the youngest patient was 9, the oldest 84. There is a steep rise in incidence in the 3rd and 4th decades, a moderate decrease in the fifth and maximum incidence in the seventh increment. (Fig.II)

When dissociated according to sex (Fig. III) males show a steadily increasing incidence with a peak at the sixth decade, while females present two incidence peaks, one at the fourth and one at the

seventh decades, which might indicate a heterogeneous population, possibly related to different hormonal conditions, before and after menopause. It must be noted that both sex groups show the same reduced incidences in the fifth age group. The sharp decline in the eighth and ninth increments is artefactual and results from the small number of cases seen in these age groups. (Standardised incidence could not be calculated due to lack of information regarding standardised mortality ratio).

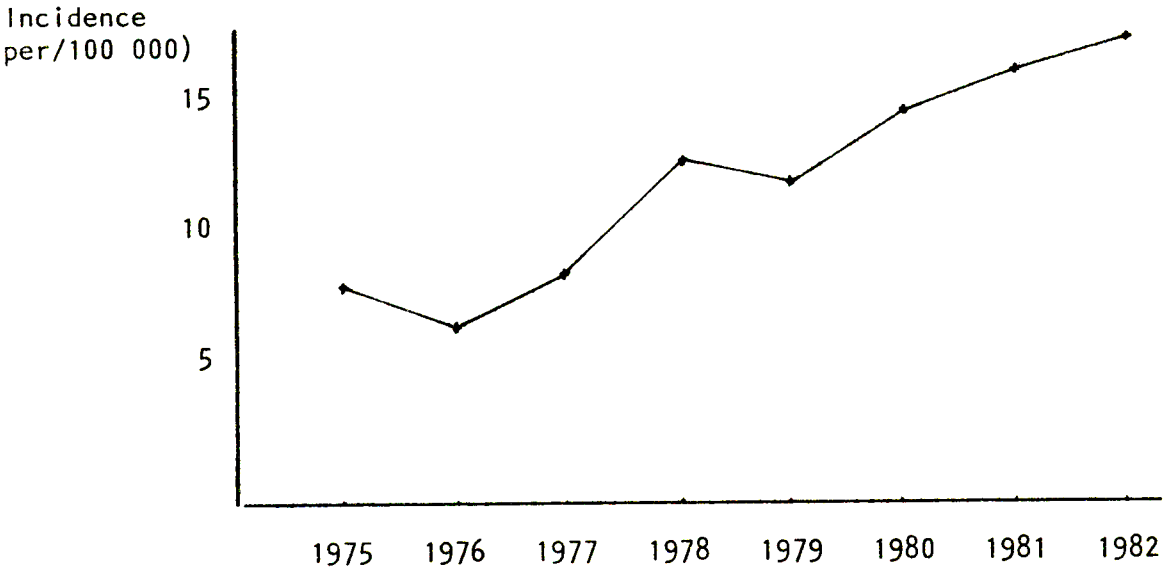



FIG. I CRUDE INCIDENCE (PER 100 000 POPULATION)

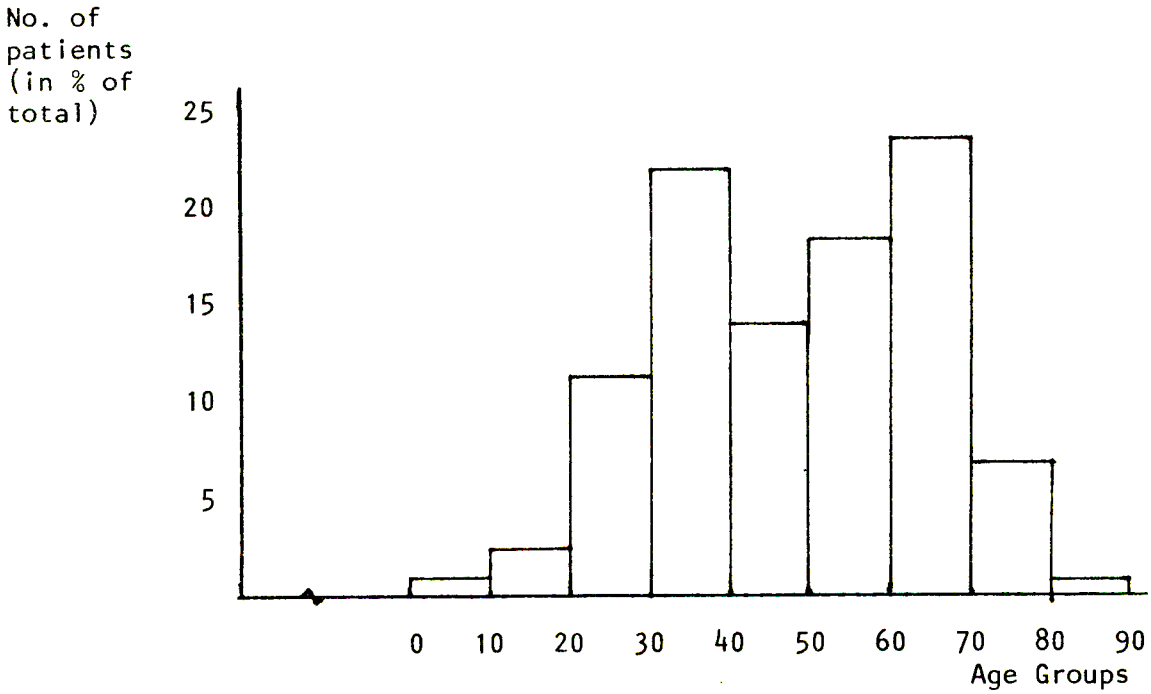



FIG. II AGE RELATED INCIDENCE

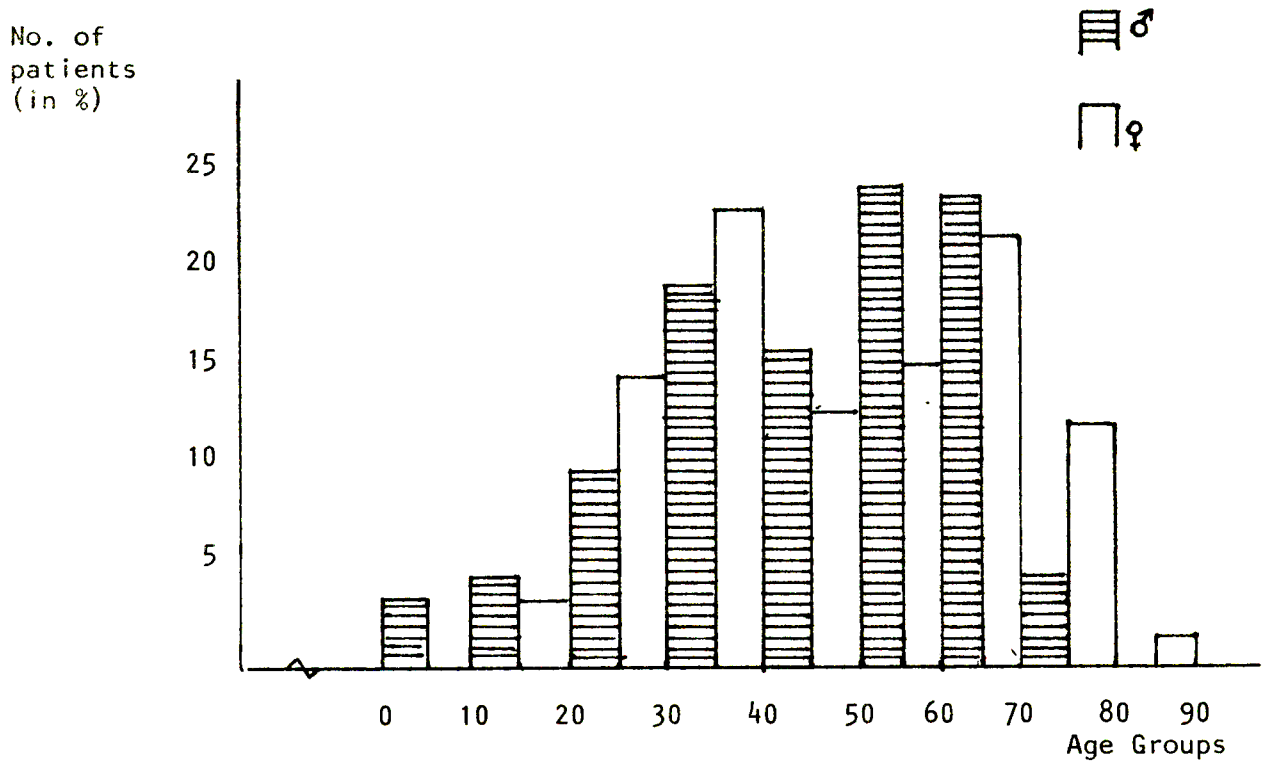



FIG. III INCIDENCE ACCORDING TO SEX AND AGE

REGION OF RESIDENCE, OCCUPATION

Although the patients studied in this series come from the whole Province, 79,4% proved to be urban dwellers (n = 433) and 20,5% to be living in rural areas, (n = 112) giving a 4 : 1 ratio while the urban/rural ratio for the White population in the Province and Kwa-Zulu is 6 : 1. Furthermore, of the rural population, 60% (n = 67) were found to be concentrated along a 70 kilometre wide coastal fringe. Only 2,6% (n = 3) of all rural persons presenting with a melanoma happened to have indoor occupations, against 73% amongst urban residents (n = 316).

RELATED HISTORY

The tumour was related to a pre-existing mole by 30% of the patients (n = 153), alternatively to a "birth-mark"; often the lesion was described as a mole which gradually enlarged and became darker, or itchy, or bled. Only two patients (0,36%) related the lesion to previous trauma: in one case a wound of the big toe which subsequently failed to heal, in the second case a wound of the knee on a long standing naevus which gave rise to a multifocal lesion.

ANATOMIC DISTRIBUTION

The following sites have been considered: Head and neck, upper limbs, back, chest, abdomen and lower limb.

The overall incidence of "head and neck" and "lower limb" tumours is similar; upper limb and back lesions show also a comparable percentage while chest and abdomen lesions are relatively uncommon.

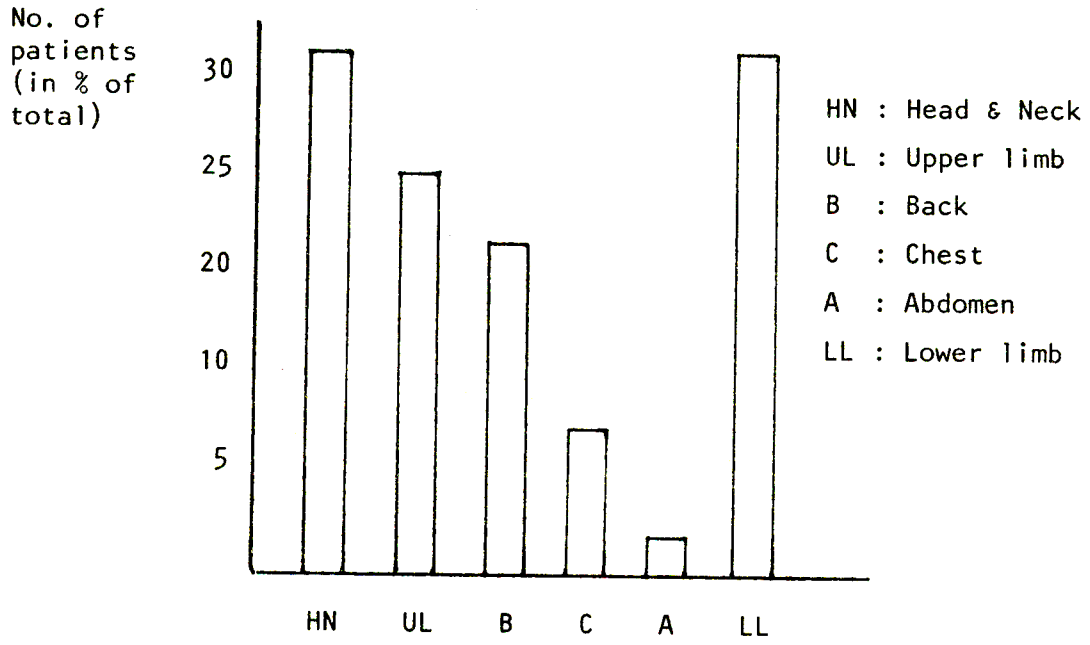



FIG. IV SITE RELATED INCIDENCE

However, when dissociated according to sex, the distribution shows a different pattern. (Fig. V)

Males present a high percentage of lesions of the head and neck and back, whereas females present a higher number of lesions of both upper and lower limbs. The relative rarity of chest and abdomen lesions is identical to both groups. Of the lower limb lesions in females, leg tumours accounted for 83%, while thigh lesions represented only 17%; of the upper limb lesions in females, arm and forearm lesions represented 56% and 44% respectively. Ear lesions in males accounted for 32% of all head and neck lesions, but cheek lesions for only 8%. The nose gave rise to a tumour in only one case.

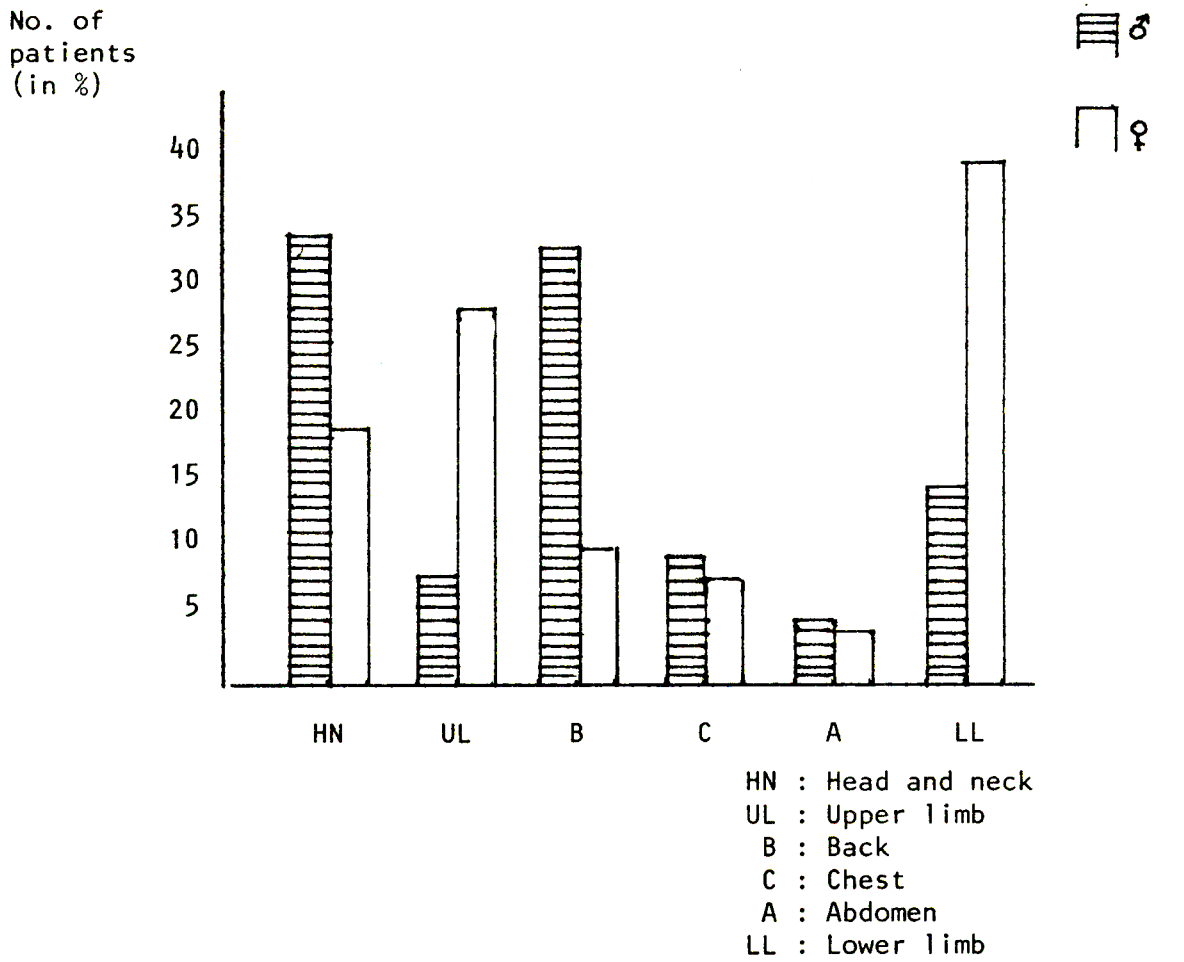



FIG. V SITE INCIDENCE ACCORDING TO SEX

AGE AND SITE

A possible relationship between age and site has been investigated. (Fig. VI - Fig. VII)

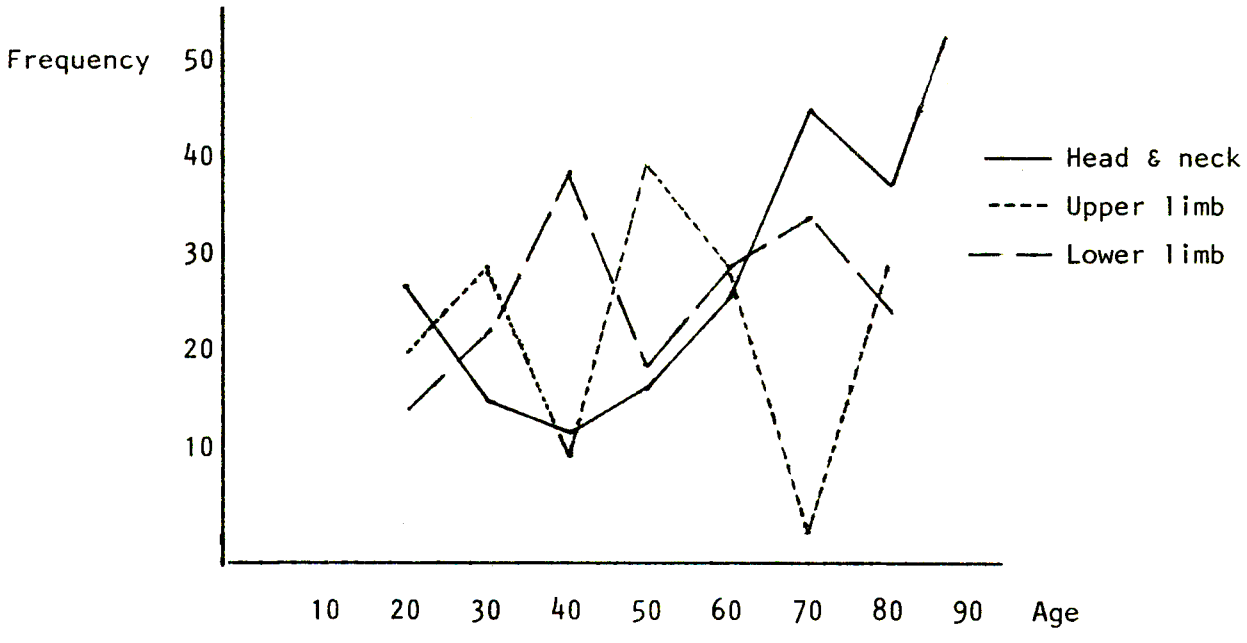



FIG. VI AGE AND SITE INCIDENCE (HEAD/NECK, UPPER LIMB, LOWER LIMB)

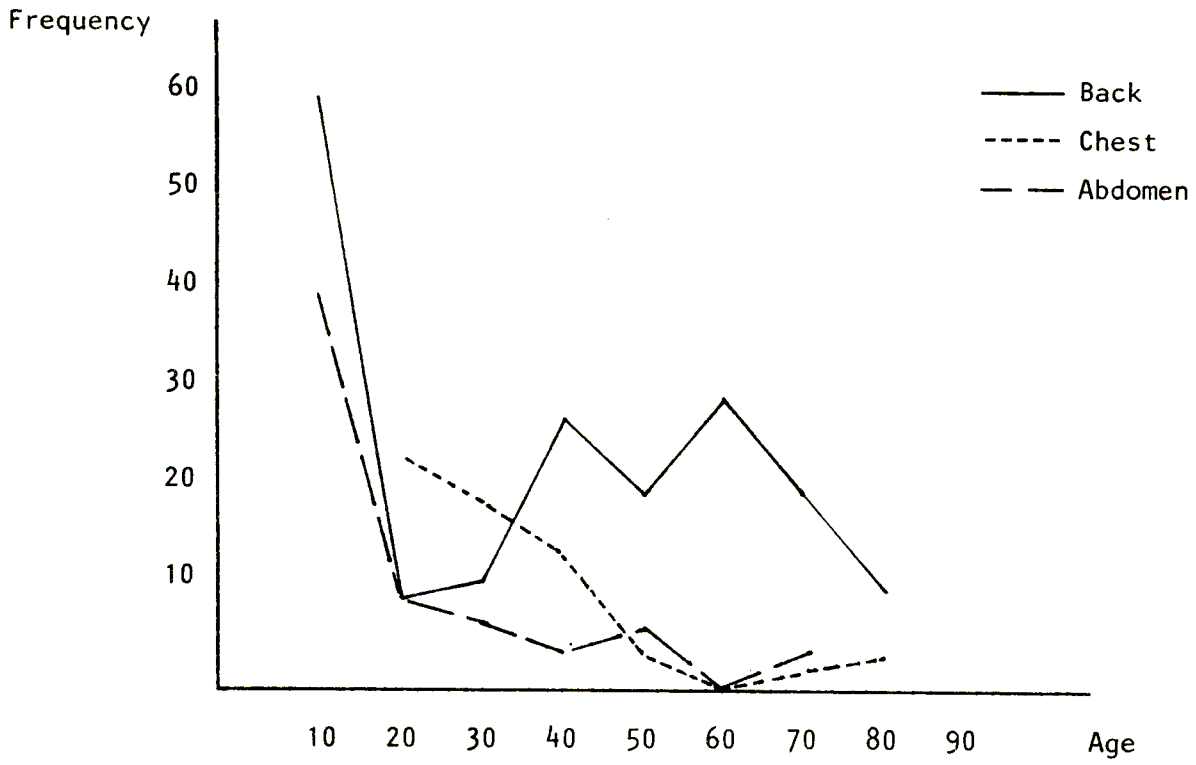



FIG. VII AGE AND SITE INCIDENCE (BACK, CHEST, ABDOMEN)

A remarkable feature of the head and neck lesions is the high incidence in the last three decades, a moderate peak in the second decade and the less number of lesions in mid-life. Upper and lower limb lesion frequencies show a rather disorganized pattern but their mean values do not differ much ($13 < \tilde{x} < 16,7$). The high incidence of back and abdomen lesions in the first decade is artefactual and results from the small number of cases represented in this age group; it is evident, however, that back lesions are most common between the fourth and sixth decades, and that chest and abdomen melanomas incidence decreases steadily after the second decade and would appear, therefore to be tumours arising in young persons.

HISTOLOGICAL TYPE IN RELATION TO SEX AGE AND SITE

The occurance of the five types of malignant melanoma: Lentigo maligna, nodular, superficial spreading, acral and amelanotic has been studied in relation to the following parameters: sex, age, and anatomic distribution.

SEX AND HISTOLOGICAL TYPE

The results are represented in Table II.

| Histological Type | Percentage in each Group | | | | Total |
|---|---|---|---|---|---|
| | Males n = 225 | | Females n = 282 | | n = 508 |
| | % | n | % | n | |
| Nodular | 50,4 | 114 | 41,8 | 118 | 232 |
| Superficial Spreading | 32,3 | 73 | 32 | 125 | 198 |
| Lentigo Maligna | 7 | 16 | 12,4 | 35 | 51 |
| Acral | 1,7 | 4 | 1,4 | 4 | 8 |
| Amelanotic | 8,4 | 19 | 0 | 0 | 19 |

TABLE II HISTOLOGICAL TYPE IN SEX GROUPS

It appears that the nodular type was slightly more common amongst males, and also the commonest lesion and that, in this series, the amelanotic type affected males only. Superficial spreading lesions were equally shared between the two sex groups, as well as the acral types. Lentigo maligna was found to be more prevalent in the female group.

AGE AND HISTOLOGICAL TYPE (Fig. VIII)

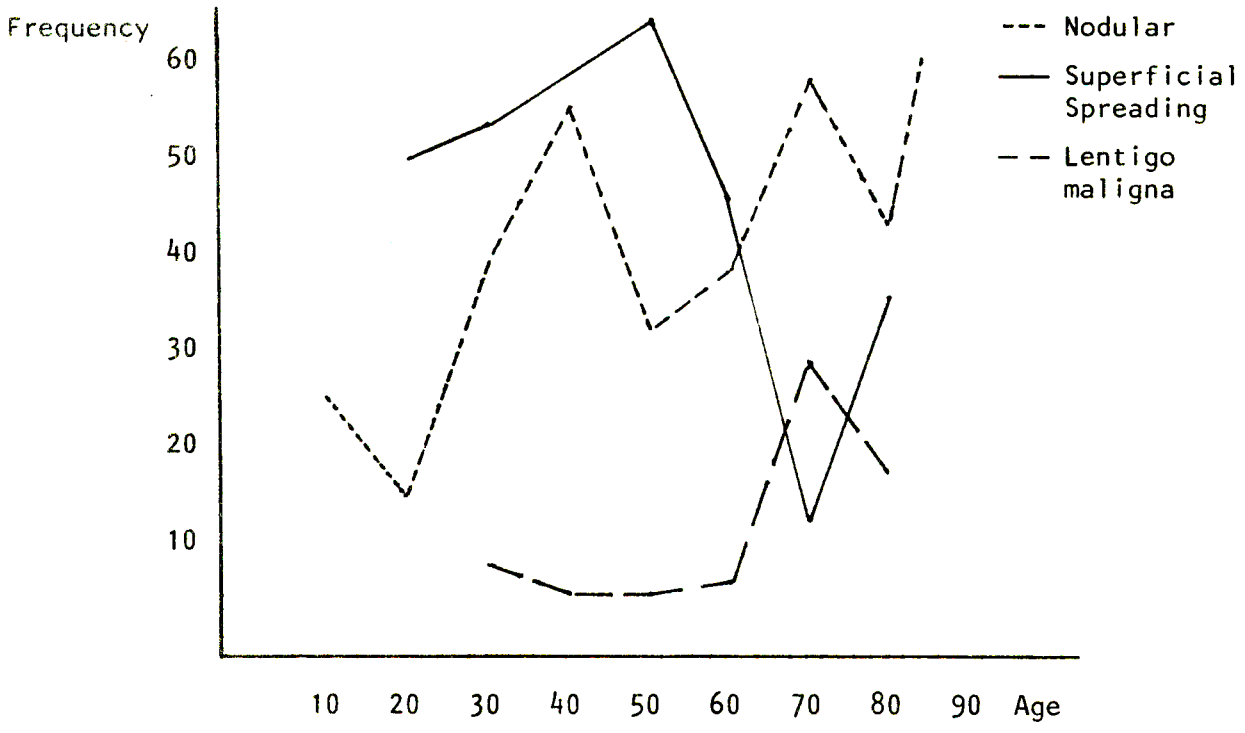



FIG. VIII HISTOLOGICAL TYPE DISTRIBUTION IN AGE GROUPS

No conclusion could be derived from the present data about the acral and amelanotic variant because these lesions were too few in numbers. (respectively 1,5% and 3,7%)

The curves related to nodular, superficial spreading and lentigo maligna types show interesting characteristics: nodular melanomas present an overall high incidence with a peak at the fourth and seventh decades; superficial spreading lesions are prevalent during the first five decades and then show a rapid incidence drop; lastly, lentigo maligna prevails in the last decades of life, with a sudden increase in the seventh 10 year age group.

It can be concluded that the superficial spreading type affects the rather young population cohort, lentigo maligna the not so young, and nodular melanomas affects everyone.

SITE AND HISTOLOGICAL TYPE

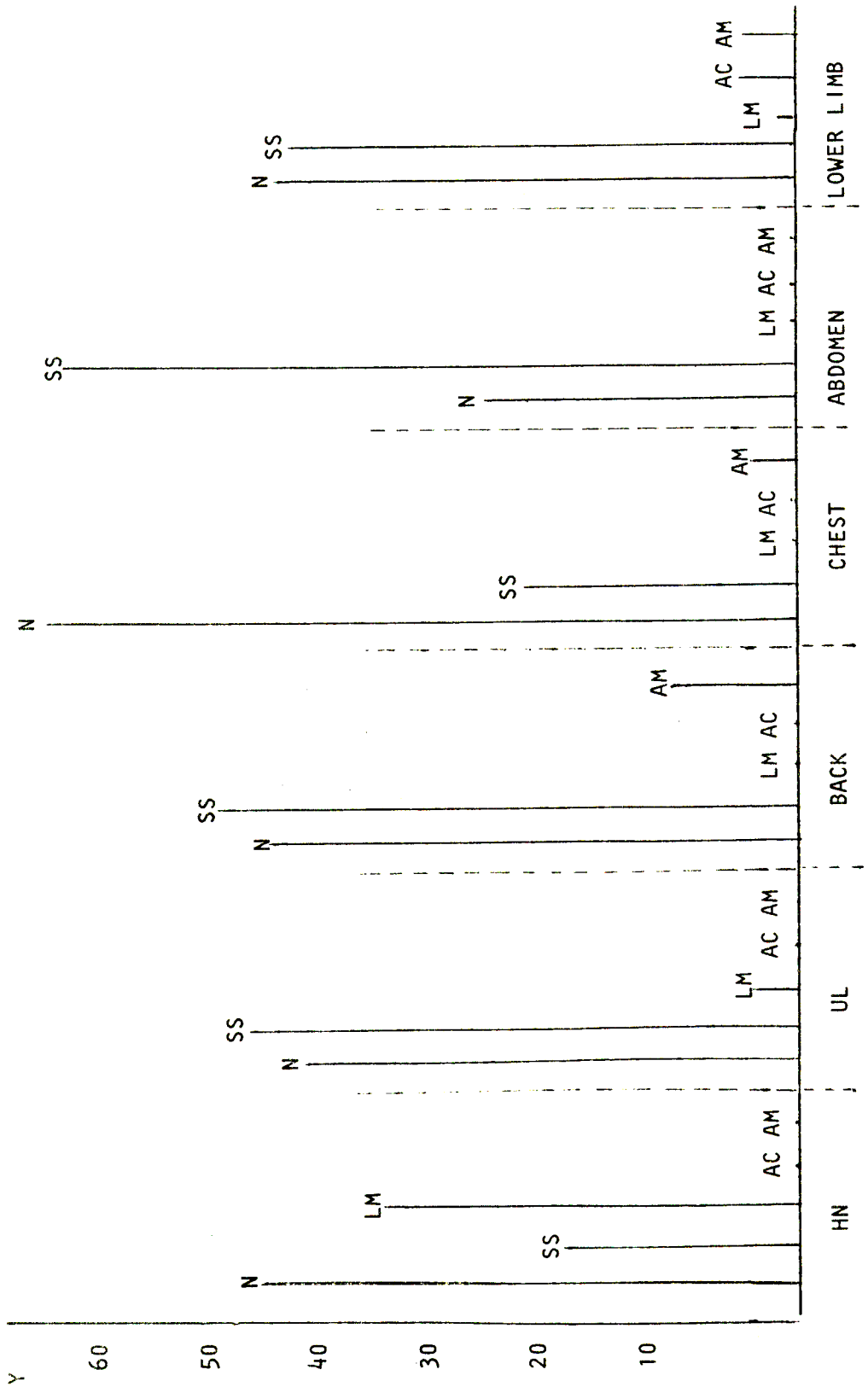
The relative incidence of the five melanoma types was studied in relation to the following anatomic sites: head and neck, upper limb, back, chest, abdomen and lower limb. (Fig. IX)

Nodular and superficial spreading types accounted, in close proportions, for most lesions of the upper limb, lower limb and back.

On the head and neck, both the nodular and lentigo maligna types prevailed. A reversal in incidence appears between nodular and superficial spreading lesions of the chest and abdomen. Besides the head and neck site, lentigo maligna accounted for only a few lesions on upper and lower limbs and was present neither on back, chest nor abdomen. Amelanotic lesions were found in three sites only : back, chest and lower limb. Acral melanoma, in this series, affected only the lower limb (Plantar skin and toes).

LEVEL OF INVASION : TUMOUR THICKNESS

Levels of invasion were recorded according to Clark's classification, tumour thickness measured as advocated by Breslow : however,




HN : Head and Neck, UL : Upper Limb, Abd : Abdomen, LL : Lower Limb, N : Nodular,
SS : Superficial spreading, LM : Lentigo maligna, AC : Acral, AM : Amelanotic

FIG. IX HISTOLOGICAL TYPE DISTRIBUTION FOR BODY SITES

Breslow's technique was not utilized before 1980; no requests were made for earlier tumours to be so measured, because one cannot be sure that previous sections have not intersected the thickest part of the specimen already, and measurements of the remnants may give erroneous results; thus tumour thickness was available for only 242 specimens..

The incidence for each level of invasion is represented in Table III.

| Clark's Level | I | II | III | IV | V | Total |
|---|---|---|---|---|---|---|
| % (of total) | 5,1 | 23 | 30,5 | 31 | 10,4 | 100% |
| no. of patients | 26 | 117 | 155 | 157 | 53 | 508 |

TABLE III LEVEL OF INVASION

There was no significant difference between males and females; however, patients who reported to hospital clinics for treatment of a primary lesion presented tumours which averaged deeper levels of invasion than lesions excised from patients privately treated. This trend may be explained by the different socio-economic status of these subsets of patients.

Clark's levels of invasion and tumour thickness have been matched (Fig. X) for the 242 available thickness measurements. It appears that level of invasion and tumour thickness correlate well only for Clark's level II; there is much dispersion of thickness values in Clark's level III, IV and V, but particularly level IV.

The implications of such poor correlation will be examined in conjunction with survival rate.

The size of the lesions was studied in relation to level of ivasion, with the following results (Table IV) which shows that no

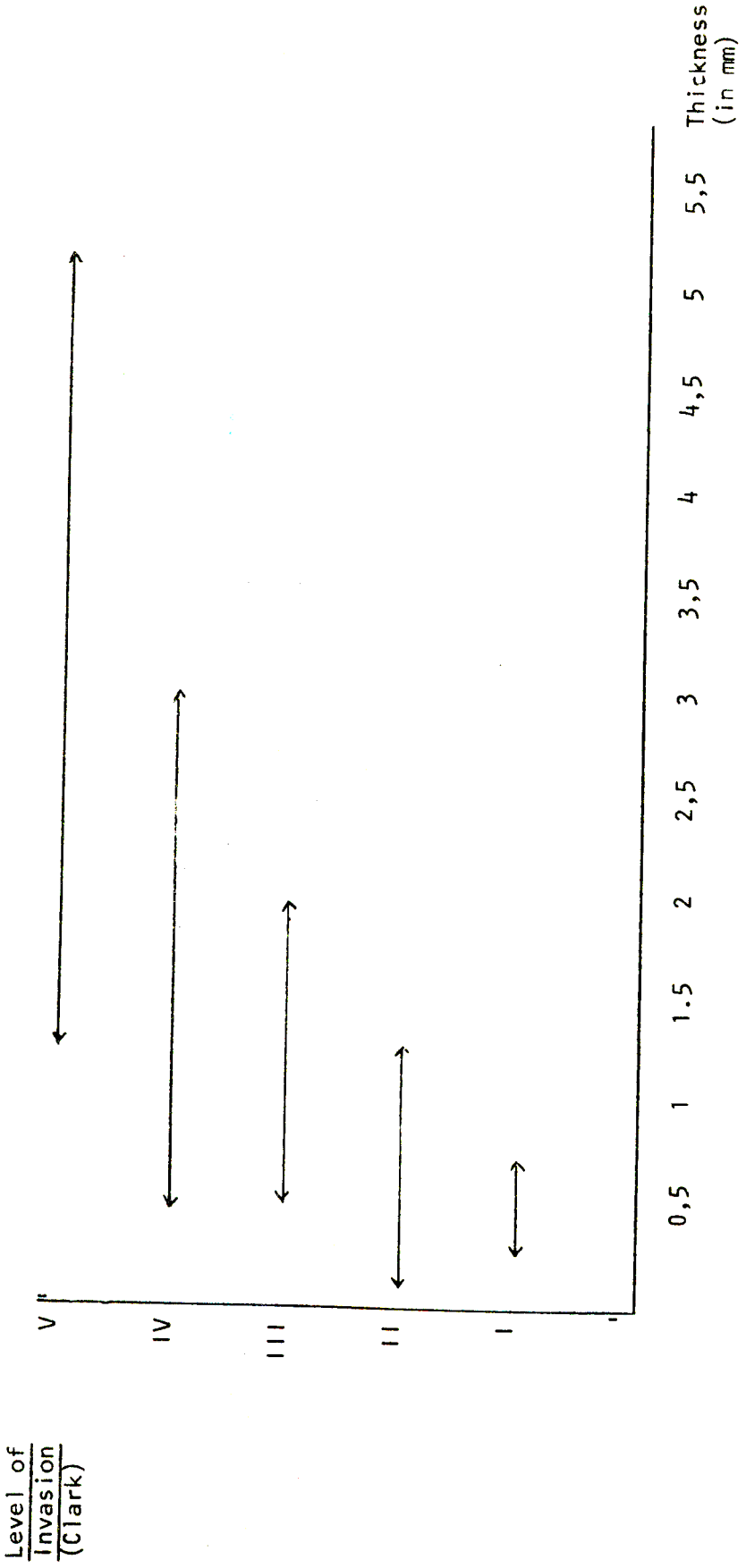



FIG. X LEVEL OF INVASION AND TUMOUR THICKNESS

correlation exists between the two parameters.

| Clarks' Level of Invasion | I | II | III | IV | V |
|---|---|---|---|---|---|
| Size of Tumour (Mean, in mm) | 16 | 8,9 | 15,2 | 11,1 | 13,8 |

TABLE IV LEVEL OF INVASION AND SIZE

## DISCUSSION

The rising incidence of melanoma appears to be a worldwide phenomenon among White population groups (20-21-22) and with reference to the results of the present survey, South Africa is no exception. Yet, despite close similarities in geographical features, and although amongst the highest, incidence in South Africa is lower than in the Australian Queensland (35/100 000 in 1977), not even close to New South Wales findings of 22/100 000 for the same year, but where a doubling in incidence rates over a seven year period has been reported. (Fig. XI) (22). There is no previous report of such an increase in melanoma rates in South Africa.

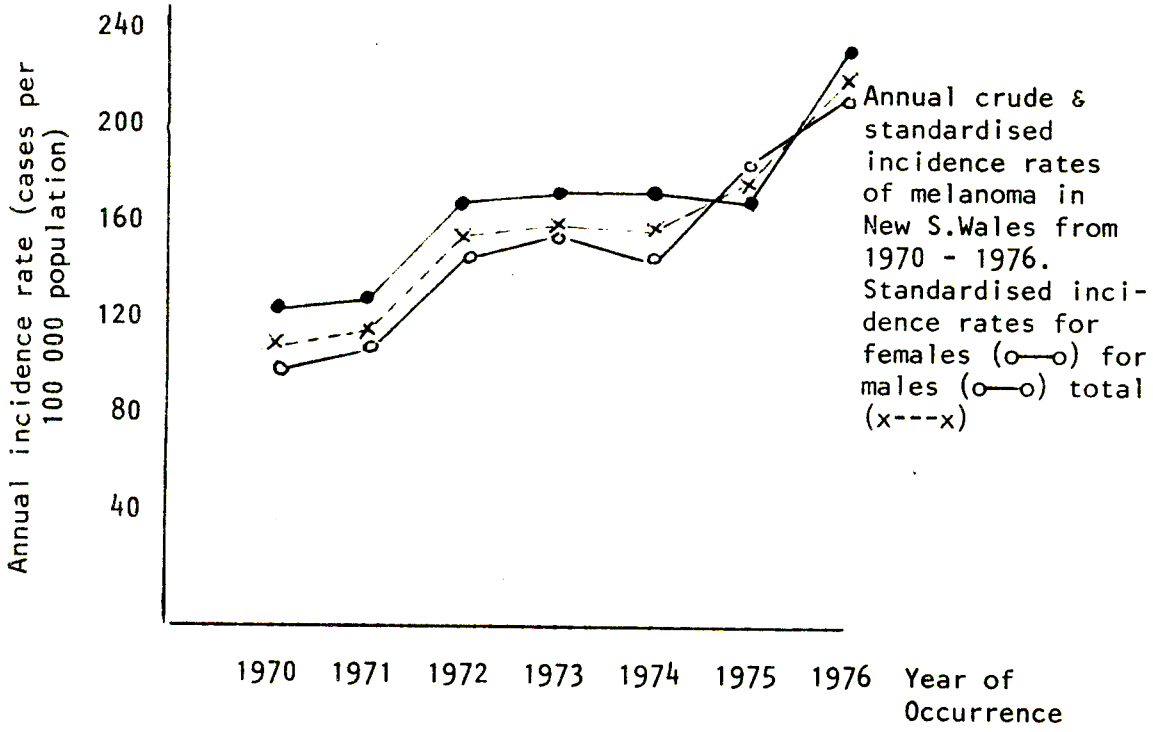



FIG. XI

This increase in incidence can result from the following factors :

1. Artefactual errors - lesions which were previously classified as non-malignant.
2. A cohort effect, whereby a susceptible population group happens to be included in the survey.
3. A true rise in incidence, a possible aetiology of which will be proposed further.

ARTEFACTUAL ERRORS

It is possible that more early stage lesions are now being excised; such tumours, labelled melanoma "in situ" were and are often denied malignant potential, and have been included in the survey. Their number is however so small (n=26) that they cannot account solely for the rise in incidence; diagnostic errors can be ruled out because histological sections were examined by trained pathologists in all cases. Since similar reports originate from different countries, because the increase affects both sex and age groups and presents a near linear increase, it can be concluded that the rise is real and not artefactual.

COHORT EFFECT

A cohort effect cannot be assessed in an eight year survey. The near linear pattern of the increase together with the involvement of all age groups argue against, but do not allow for exclusion of such an explanation.

VALIDITY OF RESULTS

The validity of the results can be questioned in terms of over and/or underestimation.

- overestimation is unlikely, since it could only result from erroneous histological diagnosis and, as previously stated, all specimens were examined by trained pathologists.

- underestimation remains a possibility. It still unfortunately happens that lesions be cauterized by a medical practitioner, or shaved; three such patients history appeared in the data and it is likely that such form of treatment is still carried out without our being able to assess how often.

It is also possible that patients living on the borders of the Province may seek medical attention outside these boundaries, but it may be assumed that this would apply to few patients. Likewise, it may be that patients from the neighbouring provinces may seek treatment in Natal for convenience, and it may be assumed that their numbers in either groups would balance.

OCCUPATION - RELATED HISTORY

In recent years, it has become apparent that the incidence of melanoma in Whites correlates with socio-economic status, both sex groups being equally affected. Furthermore, outdoor work does not seem to predispose to a high incidence for a similar socio-economic status. (23)

As regards this particular epidemiological aspect of melanoma, the present survey is of necessity biased since the number of urban dwellers and indoor workers by far exceeds the number of outdoor workers in rural areas; thus conclusions must be considered with caution. These short-comings being appraised, the results of the survey are consonant with Lee and Strickland's findings (23) as well as others (24-25), although the data could not be broken down in subsets according to socio-economic status through lack of information in this regard. Authors who published on this particular aspect of the disease dealt with population groups from northern countries, U S A, Britain, Scandinavia, and the explanation proposed a greater but mostly brief and intense sun exposure through facilitated travel to sunny countries permitted by high social status. But in South Africa, irrespective of

of income, everyone gets more than his fair share of sunlight daily, willingly or not, and this hypothesis fails to enlighten the problem in our country. Another explanation must be found.

The occurence of a melanoma in or from a pre-existing naevus has been diversely appreciated and reported, as well as trauma. This aspect will be discussed in the chapter devoted to the aetiology of melanoma.

As regards growth patterns in relation to age, sex and site, the findings do not differ from those reported elsewhere (26-27), but, as mentioned, the nodular type of lesion appeared to be the commonest, unlike other series where the superficial spreading type was the most prevalent.

## SURGICAL TREATMENT AND SURVIVAL

Except for a subset of 49 patients treated by one surgeon (self) in the Department of Plastic Surgery, lesions have been excised in various Hospitals by different surgeons.

The results of surgical and subsequent medical treatment could be followed on only 164 patients, namely patients who happened to be hospital patients, whose files were reaily available or, when privately treated patients, whose files were made accessible. Thus, rates of recurrence, occurence of metastases, medical treatment and survival could be studied on this subset only.

## SURGERY OF THE PRIMARY LESION IN STAGE I MELANOMA

1. Biopsy : Biopsy results were available for 508 patients with the following findings:

   No incisional biopsies were performed. A wedge excision of the lesion was carried out in 19% (n=96) against excision and skin graft in 81% (n=412).

A positive clinical diagnosis, as reflected on the histology request form was made in 62% of cases (n=314).

2. Adequacy of excision :

Only three excision biopsies happened to be incomplete, two of them leading to re-excision; the third one did not trigger such response and was soon followed by a recurrence (4 months delay).

The available data for the 164 patients as defined above showed that, following histology results, and although excisions proved complete, in 43 patients (38,7%) a re-excision was carried out with wide margins, and wound cover achieved by split-thickness grafts in 156 patients (95%), full-thickness graft in 3 patients (2%) and flap in 5 patients (3%). One amputation was performed, for a toe lesion. No malignant cells were ever found in re-excision specimen when the excision biopsy had been complete.

3. Excision margins : The clearance margin from the tumour varied between 0,8cm to 10cm with a mean 4,3cm, the wider margins for trunk lesions, the smaller for head and neck lesions. The concept of wide clearance margins let, however, to widely different interpretations ; where some defined their measurements as the diameter of the excision, many did not perform a circular excision and used different measurements in width and length, with a mean width/length ratio of 1 : 2; as a result, the lines of excision in width were never found to be more than 2,4cm (mean) from the site of the tumour, with extremes ranging from 1,5cm to 4cm, thereby, in most instances negating the whole concept.

The excision usually affected the shape of an ellipse, with the site of the lesion as one of the foci, and the great axis in a proximalward direction in order, it is believed, to include a greater length of lymphatic vessels in their drainage direction.

The deep fascia was never excised, except for the amputation cases, not even in one patient who was submitted to an integumentectomy for recurrence of a primary lesion on the leg.

4. Prophylactic lymph node dissection : A block dissection of the neck was performed in 1,2% (n=6), of the axilla in 1,8% (n=9) and of the groin in 65,% (n=33), and the decision taken as would retrospectively appear, on the histology report results : level of invasion III, IV and V and/or tumour thickness greater than 1,5mm. All specimens, but two, were reported free of metastatic involvement.

5. Local recurrence : The incidence of local recurrence has been calculated on the subset of 163 patients as defined above (one was a stage III melanoma at the time of the first consultation = 164). Recurrence took place in 11 cases (6,7%) despite complete excisions.

RECURRENCE IN RELATION TO PRIMARY TUMOUR

When examined in relation to the primary tumour characteristics, the following appear : (Table V)

| | RECURRENCE | | |
|---|---|---|---|
| Type | Number of Patients/Total | Percentage % | (% of Total) |
| Nod | 7 / 74 | 9,5 | (64) |
| SS | 2 / 65 | 3 | (18) |
| LM | 1 / 17 | 6 | ( 9) |
| Amel | 1 / 6 | 16 | ( 9) |
| Acral | 0 / 1 | 0 | ( 0) |
| Level of Invasion | | | |
| III | 1 / 59 | 1,7 | ( 9) |
| IV | 8 / 87 | 9,2 | (72) |
| V | 2 / 18 | 11 | (18) |

RECURRENCE (cont)

| | Number of patients | Percentage |
|---|---|---|
| Tumour Thickness (in mm) | | |
| Mean | 2,6 | |
| Range | 1,33 - 4,58 | |
| Ulceration | 4 | 36 |

TABLE V TUMOUR CHARACTERISTICS AND RECURRENCE

The nodular type of melanoma is accounted for in 64% of total local recurrences in association with 72% of level IV depth of invasion.

RECURRENCE VERSUS CLEARANCE MARGINS

Table VI outlines the incidence of local recurrence in relation to the clearance margins of excision.

| Margin (in cm) | No.of patients (total 163) | Local Recurrences Number | % |
|---|---|---|---|
| <1 | 13 | 2 / 13 | 18 |
| 1 | 17 | 1 / 17 | 9 |
| 2 | 18 | 0 / 18 | 0 |
| 3 | 38 | 3 / 38 | 8 |
| 4 | 44 | 3 / 44 | 6,8 |
| 5 | 25 | 1 / 25 | 4 |
| >5 | 8 | 1 / 8 | 12,5 |

TABLE VI CLEARANCE MARGIN AND RECURRENCE

Except for the subset of patients who had a clearance margin less than 1cm, there is no significant difference in the rate of recurrence when the clearance margin exceeds 1cm.

SURGICAL TREATMENT : STAGE IIa AND IIb MELANOMAS

Only five patients presented with a stage IIa melanoma when first reporting for treatment (2,4%) and all had wide excision of the primary lesion with clearance of regional lymph nodes. No dissection

in continuity was undertaken. One patient refused a block dissection. Three patients presented two enlarged nodes, one fifteen nodes and one a simple node; all presented metastatic deposits on histological sections; however, out of the fifteen clinically enlarged lymph nodes that one patient presented, only six showed involvement.

Twenty seven patients (13%) who received treatment for a Stage I melanoma and were clinically and histologically clear of tumour subsequently developed regional metastases; the delay between primary treatment and onset of regional involvement varied between 3 and 36 months with an average of 15 months.

The surgical treatment consisted of regional lymph nodes clearance; no dissection "in continuity" was performed. In an attempt to determine the parameters of the primary lesion which could explain the occurence of regional metastases, stage IIb patients were screened regarding the characteristics of the primary tumour : level of invasion and tumour thickness when available, histological type of the primary lesion, presence or absence of ulceration, and anatomical distribution. The findings are summarized in Table VII.

The nodular type of melanoma was responsible in 18 cases, with a Level IV of invasion thirteen times, a Level V three times, Level II and III only once, with corresponding tumour thickness values ranging from 1,3mm to 5.1mm. Ulceration was present in only 9 cases and does not seem to bear any significance, nor do anatomic sites, the respective number of which are consonant with the overall anatomic site distribution.

Thus it would seem that three parameters pertaining to the primary lesion are of significance in the onset of regional metastases, namely the type of the tumour and the level of invasion and tumour thickness.

| Level of invasion | Tumour thickness | Type | Ulceration | Site | Prophylactic lymph node dissection |
|---|---|---|---|---|---|
| IV | - | nod | + | HN | + |
| IV | 3,1 | nod | 0 | back | 0 |
| V | 3,8 | nod | 0 | LL | 0 |
| IV | - | nod | 0 | LL | 0 |
| IV | 2,5 | nod | 0 | UL | 0 |
| V | - | acral | + | L | 0 |
| IV | 4,56 | nod | + | LL | 0 |
| IV | - | nod | 0 | UL | 0 |
| II | 1,3 | nod | + | back | 0 |
| III | - | nod | 0 | HN | 0 |
| IV | 1,4 | nod | 0 | HN | 0 |
| IV | - | nod | 0 | LL | + |
| V | - | acral | + | LL | 0 |
| IV | 3,4 | nod | 0 | chest | 0 |
| III | 2,3 | SS | 0 | HN | 0 |
| IV | - | nod | 0 | chest | 0 |
| V | 3 | nod | + | chest | 0 |
| IV | - | nod | 0 | UL | 0 |
| III | 1,9 | SS | 0 | LL | 0 |
| IV | - | SS | 0 | LL | 0 |
| IV | - | nod | + | UL | 0 |
| IV | - | LM | 0 | HN | 0 |
| V | 6,1 | nod | 0 | UL | 0 |
| IV | 2,7 | amel | + | back | 0 |
| IV | 1,8 | SS | + | abd | 0 |
| IV | 2,2 | nod | 0 | LL | 0 |
| III | 2,1 | LM | 0 | UL | 0 |

TABLE VII METASTASES AND TUMOUR CHARACTERISTICS

HN = Head & Neck : UL = Upper Limb : LL = Lower Limb : Abd. = Abdomen

## STAGE III MELANOMA

Of the 32 patients who were treated for a stage II melanoma, 21 developed generalized metastases. Eight stage I melanoma patients likewise developed generalized metastases without at any stage showing signs of regional lymph node involvement. Only one patient in the whole series presented with a stage I/II melanoma at the time of first consultation.

The sites of metastatic deposits are summarized in Table VIII. It is of interest to mention that two patients who developed extensive regional metastases had had a prophylactic lymph node dissection.

The histologic type of tumour of the eight stage I patients who developed metastases was nodular in six cases, lentigo maligna melanoma and superficial spreading in the two other cases, with levels of invasion IV and V, tumour thickness between 2,6 and 4,6mm. The delay between excision of the primary lesion and occurence of metastatic deposits varied between 58 and 6 months (mean 33).

The tumour characteristics of stage IIb patients who subsequently developed generalized metastases are summarized in Table IX.

## RECURRENCE AND SURVIVAL

Recurrence and survival in relation to surgical treatment alone were examined on a population of 113 patients, 51 of the 164 were excluded since they received medical treatment after surgery. Their survival will be studied separately. Five year survival was computed according to Kaplan and Meier's method which allows for inclusion, in calculation, of incomplete data. (28)

| Brain | Liver | Lung | Bone | Intestine | Skin | Lymph-nodes |
|---|---|---|---|---|---|---|
| | | + | | | | |
| | | + | | | + | |
| | + | | | | + | + |
| | | + | | | | |
| | | | | | + | + |
| + | | + | | | + | |
| | | + | | | | + |
| | | | | | + | + |
| | | + | | | | |
| + | | + | | | + | |
| | | | | | + | + |
| | | | | | + | + |
| | | + | | | + | + |
| | | + | | | | |
| | | | + | + | + | + |
| | | | + | | + | + |
| | | | + | | | |
| + | | | | | | + |
| | | | | | + | |
| | | + | | | | |
| + | + | | | | | |
| | | + | | | + | + |
| | + | | | | | |
| + | | | + | | | |
| | | | | | + | + |
| | + | + | + | + | + | + |
| | | | + | | + | + |
| | | | | | + | + |

| 5 | 4 | 12 | 6 | 2 | 17 | 15 | TOTAL |
|---|---|---|---|---|---|---|---|

TABLE VIII LOCALIZATION OF METASTASES

| Level of invasion | Tumour thickness | Type | Ulceration | Site | Prophylactic HN dissection |
|---|---|---|---|---|---|
| IV | - | nod | + | HN | + |
| IV | 3,1 | nod | 0 | Back | 0 |
| V | 3,8 | nod | 0 | LL | 0 |
| IV | - | nod | 0 | LL | 0 |
| IV | 2,6 | nod | 0 | UL | 0 |
| V | - | acral | + | LL | 0 |
| IV | - | nod | 0 | UL | 0 |
| II | 1,3 | nod | + | Back | 0 |
| IV | 1,4 | nod | 0 | HN | 0 |
| IV | - | nod | 0 | LL | + |
| V | - | acral | + | LL | 0 |
| IV | 3,4 | nod | 0 | Chest | 0 |
| III | 2,3 | SS | 0 | HN | 0 |
| III | 1,9 | SS | 0 | LL | 0 |
| IV | - | nod | + | UL | 0 |
| IV | - | LM | 0 | HN | 0 |
| V | 6,1 | nod | 0 | UL | 0 |
| IV | 2,7 | amel | + | Back | 0 |
| IV | 1,8 | SS | + | Abd | 0 |
| III | 2,1 | LM | 0 | UL | 0 |
| IV | 4,56 | nod | + | LL | 0 |

TABLE IX METASTASES AND TUMOUR CHARACTERISTICS

RECURRENCE AND SURVIVAL IN STAGE I PATIENTS

Recurrence of the disease occured in 31 cases (29%) in less than two years after treatment of the primary lesion, and the total number of recurrences at five years amounted to 35 patients (33%). Of these, 27 presented regional lymph node involvement and became Stage IIb,

8 developed generalized metastases, without at any time showing signs of regional lymph node involvement and therefore became Stage III patients.

At two years, 26 patients had died, five are still alive, four free of disease, one with disease. At five years, 27 patients had died.

Their results are summarized in Table X and Fig. XII.

| No. of Stage I patients | Recurrence at 2 years | | Survival at 2 yrs | | Recurrence at 5 yrs | | Survival at 5 yrs | |
|---|---|---|---|---|---|---|---|---|
| | n. | % | n. | % | n. | % | n. | % |
| 107 | 31/107 | 29 | 81/107 | 76 | 35/107 | 33 | 80/107 | 75 |

TABLE X RECURRENCE AND SURVIVAL IN STAGE I

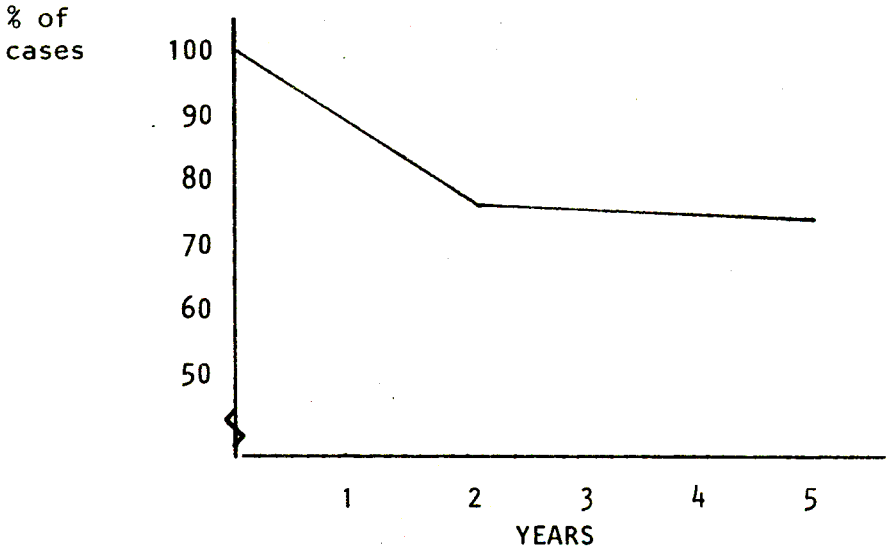



FIG. XII STAGE I SURVIVAL

## STRATIFICATION ACCORDING TO RISK

When trying to predict the outcome of the patients by using either Clark's Classification or tumour thickness, it was found that neither technique could be relied upon. As showed in the chapter devoted to epidemiology, there is a wide dispersion of results when matching the two methods, particularly when dealing with Clark's Level III and IV invasion where great overlap is observed between the thickest

level III melenomas and the thinnest level IV lesions.

In an attempt to introduce more accuracy and to determine which patients were most at risk and would therefore benefit from additional therapy, a classification based on the parameters considered to be determinant in the behaviour of the disease, is proposed; the characteristics concerned are: level of invasion, tumour thickness and growth pattern, the combination of which leading to a three level stratification; the accuracy of this classification will be improved further when individuals's reactions to immunotherapy are introduced. The three levels are defined as follows:

Low Risk : tumour thickness less than 0,76mm and Clark Level I or II in either a lentigo maligna or a superficial spreading type.

Moderate Risk : tumour thickness less than 0,76mm and Clark level II in a nodular type, or tumour thickness between 0,76 and 2mm but Clark Level III or ir IV in all but the nodular type.

High Risk : tumour thickness between 0,76 and 2mm, Clark Level III in a nodular type and tumour thickness greater than 2mm, Clark Level IV or V irrespective of the growth pattern.

The decision to adopt 2mm as a borderline between low and moderate risk groups was not taken arbitrarily. Several authors (19, 29,30) have adopted different measurements to define high risk patients, varying between 1,5 to 3mm, but they were considering tumour thickness as the only parameter useful in predicting survival. The same measurements were tried when the proposed classification was drafted, and it was found that the 2mm thickness value gave the most "clear-cut" results. Likewise, it was considered important to include the type of the tumour as a decisive parameter and to differentiate the nodular type from others, since it was found through this survey that it readily gives rise to local recurrences and metastases, whether regional or visceral,

irrespective of level of invasion or tumour thickness. Drzewiecki reported no difference in electronmicroscopy in cell structures amongst the different types of melanoma (31) and it is likely that the ability of the tumour to give in-transit metastases early is in direct relation to the speed at which the tumour grows, which also implies poor immune response.

Survival was markedly different for each such groups. (Table XI).

| Risk Group | No. of Patients | Reccurrences No. | % | Deaths No. | % |
|---|---|---|---|---|---|
| Low | 28 | 1/28 | 3,5 | 0/28 | 0 |
| Moderate | 36 | 13/36 | 36 | 8/36 | 22 |
| High | 43 | 21/43 | 49 | 19/43 | 44 |
| Total | 107 | 35 | | 27 | |

TABLE XI RISK AND SURVIVAL

Of the seven patients who presented a recurrence, but are alive at five years without disease, one was entered in the low risk group and six in the moderate risk group. The patient alive at five years with disease had been classified as a high risk patient. Forty eight stage I patients had a prophylactic regional lymph-adenectomy; they were retrospectively classified as moderate risk (n=20) and high risk (n=28) melanomas. Survival at five years for this subset is summarized in Table XII.

| Risk Group | No. of Patients | Recurrences No. | % | Deaths No. | % |
|---|---|---|---|---|---|
| Low | 0 | 0 | 0 | 0/0 | 0 |
| Moderate | 20 | 7/20 | 35 | 4/20 | 20 |
| High | 28 | 13/28 | 46 | 10/28 | 36 |
| Total | 48 | 20 | | 14 | |

TABLE XII RISK, LYMPH NODE DISSECTION AND SURVIVAL

Survival was not improved by lymphadenectomy. (As mentioned earlier, two of these patients developed extensive regional cutaneous metastases),

STAGES II AND III SURVIVAL

Thirty two patients (28%) were treated for Stage II melanoma (5 Stage IIa and 27 Stage IIb); at five years, nineteen had died (59%), eight are alive with disease, five are alive free of disease. When survival was related to the number of involved lymph nodes, it appeared that when more than two nodes were invaded, the prognosis was poor. (Table XIII).

| Number of Patients | Number of Involved nodes | Dead No. | Dead % | |
|---|---|---|---|---|
| 4 | 1 | 1 | 25 | |
| 7 | 2 | 3 | 26,5 | |
| 13 | 3 | 9 | 59 | |
| 8 | 3 | 6 | 75 | |
| 32 | | 19 | 59,4 | TOTAL |

TABLE XIII SURVIVAL AND LYMPH NODE INVOLVEMENT

However small the series, the results correlate with the findings of others, particularly Balch et al (32).

Stage III patients, as could be expected, had a very poor prognosis; of thirty (one de novo and 29 as a result of further spread of the disease) twenty-six are dead and four alive with disease. These results, both of Stage II and III melanomas emphasize the need for adjuvant therapy when such stage of the disease has been reached; but most of all, means to prevent the deterioration from a stage I to a stage II or III melanomas are needed.

DISCUSSION

The problem of clearance margins. The concept of wide excision margins as a mandatory treatment of melanoma has recently been criticized and its

value questioned. The first argument against this surgical attitude proceeds from the awareness that Handley's report (33) related to the autopsy findings of a case of advanced disease; in fact he said at the time that he never had the opportunity to deal with a primary lesion; "No opportunity of investigating the spread of permeation around a primary focus of melanocytic growth has fallen to me." It is likely that he was encountering situations which are most unusual nowadays, except perhaps when dealing with poorly educated population groups. His approach to this specific problem is akin to Halsted's treatment of breast cancers : both, in their time, offered what best they could to treat what we now regard as incurable and inoperable conditions. Halsted's radical mastectomy is no longer performed today, because patients are seen at an earlier stage and because survival was not improved by this radical and mutilating surgery.

Handley's observation on lymphatic spread and permeation is a classical description of intransit metastases with retrograde lymph flow resulting from lymph node obstruction, as would likewise occur after a lymphadenectomy. J S Stehlin has been amongst the first authors to draw attention to the limited value of Handley's concept and to adopt a critical attitude towards this surgical form of treatment. (34)

Two theories have been proposed to explain the origin and growth of melanoma, although not proven. According to one, the tumour results from malignant changes in melanocytes in a given area and the tumour grows by a simple cell division; in the other, it is postulated that the tumour arises in several fields of skin and grows not only by division but also by malignant transformation of adjacent melanocytes (35). The spread of the lesion, in the latter concept, would occur by transference of malignant potential from tumour cells to normal melanocytes (36,37) and metastases could arise through freeing of particles from tumour cells to the surrounding tissues.

In support to the second theory, the observation of Cochran(38) who found junctional changes of melanocytes around superficial spreading and lentigo maligna types of lesions, of McGovern (39) who stated that there was a melanoma producing potential to some distance of the lesion and finally Wong (40) who reported an increase in melanocytes at a distance of 5 cm from the tumour in 7 out of 12 patients who presented a cutaneous melanoma.

Yet, whenever a tumour had been completedly excised and re-excision performed to satisfy the wide resection concept, no foci of malignant cells were ever round, whether it be in this study or others (29,30,37,41). Drzewiecki (42) on the contrary, showed that between 1cm to 5cm around the lesion, the density of melanocytes was lower than in a symmetrical body location when the tumour was of the superficial spreading type, and that no difference in the number of melanocytes could be found when dealing with the nodular type; further, the density of melanocytes in melanoma patients is greater than in normal population groups. The findings of this study, that beyond a 1cm resection the incidence of recurrence does now show significant variations, correlate well with Drzewiecki's study, and other reports have similarly reached the same conclusions, (30,34,41,43), including Olsen (37) who, although advocating a 5cm clearance, could not find any rate of recurrence improvement with wide excisions.

Survival depends upon the absence or presence of in-transit metastases, which are related to the characteristics of the tumour : level of invasion, thickness, growth pattern. In-transit metastases cannot be controlled by increasing the size of resection. Thus, extensive excisions, which improve neither the rate of recurrence nor survival but are not void of morbidity and are unsightly, are ill-advised. It is believed that recurrence following a complete excision is the result either of poor surgical technique with inconsiderate manipulation of the

tumour, and therefore excision of melanomas should not be left to inexperienced surgeons, or the patient's poor immune response : one cannot control a systemic break-down by a more radical excision.

PROPHYLACTIC REGIONAL LYMPH NODE DISSECTION

There is controversy concerning prophylactic lymph node dissection. The proponents of prophylactic lymphadenectomy claim a 10 to 20% survival improvement when such dissection is done routinely for stage I melanoma (44,45,46,47,48), without apparent impairment of the host tumour balance since the incidence of recurrence is similar to that of patients who had no lymphadenectomy. Conversely, some series show no significant difference in survival between patients treated by resection alone and those who underwent resection with lymphadenectomy (23,32,36,37,38,39).

The introduction of Clark's classification and later Breslow's technique of measuring tumour thickness did not end the controversy. Some advocate lymphadenectomy for levels II and IV of invasion (49) while others propose it for levels IV and V lesions (50). Using tumour thickness as a decisive criterion, controversy exists concerning which measurement is meaningful : 1,5 min for some (51), less for others (52,53,54,55). As more parameters are introduced and their interaction considered to reach a decision as to whether such patients should or not have a prophylactic lymph node dissection, the situation becomes even more obscure. (56)

If "routine" or "elective" or "prophylactic" lymph node dissection was of undeniable value, data would abound to support the superiority of the results; lack of, or contradictory data rather proves its ineffectiveness in improving cure rates.

Patients who had a regional lymphadenectomy in the present series are few in number and no meaningful conclusion can be drawn; the results show, however, that they did not fare better than patients treated by excision alone. Thus it is difficult to justify this surgery

and its morbidity, if improvement remains hypothetical. The same argument of a systemic break-down of the host's immune sytem, postulated as a cause for local recurrence, can be applied here too, and so the conclusion : surgery alone is inadequate in controlling a systemic disease.

CURABILITY

Some anatomical sites have traditionally been associated with poor prognosis : trunk, head and neck and extremities, leading to as extensive resections as possible, associated with regional lymph node dissection,and the operative protocol defined in relation to the site of the tumour (57,58,59). There is no convincing difference in survival for the various protocols proposed. Again, the parameters of importance in predicting the outcome of the disease pertain to the tumour itself i.e. how advanced the lesion is at the time of presentation, and its growth pattern; the site of the lesions did appear to bear significance in survival neither in this series, nor in others (49,60) and there is no justification for more radical and mutilating surgery according to site. Clearly, major improvement in survival for melanoma, irrespective of its localization, can only be achieved through earlier diagnosis and effective adjuvant therapy.

# MEDICAL TREATMENT

## MEDICAL TREATMENT

Medical treatment, or palliative as often qualified, consisted of the following :-

Radiotherapy (cobalt)

Chemotherapy (DTIC, CCNU, Vindesine, Oncovin)

Immunotherapy (Bacillus Calmette-Guerin)

Combination of chemotherapy and immunotherapy

Combination of radiotherapy, chemotherapy and immunotherapy.

Immunotherapy, in the form of BCG injections, was only introduced routinely in the treatment as from 1978; previously chemotherapy and/or radiotherapy were the only alternatives. BCG is given at a dose of 0.01ml injected intra-lesionally or around the lesion, or at the site of excision, at three week intervals; DTIC and CCNU are administered at five or six week intervals, with a 500 mg dose of DTIC and 200 mg dose of CCNU. Vindesine and Oncovin are used when the former are not well tolerated.

## PATIENTS SELECTION

Twenty two Black patients started a course of immunotherapy with chemotherapy. Attendance was so poor and at so irregular intervals that no meaningful conclusions concerning medical treatment can be drawn from this group. Transport difficulties and related cost may account for this state of affairs, but negligence and lack of motivation play a great role too. A possible answer to the problem would be the use of oral BCG, that the patient could take home. Good results with this technique, used in patients presenting an advanced stage of the disease, in this similar to most of the Black patients, have recently been reported. (61).

Eighty six White patients have been referred for such treatment from 1975 to 1982. Prior to 1978, few patients had been referred to the Oncology Department for palliative therapy, however invasive the tumour may have been. It appears, rather, that only patients in a near terminal

stage of the disease qualified for referral.

Thereafter a change of attitude seems to have prevailed, resulting in more patients receiving medical treatment.

Radiotherapy : this therapy was used for treatment of visceral and/or bone metastases only.

Chemotherapy : the decision to use chemotherapeutic agents resulted mostly from exclusion; patients neither too old nor in too poor a general condition to be given aggressive treatment.

BCG injections, being nearly void of complications, have been administered routinely.

The combination of BCG therapy with chemotherapy was proposed in patients estimated to be at "high risk", namely people who had had a deeply invading or thick tumour and/or enlarged regional lymph nodes and/or had visceral metastatic deposits. However, no set parameters which could be used to select patients in terms of risk had been clearly defined in treatment selection. (Table I).

| | | | |
|---|---|---|---|
| Age | : | mean 54 : | range 19 - 80 |
| Sex | : | M - | 29 |
| | | F - | 18 |
| | | Total - | 47 |
| Primary Site | : | Head & Neck | 9 |
| | | Upper Limb | 9 |
| | | Back | 9 |
| | | Chest | 8 |
| | | Abdomen | 2 |
| | | Lower Limb | 10 |
| | | Total | 47 |
| | | No metastases | 16 |

| | | | |
|---|---|---|---|
| Site of Metastases | : | Brain | 2 |
| | | Liver | 1 |
| | | Lung | 7 |
| | | Skin | 8 |
| | | Abdomen | 2 |
| | | Lymph nodes | 13 |

TABLE I PATIENTS CHARACTERISTICS

The sixteen patients presenting no metastases were referred for prophylactic treatment, and four of them received a combination of immunotherapy and chemotherapy.

## TREATMENT

### SYMPTOMATIC TREATMENT

Three patients were referred at such an advanced stage of the disease that symptomatic treatment only could be offered.

#### Radiotherapy

Two patients had radiotherapy only to lung, brain and bone metastases and died.

#### Chemotherapy

Two patients had chemotherapy alone as treatment to lung, bone and skin metastases for one, and abdominal metastases for the other. Both died (survival twenty months and six months respectively).

#### Immunotherapy with and without Chemotherapy

Forty seven patients received BCG injections, in twenty cases with chemotherapy. Local irradiation was used on osteolytic lesions and large metastatic deposits during the course of therapy, when necessary.

## SURVIVAL

Survival was studied without using Kaplan and Meier's statistical method (28) as it could not give meaningful results in the present situation.

SURVIVAL AND IMMUNOTHERAPY WITH CHEMOTHERAPY

The summary of patients parameters and results of treatment appear in Table II. Six patients are alive, free of disease (30%), one is alive with disease, twelve are dead (60%). Of the six patients alive free of disease, two are still receiving BCG injections. (Table II : Survival with combined Immuno-chemotherapy).

SURVIVAL AND IMMUNOTHERAPY

Patients characteristics and treatment results are summarized in Table III. Twenty patients are alive free of disease (74%), two are alive with disease (7,4%) and five patients died (16,5%).
(Table III : Survival with Immunotherapy).

DISCUSSION

The clinical behaviour of melanoma suggests that the disease is influenced, if not regulated, by immunological factors. As proof, the following findings :-

a. Tumour regression, associated with lymphocytic infiltration, which can be such that the primary lesion may disappear entirely and be suspected only on the discovery of a depigmented area, whereas the patient presents with metastases.

b. Reports of transplantation of melanomas in immunosuppressed patients (62,63).

c. Regression of melanomas after transfusion with whole blood recovered from melanoma patients who had had a complete remission (64).

d. The finding of high titer of anti-melanoma antibodies in patients with localized disease or undergoing spontaneous regression, and titer as low in patients with advanced metastatic disease as found in a normal population (65).

Consequently, several agents have been used to enhance the immune system of malignant melanoma patients, either specific (tumour associated antigens (66) or non-specific : Corynebacterium Parvum and

| Sex | Age | Type | Type Level Thick | Ulc | DFI in Months | Conditions at beginning of treatment | $R_x$ | Response | Evolutions | Survival in years & months | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|
| M | 53 | N | IV 1,6 | + | 4 | no met | I + C | + | No recurrence | 4 | Alive (FD) |
| M | 67 | N | IV 1,92 | + | 3 | no met | I + C | + | No recurrence | 3 | Alive (FD) |
| M | 29 | N | V 4,3 | - | 1 | Rep.met | I + C | + | Mediastinal metastases | 11/12 | Death(Chest met.) |
| M | 61 | N | IV | - | 1 | Cut.met | I + C | - | Multiple regional cutaneous met.(had had lymph node dissection,no metastic deposits) | 6/12 | Death (multiple skin metastases) |
| M | 73 | N | IV 2.7 | + | 1 | Cutaneous and lymph node met. | I + C | + | Developed countless skin and node metastases | 9/12 | Death(laryngeal metastases) |
| M | 37 | N | V 1,8 | + | 2 | Recurrence(local) | I + C | - | Numerous skin nodules | 17/12 | Death(skin&bone met.) |
| F | 34 | SS | IV | - | 1 | Regional lymph nodes (excised) nodule in breast | I + C | + | Developed cutaneous metastases (excised) | 7 | Alive (FD) |
| F | 65 | Nod | IV | - | 1 | Occurrence (local) regional lymph nodes (excised) | I + C | + | No recurrence | 4 | Alive (FD) |
| F | 76 | Nod | III 1,3 | - | 1 | Regional lymph nodes (excised) recurrence | I + C | + | Developed skin and lump metastases | 1 | Death (lump metastases) |
| F | 60 | Nod | IV 4,56 | + | 1 | Reccurence skin nodules | I + C | - | Numerous skin nodules | 6/12 | Death (multiple skin metastases) |
| F | 80 | Nod | V 2,6 | - | 3 | Recurrence (local) | I + C | - | Numerous skin tone, node metastases | 1 | Death(multiple metastases) |
| F | 44 | Nod | IV | - | 2 | Skin metastases | I + C | + | Skin and bone metastases | 1 | Death(multiple met.) |
| F | 52 | Nod | IV | - | 3 | Recurrence (local) | I + C | + | Devel.lump skin&brain met. | 4 | Death(L,S,&B,met.) |
| F | 32 | Nod | IV 1,09 | - | 2 | No recurrence No metastases | I + C | + | No recurrence | 2 | Alive (FD) |
| F | 54 | Nod | V | + | 1 | Multiple abdominal metastases | I + C | - | Peritoneal metastases | 11/12 | Death |
| M | 48 | Nod | II 1,3 | + | 1 | Regional metastases (excised) | I + C | - | Multiple skin&lump met. | 2 | Death |
| M | 63 | Nod | 3,3 | + | 1 | Lump metastases | I + C | - | Lump metastases | 1 | Death |
| F | 25 | SS | IV 2,2 | - | 3 | No recurrence No metastases | I + C then I only | + | No recurrence (still on BCG) | 3 | Alive (FD) |
| M | 38 | Nod | IV | - | 1 | Regional metastases | I + C then I only | + | No recurrence (still on BCG) | 4 | Alive (FD) |
| M | 19 | Amel | IV | - | 1 | Regional | I + C | + | No new lesion | 3 | Alive (with disease) |

TABLE II SURVIVAL WITH COMBINED IMMUNO-CHEMOTHERAPY

DFI : disease free interval, FD : free of disease, I : immuno-therapy,

C : chemotherapy,

| Sex | Age | Type | Tumour Level thick | Ulc | Interval before Rx (months) | Condition at beginning of treatment | Response to Treatment | Evolution | Survival (years) | Result |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 38 | Nod | IV 0 | 0 | 2 | no met | + | No recurrence | 2 | Alive (FD) |
| F | 31 | SS | III 1,6 | 0 | 4 | Regional L/N | + | No recurrence | 4 | Alive (FD) |
| F | 40 | SS | IV 1,1 | 0 | 6 | no met | + | No recurrence | 6 | Alive (FD) |
| F | 36 | SS | II 0,33 | 0 | 2 | no met | + | No recurrence | 2 | Alive (FD) |
| F | 76 | Nod | III 1,2 | 0 | 3 | no met | + | No recurrence | 3 | Alive (FD) |
| F | 25 | SS | III 0,9 | + | 3 | No met. block | + | No recurrence | 3 | Alive (FD) |
| F | 67 | N | IV | + | 3 | no met | + | No recurrence | 3 | Alive (FD) |
| F | 70 | N | III 1,25 | 0 | 2 | no met | + | No recurrence | 3 | Alive (FD) |
| F | 54 | N | IV 1,7 | 0 | 2 | No met. block | + | No recurrence | 2 | Alive (FD) |
| F | 80 | N | V 3,2 | + | 1 | Brain met | - | Multiple visceral metastases | 1 | Died |
| M | 54 | N | V | + | 0 | Regional L/N block | - | Multiple metastases | 1 | Died |
| F | 79 | SS | IV 2,2 | 0 | 0 | Regional L/N block | - | Lung metastases | 1 | Died |
| M | 33 | N | V 3 | + | 2 | Regional L/N block | + | Visceral metastases | 3 | Died |
| M | 25 | N | III | 0 | 1 | Regional L/N block | + | No recurrence | 5 | Alive (FD) |
| M | 22 | N | IV 3 | 0 | 0 | Regional L/N block | + | No recurrence | 3 | Alive (FD) |
| M | 30 | N | IV 3 | 0 | 0 | no met | + | No recurrence | 3 | Alive (FD) |
| M | 50 | SS | III 0,4 | 0 | 0 | no met | + | No recurrence | 2 | Alive (FD) |
| M | 68 | N | V 2,8 | 0 | 0 | no met | + | No recurrence | 2 | Alive (FD) |
| M | 19 | Amel | III | 0 | 0 | no met | + | No recurrence | 3 | Alive (FD) |
| M | 67 | Ac | IV | + | 0 | no met | + | No recurrence | 5 | Alive (FD) |
| M | 49 | SS | IV 1,6 | + | 0 | no met | + | No recurrence | 3 | Alive (FD) |
| M | 19 | N | III | 0 | 0 | no met | + | No recurrence | 4 | Alive (FD) |
| M | 70 | LM | IV 2,1 | + | 1 | Subcutaneous nodules | + | One nodule disappeared others isq. | 3 | Alive with disease |
| M | 33 | N | V | + | 1 | Subcutaneous nodules | + | Stable | 5 | Alive with disease |
| M | 24 | N | III | 0 | 1 | No met. block | - | No recurrence | 4 | Alive (FD) |
| M | 67 | N | III 1,92 | 0 | 0 | no met | + | No recurrence | 3 | Alive (FD) |
| M | 19 | amel | IV 4,2 | + | 1 | Altaneous metastases | + | Regional L/N | 1 | Died |

TABLE III SURVIVAL WITH IMMUNOTHERAPY

FD = Free of disease

Bacillus Clamette-Guerin, or both (67). BCG, of all agents, is the easiest to use and the most readily available.

There is controversy concerning the value of BCG immunotherapy, variably described as high, as an improvement or simply disappointing. It is likley that different sets of patients have been considered. Should a patient lack immuno-competence, or present either a large tumour or disseminated metastatic deposits, little can be expected in terms of survival. To test patients' immuno-competence, a study of delayed cutaneous hypersensitivity to DNCB has been advocacted prior to initiating treatment (68). No such tests were performed in the present study; however, the patients' immune response could be appreciated by the intensity of reactions occurring at the site of injection and regional lymph nodes enlargement. Lack of reaction implied a doubtful beneficial effect.

Since a positive reaction BCG injections proved to be so important, it was retrospectively considered as a fourth parameter to determine risk categories, and survival of stage I patients who had received immunotherapy and immunotherapy with chemotherapy was accordingly reviewed (Table IV).

| Risk Group | Number of Patients | Response to BCG therapy | | Death | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Low | 2 | +( 2) | 100 | 0 | 0 |
| Moderate | 3 | +( 2) | 67 | 0 | 0 |
| | | -( 1) | 33 | 0 | 0 |
| High | 17 | +(13) | 76 | 1 | 6 |
| | | -( 4) | 23,5 | 2 | 12 |
| Total | 22 | (+):17 (-):5 | | 3 | |

TABLE IV RISK, IMMUNE RESPONSE AND SURVIVAL

Low and moderate risk patients did well, which was predictable. In high risk patients, 76% showed a positive response to BCG - immunotherapy and only one died, the remaining are free of disease. Of the four patients who did not present such response, two died and two are alive with disease.

The series is allegedly small, but allows to conclude that signs of immune response to BCG bear favourable prognosis; more positive conclusions will be drawn in a few years time when a greater number of patients are available for analysis.

In stage II and III patients, the results are less favourable, whether the patients received BCG immunotherapy alone or in conjunction with chemotherapy. Nine stage II patients responded to immunotherapy, four died; three patients did not respond, two died. Seven stage III patients showed a positive response to BCG, three died; four did not respond and died. Immunotherapy does not seem to have a positive action on visceral metastases, irrespective of the patient's response. However, the group of patients who have received adjuvant treatment after surgery shows a better overall survival than the group of patients who were surgically treated only.

As a result of these findings, it can be said that lack of response of the host's immune system to BCG aggravates the prognosis, while a positive response, mainly in stage I patients allows for optimism. Since BCG immunotherapy is nearly void of morbidity, there is no reason why all stage I patients, irrespective of their risk group, should be deprived of the benefits of this therapy. Yet the question remains as to how long such treatment should be continued; would lack of response be an incentive to persevere, or a reason to abandon? Could it be that, after some time (which would have to be defined), the efficacy of the treatment would decline and if so, would a rebound

effect take place? If this were the case, what then would be the optimal duration of the therapy? Answers to these questions can derive only from a survey extending over many years for as many patients as possible; they are an incentive to further studies.

# REFLECTIONS UPON THE AETIOLOGY OF CUTANEOUS MELANOMA

## - A NEW HYPOTHESIS -

# BACKGROUND

## LIGHT AND LIFE

Solar light and water are the two main components of our biosphere and light the only spring of energy of the system; it is responsible for terrestrial life as well as the origin of life (69,70). Organism must be sensitive to such energy if they are to use the sun to maintain life and to survive, but this implies the possibility of overdose; for example, DNA can be damaged by solar radiation and therefore some form of control is needed. Sensitivity also implies the creation and transfer of information. Living organisms develop means to see and de-limit a band of the spectrum as "light". They identify subjects of vital interest - food, mates, predators - through reflected light; they modify their own reflectance by appropriate colouring to improve their chance of avoiding predators or catching preys (71). Lastly a fraction of available light is suitable and used for chemical work; animals have come to synthetize vitamin D from precursors with energy from ultra-violet light.

Natural ultra-violet presents three wave-lengths with different sections: UVa (320 - 400 μm) held to be inocuous and responsible for tanning; UVb (280 - 320 μm) responsible for erythema and burning and UVc (200 - 280 μm), absorbed by the ozone layer, highly energetic and therefore dangerous. Natural UV radiation is greatly enhanced by white surfaces : sand, snow, light building and water. Its skin absorption is increased by moisture. (McCarthy).

The pigmentation of vertebrates results mostly from the production of melanin by melanocytes, specialized cells derived from the neural crest. Melanin is the end product of complex reactions, starting with tyrosine and ending into polymerisation of indol-quinone; it is then linked to proteins to form a melanoprotein. The melanocytes

are able to expand and contract to produce colour changes, are located in the basal layer of the skin and are responsible for pigmentation whether it be a racial characteristic of the result of increased solar exposure (72).

Melanocyte activity is controlled by the system melanocyte-stimulating hormone (MSH) / melatonin in response to light levels, via the hypothalamus. High levels induce production of MSH, whereas low levels trigger the production of melatonin. In albino patients, the levels of melatonin are 10 to 15 higher than in normally pigmented persons (73).

As MSH is secreted at the same time as ACTH, and since they share a short same sequence of amino-acids, it is likely that melanocyte activity is in fact under the control of both hormones (74).

It must be noted that very little research on MSH and its action has been carried out, and information is very scanty.

LIGHT AND VITAMIN D

It has been assumed that the pallor of White people is a means to provide for adequate systhesis of vitamin D under the climatic conditions of North West Europe (75). The actual problem of rickets among the Non-White immigrants in the United Kingdom tends to support this view (67). However, like most broad generalizations, to explain the light skin colour of Europeans through their need for vitamin D present some difficulties : should this be the explanation, the White population of South Africa would indeed show a high incidence of excess production of vitamin D, a highly toxic substance, and lethal calcifications, unless there was a feed-back mechanism between blood levels of vitamin D and melanin production.

In so far, there is no proof that such mechanism exists. It is true that there is a high incidence of rickets among the Black population of South Africa, but this is more likely to be related to

nutritional problems; and what could be the advantage of being Black to a person living in the tropics since heat reflectance is thus grossly impaired?

But whatever the reason for the lack of pigmentation of the European, the price paid is the accumulation of actinic damage to the skin and the high incidence of basal cell and squamous cell carcinomas of the skin.

## MELANOMAS AND OTHER SKIN CANCERS

Melanocytes can undergo malignant changes and produce melanomas which may occur on any part of the body where melanocytes exist, that is to say not only skin but also mucosa, as found in the nasal cavity as well as the vagina. Melanomas are much less common than basal cell or squamous cell carcinomas.

Basal cell carcinomas are not rare on areas usually protected from direct sunlight, and so are squamous cell carcinomas. Basal cell carcinomas are exceedingly rare in Negro population groups, squamous cell carcinomas less so. Most of the latter appearing on unusual sites, irrespective of the population group, result from intercurrent factors such as burn or irradiation. The distribution of neither basal cell carcinomas nor malignant melanomas fits adequately the distribution of sunlight and shade.

The Ozone layer problem: Malignant melanoma is of particular interest for the following reasons : its incidence is increasing amongst population of Northern European descent with an increasing death rate, and amongst the Zulu population too.

Secondly, the incidence of melanoma has been linked to exposure of Europeans to sunlight. This is a matter of much controversy, as will be discussed below. These issues result from the deep concern that human activities are introducing changes to earth's upper atmosphere.

As sunlight reaches the outer layer of earth's atmosphere, oxygen molecules are being re-arranged as ozone ($O^3$). Ozone absorbs radiations from abour 310 μm wave length and is opaque at 296 μm. As a result, life on earth is shielded from a considerable amount of UV radiations and has evolved under these conditions ever since oxygen appeared. Ozone concentration at ground level varies proportionally to the intensity of UV radiations and varies from 15 ppb in heavily irradiated desertic zones to 50 ppb at 3000 M altitude and reaches a maximum between 18 and 35 km. In cities presenting high levels of pollution, the ozone concentration reaches 1 ppm and more. Conversely, there had been fears that the ozone concentration of the upper atmosphere would decrease, as a result of supersonic aircraft exhaust gases (77).

It would now appear that such fears were unjustified (78), although satellite observation suggests that the thickness of ozone layer is becoming thinner (79). What can be ascertained however, is that changes have been minimal, and that changes of UV flux at ground level cannot account for the increasing incidence of melanoma.

As with many cancers, no animal model allows for experimental production of melanoma, depriving us of insight as to its aetiology. Although transfers of naturally occurring melanomas to experimental models have been successful, and repeated exposure to carcinogens have induced melanomas, only recently haye experimentally created tumours shown resemblance to the human disease (80). No experimental system, in so far, has allowed for reproducible induction of melanoma through UV irradiation, and there can only be speculations regarding the shield effect of the ozone layer and its changes, which effect only a narrow band of the spectrum below 310 μm. There are reasons, but no proof, that erythema in man, carcinogenesis in mice, DNA absorption spectrum, should be in this range.

Despite these uncertainties, the question yet must be addressed as to whether UV-b is a limiting factor for the incidence of melanoma of the skin, and if it is, what is the quantitative relationship between increased intensity and increased incidence of melanoma.

## RISK AND PHYSICAL CHARACTERISTICS

### SKIN PIGMENTATION

Since the report of Rudolph Matas in 1896 on "The surgical peculiarities of the Negro" it has been accepted that dark skinned persons were at reduced-risk of developing melanomas. All the authors reporting on this affection in Africans emphasize the low overall incidence rate (10,15,80,81,82) but stress the high incidence of melanoma of the sole of the foot, whether living in America or Africa.

Variations from community to community are minimal, and the occurrence of the tumour at such site bears no relation to sunlight exposure.

Similarly, Blacks present lower rates for ocular melanomas as compared to Whites, as well as lower rates for internal cavities. This implies that there is more to the problem of pigmentation than melanin acting as a "sun screen". Rates of malignant melanomas in European population groups show great variations, whether still residing in their country of origin or abroad. Despite living under the highest latitudes, people of Scandinavia show a very high rate of incidence (but not the Icelandic Group , which benefits in summer of uninterrupted solar exposure) (83,84); despite high medical standards, death rates are also high. Death rates from Scotland and Ireland are low, yet in Australia people from Irish descent present higher rates than their British Isles fellowmen (85,86).

Population groups from Mediterranean countries or from such origins show a very low incidence and low mortality rate, however served by a lesser medical service; such findings do not correlate

with a latitude reversal effect.

MOLES AND PRECURSOR LESIONS

In the eighteen century in Europe and mostly in France, moles were regarded as "beauty marks". Indeed, if ladies were unfortunate enough to be deprived of such marks, they would readily use black plasters of various shapes in various locations as a palliative measure.

Traditionally, malignant melanomas have been associated with naevi, although the closeness of the relationship is not always easy to define at the time of histologic examination, since often there has already been destruction of the initial lesion.

Allen and Spitz (87) state that, with few exceptions, melanomas arise in junctional or compound naevi. For Lennox (88), less than 50% of melanomas arise in previously existing naevi, less than 25% according to Becker (89).

Hewer (90), studying melanomas in Sudanese Negroes, disregards any relation with pigmentation but relates the high incidence of foot lesions to trauma.

Pack (91) found that naevi were uncommon in pigmented races and Heselson (92) presented the following results of a survey of moles and melanomas in South Africa.

| Melanoma | | Moles |
|---|---|---|
| 2 | to | 1 (Head and Neck) |
| 30 | to | 1 (Genitalia) |
| 50 | to | 1 (Sole Foot) |

The lesser pigmented skin and mucous membranes in Negroes presents with naevi and lentigenes. According to A J J Emmet and M C E O'Rourke (43) "naevi on the palms, soles, genitalia and mucous membranes are said to be junctional, but many are compound naevi. Junctional naevi occur anytime after birth; their great importance lies in the fact that they may develop into a malignant melanoma."

Lewis (93) showed that there is a close relationship between the incidence of naevi and the incidence of malignant melanomas of the sole of the foot. If such a relationship does exist, similarities in incidence rates must appear for other sites and be linked to sex and age. There is no record, however, of such a survey having been carried out in the past and it was decided to conduct such a study.

## MELANOCYTIC NAEVI SURVEY (Bantus)

### MATERIAL AND METHOD

Four hundred patients, 200 males and 200 females were asked to participate in the survey; all presented with dark brown or black skin and were attending the Plastic Surgery Clinic for unrelated affections. Patients presenting burns or burn scars, degloving injuries, crush injuries to hands or feet and lip bites, were excluded.

The diagnosis of melanoctyic naevus was made on clinical grounds and defined as a well circumscribed pigmented papular lesion. Mottled areas were excluded. On six occasions, in-patients (burn cases) agreed to having biopsies taken from what was defined clinically as melanoctyic naevus, to confirm the diagnosis for the whole survey; two biopsies were taken from the plantar skin, volar skin and muco-cutaneous junction of the lip respectively; one biopsy from the sole of the foot showed signs of junctional activity and every lesion was histologically described as a naevus.

### RESULTS

The lesions were recorded according to the following sites and sub-sites. Head and neck, lip, upper limb, fingers and volar skin, trunk, lower limb, toes and plantar skin, as well as age and sex.

Thirty patients (7,5%) presented no lesions, 17 males and 13 females. Of the 17 males, 15 were in the 0 - 10 age group, 1 in the 40 - 50 age group, 1 in the 70 - 80 group; of the females, 12

were in the 0 - 10 age group, one in the 40 - 50 age group.

The average number of melanocytic naevi was 9,94 per patient with a total number of 3680 lesions, 2208 for the female group, 1472 for the male group. (ratio 1,5 : 1)

The distribution in percent according to sites is illustrated in Table I.

| Head Neck | Lip | Upper Limb | Finger Volar Skin | Trunk | Lower Limb | Toes Plantar skin |
|---|---|---|---|---|---|---|
| 5,2 | 4,1 | 4,4 | 17,3 | 28 | 3 | 38 |

TABLE I SITE RELATED INCIDENCE

There was no significant differences in sex/site related incidence. The sex/age related incidence is shown in Fig. II. The sharp rise in incidence at puberty is followed by a gradual decline and the curves for males and females are very similar.

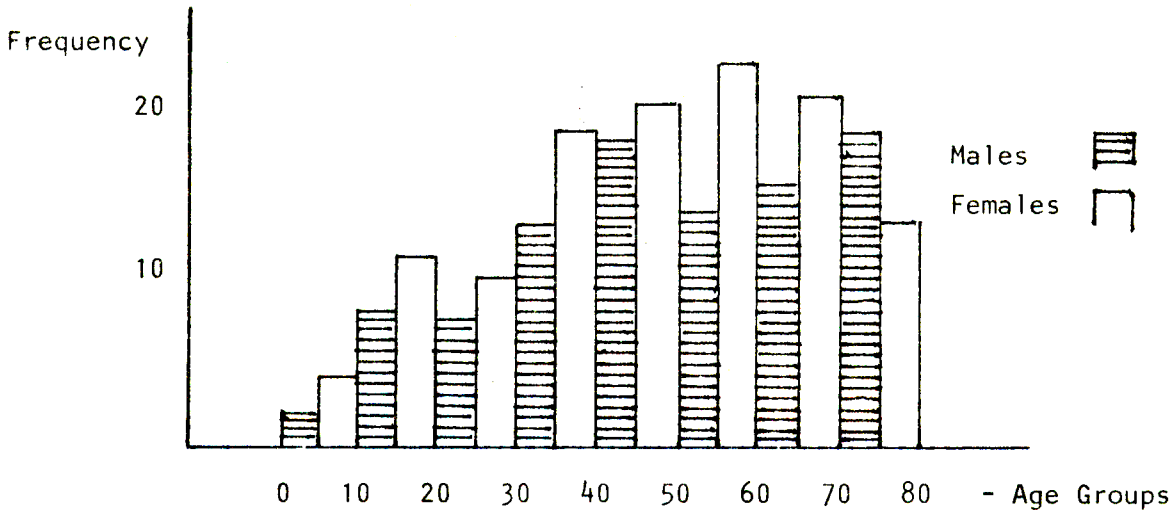



FIG. II SEX/AGE RELATED INCIDENCE

Naevi appear in significant number at the time of puberty, and in each age groups, females presented more lesions than males.

## DISCUSSION

The average of 9,9 lesions per patient correlates well with Lewis' findings in Uganda (11/patients) but not with Pack's figures of 3 per person in the South African Bantu (89) - similarly, the finding of 92,5% of persons with naevi is in accordance with both Lewis' and

Hewer's reports (88,91).

The high incidence of melanocytic naevi of the plantar skin, nearly always on pressure areas, volar skin and mucosa, in contrast to the low incidence of these lesions in pigmented skin, correlates well with the incidence of melanomas in Negroes in these subsites and the rarity of tumours arising in pigmented skin. (Table II)

| | Head/ Neck | Lips | Upper Limb | Fingers Volar Skin | Trunk | Lower Limb | Toes Plantar Skin |
|---|---|---|---|---|---|---|---|
| Melanocytic Naevi (%) | 5,2 | 4,1 | 4,4 | 17,3 | 28 | 3 | 38 |
| Melanoma (%) | 0 | 2,04 | 0 | 17,3 | 0 | 4,08 | 76,5 |

TABLE II MELANOCYTIC NAEVI AND MELANOMAS

## MELANOCYTIC NAEVI SURVEY (WHITES)

### MATERIAL AND METHOD

The same study was extended to the White population group, as Sagebiel reported that in a series of early malignant melanomas, histologic evidence of pre-existing naevi could be identified (94); again no record could be found of a study examining the relationship of naevi and melanomas by site and sex. Four hundred patients attending the Plastic Surgery clinic for unrelated complaints participated in the survey, equally divided into males and females, with the same exclusions as for Black patients.

### RESULTS

Of the four hundred persons, 23 had no apparent lesion, all of them in the 0 - 10 age group. The mean number of lesion was found to be 15,2 per patient, with a maximum of 34 in one female patient.

Since melanomas in Whites occur in different sites than in Negroes, the sites and subsites were defined as : head and neck, upper back, chest, lower back, abdomen, upper limb, lower limb. The results are shown in Table III.

| | Head Neck | Back | Chest | Abdomen | Upper Limb | Lower Limb |
|---|---|---|---|---|---|---|
| Males | 7 | 12 | 5 | 4 | 11 | 9 |
| Females | 4 | 7 | 3 | 3 | 16 | 15 |

TABLE III MELANOCYTIC NAEVI AND SITES

The age and sex related incidence is represented in Fig.III. The sharp rise in incidence at puberty is followed by a gradual decline and the histograms for males and females are very similar. As with Black patients, there is a higher incidence of melanoma in sites which present the more melanocytic naevi.

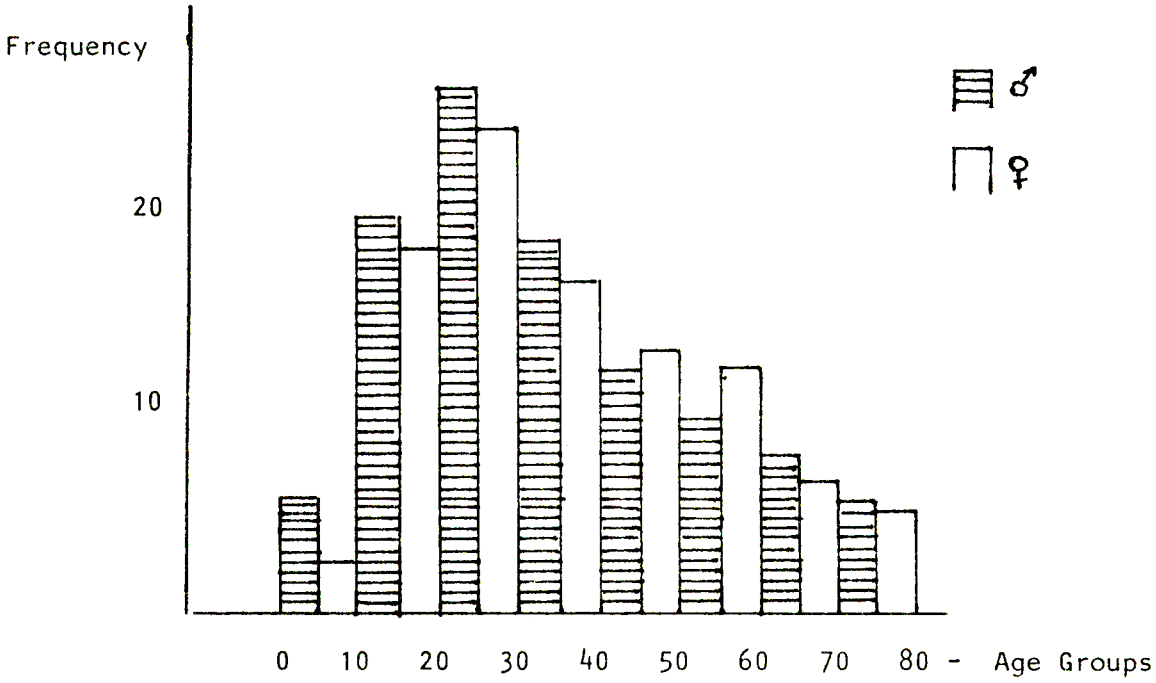



FIG. III SEX/AGE RELATED INCIDENCE

## MELANOCYTES

A study of the skin in 50 specimens examined for basal cell or squamous cell carcinomas, (therefore from skin exposed to UV radiations) and regarded as clinically normal and histologically free of tumour, showed that the number of melanocytes in the basal layer decreases with age; however, since these cancers are associated with actinic damage to the skin, the material may not be representative. Yet, a recent study of normal skin biopsies tend to confirm this finding (95).

Drzewiecki (42), studying normal skin in malignant melanoma patients showed that the overall melanocyte population in such patients is greater than in a non-affected person, and that often there were more melanocytes in the normal skin than in the direct vicinity of the lesion; this finding could be related to a host immune reaction.

Recently a syndrome of familial malignant melanoma, variously reported as "familial atypical multiple mole melanoma syndrome" (96), "dysplastic naevus syndrome" (97) or "BK mole syndrome" (from the family names of two sets of patients) has been recognized and is associated with abnormal naevi, both clinically and histologically. Its recognition is of importance for studies of the pathogenesis of malignant melanoma and clinical prophylaxis, whenever possible, for the families. It was recognized however, that such syndrome can occur sporadically, and it is of great interest to know that melanomas can arise from naevi when patients have to be immuno-suppressed (98).

## REACTION TO EXPOSURE

The physical characteristics of melanoma patients compared to non-affected persons have not been very actively investigated, the main reasons being the great size of population groups required, sophistication and therefore cost.

Three studies in White population groups from Australia (99), New York (100) and Norway (101) show some degree of unanimity. For Lancaster and Nelson (99): "Those who produce little pigment in the skin are more prone to melanoma than those who produce pigment readily, and that sunlight appears to be as important in the production of melanoma of the skin as it is in the production of basal cell carcinoma and other skin cancers."

Gellin (100) stated that .. "There is a tendency for patients with malignant melanoma to have light complexions, light eyes, blond or

red hair and to spend a greater amound of time outdoors, when compared with the control group. There is a close correlation of findings in these respects with our previously reported study of patients with basal cell epithelioma."

Kleppo and Magnus (101) reported that .."highly significant differences were demonstrated as regards the tolerance of sun exposure and propensity to freckling. The melanoma patients tolerated sun exposure less well and freckled more easily than the controls."

It is likely that these groups of investigators happened to find the same systemic difference between their melanoma patients and control groups although they did not deal with large numbers, and did not use statistical methods which could handle interactions. A recent case-control study shows, however, that there is excess of freckling in melanoma patients (102). More recently an attempt has been made to relate the reaction to light exposure of melanoma patients in a systemic way, classifying the skin in four types (103,104):

| | | |
|---|---|---|
| I | Always burn | Never tan |
| II | Always burn | Sometimes tan |
| III | Sometimes burns | Always tan |
| IV | Never burns | Always tan |

This classification was retrospectively applied to 200 white patients of the present series, after personal interviews, with the following results :

Type I : 13%, Type II : 14,3%, Type III : 65,5%, Type IV : 7,2%.

It has been found (94) that in melanoma patients, erythema produced by a dose of 300 μm radiation eight times the individual's minimal erythema dose persisted for two weeks in 85% of cases, compared with 34% in controls and 92% in non-melanoma skin cancer patients.

It was found also that the number of UVc induced sister chromatid exchanges in peripheral leucocytes of melanoma patients was

higher than in normal controls.

An interesting hypothesis, unfortunately refuted by actual studies, is that melanoma patients have the same difficulty in DNA repair as Xeroderma pigmentosum patients.

## GENETIC BACKGROUND

There is evidence of familial predisposition to malignant melanoma. There has been no comparative study, however, to clarify whether such familial aggregation varies in intensity with incidence. This could work either way :- an adverse environment could induce numerous cases at random, or could selectively produce tumours in families where such predisposition exists. Unfortunately the present series could not be used to further investigate this hypothesis. It can be concluded however, that genetic predisposition could work through skin colour or through factors which do not show visible expression but produce the familial aggregation of cases. We can reasonably presume that reactivity of the skin to sun exposure, irrespective of the pigmentation, is under genetic control. Furthermore, genetic factors must influence the development of melanocytic naevi as well as dysplastic naevi.

## OCCURRENCE

In White patients, the age at which lesions of the trunk and limbs are diagnosed is markedly lower than for head and neck tumours, whereas there is no such difference in Black patients. Yet, these anatomic sites get less sun exposure.

Increases in long term risks between successive birth cohorts will reduce the increase with age observed in a set of age-specific rates derived from a single time period (102). When this effect is accounted for, the increase with age of cutaneous malignant melanoma is no different from other cancers such as those of stomach or colon(105).

The influence of age on the incidence of melanoma is in itself surprising since both the number of melanocytes in the germinal layer of the skin and the number of naevi decrease with age. It would rather be expected that melanomas, melanocytes and naevi would decrease in the same way.

A consensus of opinion has emerged that melanomas during pregnancy carry a poorer prognosis than in non-pregnant patients (106,107). Since there was no such case in our series, no opinion can be given. In order to obtain valuable data regarding this problem, a great number of cases is necessary and such a survey should be conducted on a national level.

## ANATOMIC SITE DISTRIBUTION

As far back as the 1930's, there has been great interest in Australia about melanomas. Lancaster (108) reported in 1956 : "Dr A G G Cooper of the Queensland Radium Institute, Brisbane, has believed for some years that sunlight is an important predisposing factor in melanoma, and that melanoma is more common in the northern parts of Queensland than in the southern, which is also true for rodent ulcers, and epithelioma".

As early as 1931, malignant melanoma was distinguished from other skin cancers in Australian statistics, which led to the findings that there happened to be excess incidence on the female lower limb (109), and that sunlight, pregnancy and trauma were playing a part in the occurrence of the tumour. Lancaster and Nelson (99) commented on anatomic sites : "It might have been expected, in view of the findings concerning the aetiological importance of skin characteristics, that, depending on the area of skin exposed, the site of the melanoma would be affected. This effect is not apparent." Petersen et al (110) showed that the high incidence of melanomas of the lower limb in females (Europeans) was due to extra tumours between knee and ankle and stressed

the role of exposure. The corresponding area of high incidence in males in an area of differentially exposed skin is the external ear.

Squamous cell and basal cell carcinomas are more concentrated on exposed skin than are superficial spreading and nodular melanomas. If melanomas result from skin exposure through changes in clothing fashion, one way to prove this assumption would be to divide the skin in very small areas and see how such a cohort would fare over the years.

## LATITUDE GRADIENTS

Until the sixth revision of the International statistical classification of Diseases and Causes of Death, melanomas, squamous cell and basal cell carcinomas had been grouped together. Following this revision, melanomas were separately classified and in 1956 Lancaster (108) published an analysis of the influence of latitude of residence on the death rate, from malignant melanomas of the skin in White population.

The broad latitude gradients that Lancaster found in White populations have been confirmed in smaller and more homogeneous population groups; there is north-south gradient in mortality in North America (111), England and Wales (112), Norway (113) and Sweden (114), Finland (115) and a South-North gradient in Australia (116). However, as was indicated by Lancaster in his initial study, there are discrepancies : the figures he quoted for South Africa show that mortality was higher in the Cape and Natal Provinces than in the Transvaal and Orange Free State, but a recent survey (15) shows different figures. No gradient could be identified in the Natal Province among the White population but this is too small a population group for significant conclusions to be drawn.

The discrepancies regarding latitude gradients and mortality rates derive from three sets of observations : unexpected normal rates among White persons living in a tropical environment; paradoxical latitude gradients associated with varying degrees of pigmentation;

gradations towards urban residence and economic status. It has been shown recently (117) that malignant melanoma rates were no different in Southern or Northern Queensland, nor in North Western or Southern Australia (118). Two explanations have been proposed : either this denotes a low dose - response curve to a given dose of radiation, or the propensity of Whites living in the tropics to protect themselves more than those living further from the equator. From Queensland again, there is evidence that basal cell carcinomas present to a lesser degree, the same discrepancies as melanomas. Therefore the effect, whatever its cause, may not be specific to melanomas.

Mediterranean people have low incidence and mortality rates, whether resident in the old or new world, while Scandinavians present high rates despite living markedly further from the equator; but although belonging to the same ethnic group and living under the same conditions, Icelandics have very low rates. This finding invalidates the explanation that Scandinavians pay a higher price because of their adaptation to their particular environment.

Because UVb is a part of the spectrum where changes in stratospheric ozone would act and because of experimental action (DNA absorption, cancer induction in experimental animals) a major question is the relationship of melanoma incidence to UVb. Measuring the flux of UV light over several years in 18 countries in the USA., Baker-Blocker (119) could not find any such relationship.

## IMMIGRANTS

After adjustment for age had been made, it was found that duration of residence in Israel was a major factor in melanoma risk in persons of European origins (120).

These findings maybe biased by the fact that the highest incidence was found in people living in Kibbutzim and it is possible that the earliest immigrants were concentrated in these Kibbutzim. A

differential mortality rate has likewise been observed between native Australians and immigrants from Britain and immigrants from the rest of Europe (121). No significant differences could be identified in the Natal Province, but again the White population group is too small for such a survey.

## OCCUPATION

There is evidence for the association of industrial factors with the induction of malignant melanoma : cutaneous melanomas in workers exposed to polychlorinated biphenyl (122), increases in melanomas rates in chemists (123), but these reports have been based on very small numbers. An excess of malignant melanomas has been reported among workers at the US Lawrence Livermore National Laboratory dealing with nuclear research for both civil and military purposes. The distribution by anatomic sites was not different from a general population.

These findings are currently under investigation, but there are no other reports of such findings in other nuclear laboratories.

## TIME TRENDS

### ANATOMIC SITE - MELANOMA TYPE - HISTOLOGY

In the Natal White population, as reported elsewhere (84,107) the rising trend of the incidence of cutaneous melanoma in not homogeneous by anatomic site. Rates for head and neck lesions increase more slowly than those of the trunk and limbs. The dissociation imposes constraints on hypotheses about the cause of such a rise; it rules out systemic affects unless their action is coupled with site-specific factors or unless they act on a specific target. Similarly, it rules out hypotheses brought up to account for the homogeneity of simultaneous anatomic distributions in widely different rates, in terms of a "solar circulating factor".

Conversely this anatomic site effect could theorically be explained by recent changes in personal habits. The face has to be

exposed, and hats are worn less than in the past by urban dwellers, although people involved in outdoor activities in South Africa still favour the protection they give. Any change to usually exposed site may produce little increment because of the point on the sigmoid dose-response curve at which they start, whereas exposure of a usually covered area of skin, like the trunk may produce a proportionally larger increase in incidence. Such an explanation pre-supposes that the occurrence of melanoma is dose-related, which is hypothetical.

NON-CUTANEOUS SITES

Incidence and mortality rates for non-cutaneous sites have remained identical over the years. Apparently, eye melanomas respond to the same hormonal influences as do cutaneous ones, but do not show the same latitude gradient (124).

The time trends of other melanomas unlikely to be influenced by exposure would provide a further check on the hypothesis that the incidence rise of skin melanomas is the direct result of exposure. There is unfortunately no available data on internal melanomas.

It does not appear, however, that there is a rise in incidence of acral melanomas, at least in White population groups, and they have a high mean age, which further suggest that their incidence is not rising through a year-of-birth effect.

NON MELANOMA SKIN CANCERS

If the rising incidence of malignant melanomas is due to increased exposure to sunlight, it can be assumed that this trend applies also to other skin cancers. It is however, difficult to ascertain that such a rise occurs; since they do not usually have a fatal prognosis and their treatment is a simple matter, many cases are not reported and therefore not included in statistics.

Yet from 1975 to 1982 the number of patients presenting with either basal cell or squamous cell carcinomas, or both, and referred to

the Department of Plastic Surgery has increased from 312 to 416 (a 1.3 yearly incidence increase).

## TRAUMA

Trauma has diversely been considered as an aetiological factor of melanoma. Seldom reported by White persons as the incident which initiated the occurrence of the lesion, it is frequently mentioned by Blacks.

Hewer (90) regarded trauma as the most likely aetiology. Lewis, in Uganda (18) assumes that physical or chemical agents might be responsible for the malignant changes which take place in melanocytic naevi of the plantar skin, namely heat and wood smoke. Wood is without doubt the most used fuel by the Black population as freely available, but the concentration of substances like dimethylbenzenthracene in wood smoke is not known; he also mentions application of hot nails as treatment to lesions of the foot (and elsewhere). Such practice could not be traced amongst Zulus, but Witch-Doctors endeavour to keep their technique a well-guarded secret.

Krementz (82), reviewing all cases of melanoma in Negroes treated at the Charity Hospital of Louisanna could find no evidence to support the view that trauma may bear responsibility in the occurrence of melanoma.

In the present survey, as previously mentioned, 16,2% of the patients related the tumour to previous trauma.

The diversity of opinion may be explained by the socio-economic differences of the population groups studied. American Blacks are fully integrated in a White society and follow the same habits and fashions as Whites; shoe wearing certainly minimizes the risk of trauma.

Conversely, the African Negro, even when urbanized, still abide by his tribal customs; shoe wearing is not the rule in rural areas, and certainly does not apply to children; even urban dwellers not uncommonly dispense with this expensive fashion and when wearing shoes these are often so ill-fitting that they are likely to create more harm than preventing eventual trauma.

In sub-tropical climates like in Natal, the plantar skin is subjected to constant high temperatures most of the year, not only through direct contact with the ground itself when walking barefoot, but also to high ambiant temperature when wearing shoes.

Five patients accepted to wear in their shoe, in contact with the plantar skin, a sensitive probe. The temperatures recorded during the peak hot season varied between 42° and 47,3° centigrade, more than is needed to induce protein alterations.

## INTEGRATION OF FINDINGS - AN AETIOLOGIC HYPOTHESIS

Europeans and Bantus live in South Africa under the same climatic conditions, as do Coloureds and Indians. Yet, during the period covered in the survey, only two Indians and one Coloured presented with a melanoma, precluding any study of the disease in these two population groups. This is a disturbing finding : one would expect Coloured people to show an incidence rate anywhere between that of the Bantus and Europeans or similar to either one of the two groups according to their degree of skin pigmentation, if indeed melanin was acting as a sun-screen. The White population of Natal, although living under near similar climatic conditions as the Australian Queensland population, shows an appreciably lower incidence rate of melanoma; the similarity goes beyond geographical features and applies to clothing fashion as well as outdoor activities

and socio-economic status. If sun exposure was the main factor in inducing malignant changes in melanocytes, regions of the almost permanently exposed to UV radiations beside the face - like the forearm, seldom covered through short-sleeve shirt wearing, a popular fashion in South Africa, or the dorsum of the hand, should have a high incidence of melanoma. This is not so, although they present a high rate of basal cell and squamous cell carcinomas. The advanced age at which non-melanoma skin cancers appear, the histories of prolonged exposure, whether occupational or recreational, the clinical and histologic evidence of actinic damage to surrounding skin, the concentration of lesions on exposed sites, are features of non-melanomas but not of melanomas (25,125,126). Only the lentigo maligna type bears similitude in its environmental relationship with non-melanoma skin cancers and it seems reasonable to assume that the pathogenesis of lentigo maligna melanoma is akin to that of basal cell carcinoma. Likewise the age distribution, clinical appearance and behaviour of acquired melanocytic naevi differ from those of solar keratoses.

Ten Seldan (127) commented in 1962 : "Excessive exposure of a sensitive skin to sunlight seems to be one of those aetiological factors in the causation of malignant melanoblastomas. How important has still to be assessed. It is unlikely that sunlight plays a major part in all cases, or even the majority."

Sixteen years later (115), it was said, "Taken together these findings suggest that the recognition of sunlight as the only important risk factor of cutaneous melanoma may be an over simplification of a complex problem." It may be that non-melanoma skin cancers require a long exposure to sunlight whereas melanomas would necessitate a lower dose in conjunction with other factors. But if all that is needed to induce a melanoma is a small dose of UV radiation, the relative rarity of the tumour is difficult to explain. Two possible explanations have

been proposed : variation in exposure intensity and age at exposure.

It has been postulated that outdoor workers do not present a high incidence rate because they are protected by a long acquired tan, and that the determinant factor is intermittent exposure of untanned skin to intense sunlight. Although this may well be true of Europeans, who get exposure during brief holiday times, such an explanation does not apply to South Africans, nor is it likely to apply to Australians.

The association of naevi with melanoma and the occurrence of melanocytic naevi during adolescence suggest that responsible events which determine the subsequent growth of a lesion may well take place early in life, in much the same way as early reproductive activity determines breast cancer incidence. If the events during adolescence play a major role in the long term induction of a melanoma, the low incidence rate in outdoor workers could be explained. All these speculations, however, are attempts at finding an explanation for the occurrence of melanoma in White populations only. They exclude not only other racial groups but also animals (28); yet it is difficult to believe that the melanocyte would respond to a variety of factors, or their interaction, in always the same pattern, unless these factors always have a direct action on a specific target component of the cell. The only components of the melanocyte which differentiate this cell from others is the melanin and the enzymatic apparatus for its synthesis. Vitiligo is a common occurrence in patients who survive a melanoma and therefore have build-up an immunity against the affection : melanin disappears; Albino patients, whose melanocytes lack totally or partially the ability to synthetize melanin, do not develop melanomas (129,130), and only eight cases of cutaneous melanomas have been reported in such people. Although we see many of these patients each year for treatment to basal or squamous skin cancers, no one ever presented a melanoma. The implications of these findings are three-fold : melanin is not a

sun-screen, else these patients would present multiple melanotic tumours; sunlight alone is not the main causative factor; melanin- or melanoprotein - is necessary for a melanoma to develop. In this concept, heat is presumed to be the main factor responsible for inducing alterations in the structure of the melanoprotein molecule, which would then act as a pro-carcinogen. This hypothesis allows for an explanation to the following :-

- the occurrence of melanoma in both White and Black populations could be related to sunlight, not through a direct action in terms of UV radiations, but in thermal energy received, and the differential accumulation of such energy in melanocytic benign lesions.
- the correlation between the high incidence of melanocytic naevi of the Negroes' feet and the parallel incidence of melanoma, both of which are prevalent at the pressure points.
- the controversy as whether we deal with a dose-dependant carcinogen : a fair skin briefly exposed to intense sun exposure will burn more readily than a tanned skin which has had time to become more resistant.

The fairly unusual occurrence of amelanotic lesions does not invalidate the hypothesis : it is common for a primary lesion to give rise to amelanotic metastases; the host's immune system may be held responsible for the elimination of the pro-carcinogen, without being able to control further growth.

It has been shown (131) that most cancers develop in multiple steps. As normal cells evolve into cancer cells, several stages of development take place from initiated cells to pre-neoplastic cells to malignant cells, (132) as demonstrated in a mode of skin carcino-genesis in mice (133), where an initiated cell can give rise to a skin cancer after action of a promoter.

Whether the structural alteration of the melanoprotein molecule could subsequently give rise to a malignant melanoma would be circumstantial. Repeated trauma at the site, as occurring repeatedly on the sole of the foot or the volar aspect of fingers and hand, with the subsequent increase in mitotic activity, is a likely promoter, as well as melanocyte hormonal stimulation by STH and ACTH as a response to light exposure (and fair skinned persons present a more intense stimulation), or even a stress situation, a prerogative which parallels social status. In this context, it must be remembered that sustained specific growth stimulation of a cell through application of its normal stimulant, can induce tumours even without extrinsic carcinogenic agent, and that tumours so induced are specific for the hyperstimulated cell type. Such tumours soon become autonomous and fully hormone independant.

In our present knowledge, this hypothesis cannot be substantiated by experimental study since the extraction process of the molecule of melanine itself induces structural alterations.* Histology, to date, has failed to reveal any salient difference between normal and abnormal melanocyte, which could result from molecular alterations, nor have any changes which could be related to such causative factor been exposed in electron microscopy, despite sophiscated and meticulous studies (22).

As with many cancers, the final outcome depends upon the host's immune system : the now malignant cell could simply be destroyed as soon as produced, or could remain in a latent state until such time that immunosurveillance deteriorates, as happens as age advances, or, through total lack of immune response, would rapidly give rise to a clinical tumour. (Fig. IV).

* Dr. Joubert SM (Chemical Pathology) Personal Communication

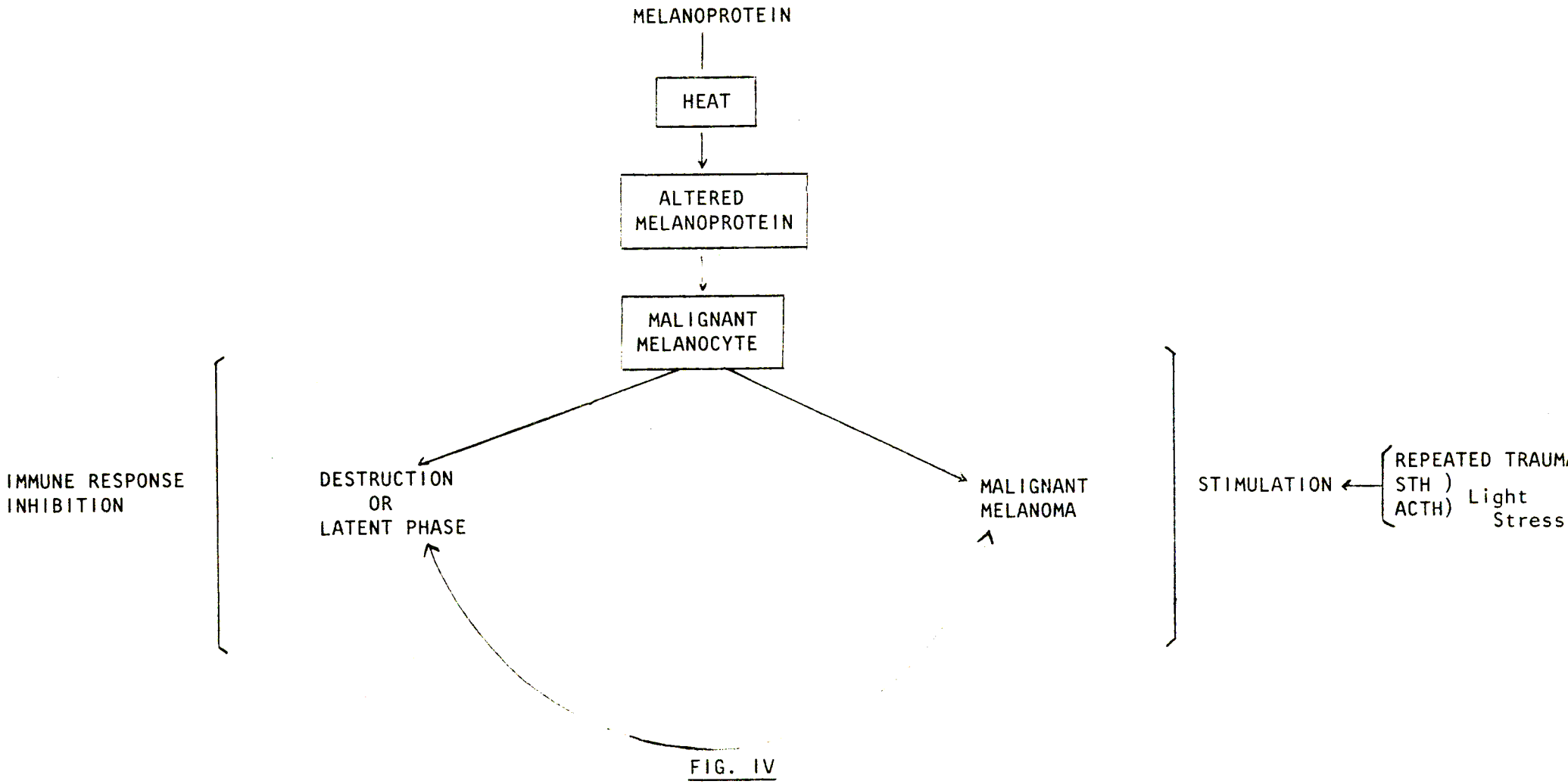

MELANOPROTEIN
HEAT
ALTERED MELANOPROTEIN
MALIGNANT MELANOCYTE
IMMUNE RESPONSE INHIBITION
DESTRUCTION OR LATENT PHASE
MALIGNANT MELANOMA
STIMULATION
REPEATED TRAUM
STH )
ACTH)
Light
Stress

FIG. IV

## CONCLUSION

Malignant melanoma has long been considered an unpredictable cancer carrying a poor prognosis. Such pessimism is not justified.

The study has revealed aspects of the disease which had not previously been investigated: the incidence increase in both Black and White populations of the Natal Province, the very low rate amongst Coloured and Indians groups. More important, the melanocytic naevi surveys enlighten the relationship between such benign lesions and melanomas, (whereas previous studies had been concerned with limited aspects of such association), and the corollary, a new hypothesis in an attempt to explain the occurence of malignancy. As regards treatment, it is hoped that the results obtained with BCG therapy will cast a new light on the subject. Further, the classification which has been proposed should help in predicting the outcome of the affection, and the treatment adapted individually. Where "low risk" patients may be adequately treated by surgery alone, moderate and high risk patients conversely can only benefit from immunotherapy eventually combined with chemotherapy. In fact, the results obtained with immunotherapy in patients who respond positively to this form of therapy is such that the following modality in these selected cases should be considered : immunotherapy, combined when deemed necessary with chemotherapy, as a first line of treatment, which could lead to two eventualities : either the lesion disappears entirely and nothing further need to be done, or the lesion regresses to such an extent that a limited excision with primary skin closure becomes feasible.

Although the present series of patients is comparable in numbers to many series published elsewhere, it is nevertheless impossible to prove beyond all doubts that this might be the best form of treatment. Only data collected randomly from thousands of patients of same racial groups, age, region of residence, presenting a similar type of melanoma

of identical level of invasion and thickness could give a definite answer. This is not feasible, except at international level, but the conclusions presented seem reasonable.

To adopt a stereotyped therapeutic approach in dealing with melanoma, clearly does not take into account the peculiarities either of the patient or of a given type of tumour. Further, to apply today a surgical treatment devised almost a century ago to excise extensive lesions which are now seldom seen is not justifiable, even less so when it becomes evident that no survival improvement may be expected by a more radical and mutilating surgery. Four factors have emerged which are considered of importance, the level of invasion of the tumour, its thickness, its type and patients response to immunotherapy, with their corresponding significance. Of these, only level of invasion and tumour thickness depend upon the host's awareness; it is hoped that more and more patients, through better knowledge, will seek medical attention at an earlier stage.

Epidemiology uses the past to predict the future and considers extreme situations in an attempt to explain the more common. To achieve these goals, studies must include the greatest possible number of patients and extend over the greatest possible periods. The difficulties encountered in collecting data for the present survey emphasize the need for a Cancer Registry in our country, and possibly the initiation of a "Melanoma project" as instituted in Australia.

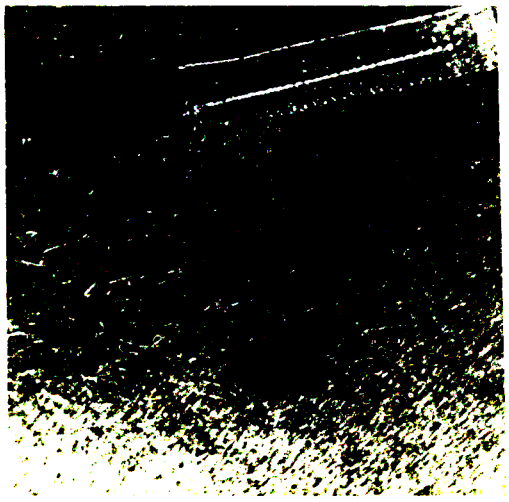
# A P P E N D I X

# M A L I G N A N T  M E L A N O M A

## WHITE POPULATION

Lentigo Maligna Melanoma

Nodular with superficial spreading component



Superficial spreading

Nodular

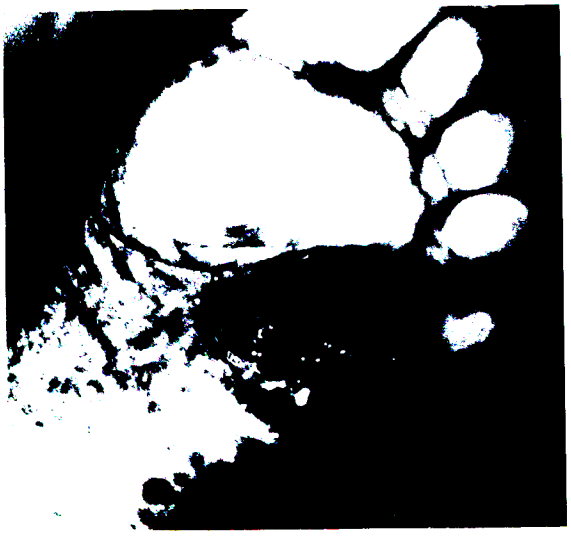
# M A L I G N A N T  M E L A N O M A

## BLACK POPULATION

## (ACRAL MELANOMA)

I. Tumour involving the whole upper lip

II. Ulceration through the nail. Tumour involving the whole distal phalanx



III. Extensive ulcerated lesion of the sole of the foot, with adjacent melanocytic naevi

# B I B L I O G R A P H Y


1. Harrer Heinrich - Seven Years in Tibet - Graves, London, Rupert Hart-Davis 1953.
2. Laënnec, R T H : cited by Pemberton, O (4)
3. Carswell R, Pathological Anatomy - London, Longman 1838, Part 9, Melanoma.
4. Pemberton O : Observations on the History, Pathology and Treatment of Cancerous Diseases., London J Churchill, 1858; part 1 ; melanosis.
5. Pringle J H : A Method of Operation in Cases of Melanotic Tumours of the Skin. Edinb. Med J 23 : 496 - 499, 1908.
6. Communication by the Peruvian Society of Anatomic Pathology in : Bulletin de le Societe Francaise d' Anthropologie, Masson, Paris, 1979.
7. Selby H et al, Aroentgen Study of Bone metastases from Melanoma - Radiology 67 : 224 - 228; 1956.
8. Clark V H from L Bernardino E A et al. The Histogenesis and biologic behaviour of Primary Human malignant melanomas of the skin. Cancer Res. 1969; 29 : 705.
9. Breslow A Thickness, cross sectional area and depth of invasion in the prognosis of cutaneous melanoma. 1970 A Surg; 172 : 901.
10. Kaplan I and Youngleson J Malignant Melanoma in the South African Bantu. 1972. Brit J Plast Surg: 25: 65-68.
11. Giraud R Rippey E and Rippey J : Pathology of Malignant Melanoma of the Skin in Black Africans. 1975 South African Med J: 49: 665.
12. Oettle A G, Higginson J: Cancer incidence in Bantu and "Cape Coloured" races of South Africa - Cancer survey in the Transvaal - 1960: J Natl Cancer Inst: 24: 589.
13. Des Ligneris M: Tumours in Northern Transvaal 1927 J M A South Africa 1:102.
14. Shah M and Goldsmith H S: Malignant melanoma in the North American Negro. 1971 Surg Gynael. Obstet. 133:437.

15. Rippey J J, Rippey E; Epidemiology of Malignant melanoma of the skin in South Africa. 1984 South African Med. J; 65:595.

16. Reed R; Acral lentiginous melanoma. New concepts in surgical pathology of the skin. 1986, Wiley, New York.

17. Arrington J et al; Plantar lentiginous melanoma : a distinctive variant of human cutaneous malignant melanoma. 1977 J. Surg. Path.; 1:131.

18. Suseelan V A, Gupta I M: Malignant melanoma in Nigeria - Pathological studies 1977 Afr. J. Med Sci; 6:209.

19. Krementz E et al: Acral lentiginous melanoma. A clinicopathological entity 1962 Ann Surg; 195:632.

20. Lee J A H: The current rapid increase in incidence and mortality from malignant melanoma in developed societies; Pigment cell; 1976; 2:414-420.

21. Magnus K: Incidence of malignant melanoma of the skin in Norway 1955-70. 1973 Cancer; 32:1225-1236

22. McCarthy et al: Melanoma in New South Wales. An epidemiologic survey; 1970-76. 1980 Cancer; 46;427-432.

23. Lee J A H and Strickland D B J: Cancer 1980; 41:757-763.

24. Teppo L, Pukkala E, Hakena M et al: Way of life and cancer incidence in Finland. Scand. J. Soc. Med. 1980; 19:50-4.

25. Beral V, Robinson N: The relationship of malignant melanoma, basal and squamous skin cancers to indoor and outdoor work. Br.J. Cancer 1981; 44:886-91.

26. Little J H, Holt J and Davis N: Changing epidemiology of malignant melanoma in Queensland. Med. J. 1980; 1:66-69.

27. Holman C D J, Mulroney C D and Armstrong B K: Epidemiology of pre-invasive and intravasive malignant melanoma in Western Australia. Int. J. Cancer 1980; 25:317-323.

28. Kaplan and Meier: Non-parametric estimation from incomplete observation. J Am. Stat. Assoc. 1958; 53:457-487.

29. Kapelanski D P et al, Characteristics of the primary lesion of malignant melanoma as a guide to prognosis and therapy.

30. Elder D E et al. Optimal resection margin for cutaneous malignant melanoma. 1983. Plast Recons Surg; 71:66-72.

31. Drzewiecki K T. Cutaneous malignant melanoma 1979, Scand J Plast Surg.

32. Balch C M et al. A multifactorial analysis of melanoma: Prognostic factors in melanoma patients with lymph node metastases (Stage II) 1981. Ann Surg; 377-388.

33. Handley W S. The pathology of melanotic growths in relation to their operative treatment. 1907. Lancet; 1:927.

34. Stehlin J S. Jr. Treatment of the primary lesion in melanoma. Surg. gynaecol and obst. 1981; 152;499-500.

35. Davis N. Cutaneous melanoma: The Queensland experience. 1976 Curr. Prob. Surg. 13:1

36. Petersen N C, Bodenham D G and Lloyd O C. Malignant melanoma of the skin. 1962. Br. J Plast Surg.: 15,49,97.

37. Olsen G. The malignant melanoma of the skin. New theories based on a study of 500 cases. Achi. Chir. Scand. Suppl. 365.

38. Cochran A. Malignant melanoma: A review of 10 years experience in Glascow, Scotland. 1969. Cancer 23:119.

39. McGovern V J. Melanoma: growth patterns, multiplicity and regression. 1972 In: Melanoma and skin cancer (Proceedings of the International Cancer Conference, Sydney) 95-106.

40. Wong C K. The study of melanocyte is normal skin surrounding malignant melanoma. 1970. 141,215.

41. W H O collaborating centres for evaluations of methods of diagnosis and treatment of melanoma - Stage I melanoma of the skin; the problem of resection margins. 1980; 16, 1079-1085.

42. Drzewiecki K T. The epidermal melanocyte system in patients with malignant melanoma. Scand. J. Plast. Reconstr. Surg 1979: 13:333-339.

43. Emmett A J J and O'Rourke M G E. In: Malignant skin tumours. 1982. Churchill Livingstone; 116-142.

44. Dellon A I, Ketchain A S: Surgical treatment of Stage I melanoma: comment on article by Courad. 1973. Arch Surg; 106:730-739.

45. Goldsmith H S, Shah J P, Kim D. Prognostic significance of lymph node dissection in the treatment of malignant melanomas. 1970 Cancer; 26:606-609.

46. Price W G, Du Val M G, Regional lymph node dissection and malignant melanoma. 1963 Arch Surg; 67:747-750.

47. Conrad I G. Treatment of malignant melanoma: wide excision alone vs lymphadenectomy. 1972. Arch Surg; 104:587-593.

48. Knutson Co, Hori J M, Spratt J S. 1971. Melanoma: Curr probl Surg; 12:1-55.

49. Proses D G et al. Selective surgical management of cutaneous melanoma of the head and neck 1981. Ann Surg; 192:629-632.

50. Rayner C R. The results of node resection for clinically enlarged lymph nodes in malignant melanoma. 1981. Br.J. Plast Surg; 34:152-156.

51. Wanebo H J, Fortner J G, Woodruff S et al. Selection of the optimum surgical treatment of Stage I melanomas by depth of micro-invasion: use of the combined microstage technique (Clark-Breslow) 1975 Ann Surg; 182:302-314.

52. Goldman L I. The treatment of malignant melanoma of the skin 1978 Surg Gynaecol obstet: 146:779-762.

53. Hansen M G, McCarter A B. Tumour thickness and lymphocytic infiltration in malignant melanoma of the head and neck 1974. Am J Surg; 128:557-561.

54. Breslow A. Tumour thickness, level of invasion and node dissection in Stage I cutaneous melanomas. 1976. Ann Surg: 182:572-575.

55. Cady G, Lepp M A, Redfern A B. Contemporary treatment of malignant melanoma. 1975. Ann J. Surg.n 129:472-482.

56. Sim F H, Taylor W F, Irvine T C et al. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma: Preliminary results. 1978. Cancer 41:948-856.

57. Ariel I M. Malignant melanoma of the trunk. A retrospective review of 1128 patients. 1982. Cancer; 49:1070-1078.

58. Calvin L D et al. A prognostic model for clinical stage I melanoma of the upper extremity 1981. Ann surg; 193:436-440.

59. Ariel I M. Malignant melanoma of the upper extremities. 1981. J. Surg One; 16:125-143.

60. Proses O F et al: Surgical management for malignant melanoma of the trunk; 1981 Ach. Surg. 116:315-317.

61. Varella A D et al: Treatment of disseminated malignant melanomas with high dose-oral BCG. 1981 Cancer: 48:1353.

62. Fairman R M et al: Inadvertent transplantation of a melanoma. 1980 Transpl. 80:328.

63. Farmsworth J D et al. Transplantation of malignant melanoma with a cadaver kidney. 1972. Transpl. 13:619.

64. Sumner W C, Foraber A G: Spontaneous regressions of human melanoma 1960. J. Cancer; 13:79.

65. Morton D L et al: Immunological factors in human carcinomas and melanomas. 1970. Ann Surg. 192:740.

66. Hollinshead A et al: Pilot studies using melanoma tumour-associated entigens (TAA) in specific-active immunotherapy of malignant melanoma 1982. Cancer; 49:1387.

67. McIllmurray M B et al. Controlled trial of active immunotherapy in management of stage II malignant melanoma - 1974. Brit.Med.J: 1:540.

68. Morton D L et al: BCG immunotherapy of malignant melanoma - 1974 Ann Surg: 180:635.

69. Dauvilliers - L'origine photochimque de la vie - Masson Paris 1858.

70. Dauvilliers - les hypothesis cosmogoniques - Masson-Paris 1963.

71. A Tetry: Adaptation - in "Biologie" - Encylopedie de la Pleiade - Paris 1965.

72. Quevedo-Fitzpatrick, Pathak et al: Hole of light in human skin colour variation; A M J Phys. Antropol 1975; 43:393-408.

73. J J Theron et al: Functions of the human pineal gland. 1983 SAM J: 64:730.

74. Guyton I: Textbook of medical physiology. 1981 - Saunders.

75. Loomis W F: Skin pigment regulation of vitamin D biosynthesis in man - science 1967; 157:601-6.

76. Heckmatt, Peacock, Davies et al: Plasma 25 Hydroxy - vitamin D in pregnant Asian woman and their babies - Lancet 1979; 2:546-8

77. Ramade. In: Elements D'Ecologie appliquee. 1974 Ediscience, Paris.

78. Park in MIT: Man's impact on the global environment-Cambridge VP Ass. 1970; 132-182.

79. Norman G: Satellite data indicates ozone depletion. Science 1981; 213:108-9.

80. A Pacolosuski; H F Haberman, A Menum - skin melanoma induced by 7,12 - dimethylbenzanthracene in albino guinea pigs and its similarities to skin melanoma of humans. Cancer Research 1980; 40:3652-3660.

81. M G Lewis: Malignant melanoma in Uganda Br. Journal of cancer 1967 21:483-495.

82. T Krementz et al: Malignant melanoma in the American Black. Ann Surg. 1976. 183:533-541.

83. N Ringertz: Cancer Incidence in Finland, Iceland, Norway and Sweden: a comparative study. Acta Path/Microbiol. Scand. (A) 1971 suppl. 224.

84. K Magnus: Incidence of malignant melanoma of the skin in the five Nordic Countries: significance of solar radiation. Int. Journal Cancer 1977: 20:477-485.

85. Lee, Storer: Excess melanomas in women in the British Isles - Lancet 1980: 2:1337-9.

86. Lane Brown, Sharpe O A B, MacMillan D S et al: Genetic predisposition to melanoma and other skin cancers in Australians. Med. Journal Aust. 1971: 1:852-8.

87. Allen A C and Spitz: 1953; Cancer, NY; 6:1.

88. Lennox B: The Histopathology of Tumours - Melanomata - In: Recent advances in Pathology - 1960.

89. Becker W S: Am NY acad. sci. - 1948; 4:82.

90. Hewer T F - J Path. Bact. 1935; 4:473.

91. Pack G T: Am. NY acad. sci. 1948; 4:52.

92. Heselson - South Afr. Med. J. 1961; 35:113.

93. Lewis M G, Johnson K: The incidence and distribution of pigmented naevi in Ugandan Africans. 1966; Br.J. Derm; 80:362.

94. Sagebiel R M: Histopathology of borderline and early malignant melanoma. Am J. Surg. Path. 1979n 3:543.

95. Gilchrist, Blog.Szabo: Effects of aging and chronic sun exposure on melanocytes in human skin. J Invest Dermatol 1979; 73:141-3.

96. H T Lynch, R M Fusaro, J Bester, J F Lynch: Familial atypical multiple mole melanoma syndrome: genetic hetero-geneity and malignant melanoma. Brit. J. Cancer 1980: 42'58-70.

97. Greene M H, Clark W H, Tucker M A et al: Precursor naevi in cutaneous malignant melanoma: a proposed nomenclature. Lancet 1980; 2:1024.

98. Greene M H, Young T I, Clark W H: Malignant melanoma in renal-transplant recipients. Lancet 1981: 1:1196-9.

99. Lancaster H O, Nelson J: Sunlight as a cause of malignant melanoma a clinical survey. Med. J. Aust. 1957: 1:452-6.

100. Gellin G A, Kopf A W, Garfinkel L: Malignant melanoma in a controlled study of possibly associated factors. Arch. Dermatol 1969; 99:43-8.

101. Kleppo, Magnus K: Some environmental and bodily characteristics of melanoma patients: a case-control study. Int. J. Cancer 1979; 23:482-6.

102. Cesarini J P: Epidemiologie des melanomes malins et des autres cancers de la peau. Rev. Med. 1979; 20:145-2.

103. Melski J W, Tanenbaum L, Parrish J A et al: Oral methoxsalen photochemotherapy for the treatment of psoriasis: a co-operative clinical trial J. Invest. Dermatol 1977; 68:328-35.

104. Beitner H Ringborn U, Wennersten G et al: Further evidence for increased light sensitivity in patients with malignant melanoma, Br. J. Dermatol 1981: 289-94.

105. Cook P J, Doll R, Fellingham S A: A mathematical model for the age distribution of cancer in men. Int.J. Cancer 1969; 4:93-112.

106. Shiv M H, Schottenfeld D, Maclean B et al: Adverse affect of pregnancy on melanoma. Cancer 1976; 37:181-7.

107. Houghton A N, Flennery J, Viola M V: Malignant melanoma of the skin occurring during pregnancy. Cancer 1981; 48:407-10.

108. Lancaster H O; Some geographical aspects of the mortality from melanoma in Europeans. Med J. Aust. 1956; 1:1082-7.

109. McGovern V J: Melanoblastoma. Med. J. Aust. 1952; 1:139-42.

110. Petersen N C, Bodenham D C, Lloyd O C: Malignant melanomas of the skin. A study of the origin, development, aetiology, spread, treatment and prognosis. Br.J. Plastic Surgery 1962; 15:49-93, 97-111.

111. Elwood J M, Lee J A H, Walter S W et al: Relationship of melanoma and other skin cancer mortality to latitude and ultra-violet radiations in the United States and Canada. Int.J. Epidemiol 1974: 3:325-32.

112. Swardlow A J: Incidence of malignant melanoma of the skin in England and Wales and its relationship to sunshine. Br.Med.J. 1979: 2:1324-7.

113. Magnus K: Incidence of malignant melanoma of the skin in Norway, 1955-70: Variations in time and space and solar radiation. Cancer 1973; 32:1275-85.

114. Eklund G, Mevec E: Sunlight and incidence of cutaneous malignant melanoma: effect of latitude and domicile in Sweden. Scand.J. Plast.Reconstr. Surg. 1978; 12:231-41.

115. Teppo L, Pakkanen M, Hakulinen T: Sunlight as a risk factor of malignant melanoma of the skin. Cancer 1978; 41:2018-27.

116. Beardmore G L: The Epidemiology of malignant melanoma in Australia. In McCarthy ed. Melanoma and skin cancer 1972: 39:64.

117. Little J H, Holt J, Davis N: Changing Epidemiology of malignant melanoma in Queensland, Med.J. Aust. 1980: 1:66-9.

118. Homan C D J, Mulroney C D, Armstrong B K: Epidemiology of pre-invasive and invasive malignant melanoma in Western Australia. Int. J. Cancer 1980: 25:317-23.

119. Baker-Blocker A: Ultra violet radiation and melanoma mortality in the United States. Environ. Res. 1980; 23:24-8.

120. Anaise D, Steinitz R, Ben Hur N: Solar radiation: a possible aetiological factor in malignant melanoma in Israel; a retro-spective study (1960-72) Cancer 1978: 42:299-304.

121. McMichael A J, Bonett A: Cancer profiles of British and Southern European migrants. Med. J. Aust. 1981; 1:229-32.

122. Bahn A K, Rosenwaike I, Herrman N et al: Melanoma after exposure to PCB's. N. Engl. J. Med. 1976:295-450.

123. Hoar S K, Dell S: A retrospective cohort study of mortality and cancer incidence among chemists. J. Occup. Med. 1981; 23:485-95.

124. Lee J A H, Storer B E: Malignant melanoma female-male death ratios. Lancet 1981: 2:1419.

125. Lee J A H, Merril J M: Sunlight and the aetiology of malignant melanomas: a synthesis. Med.J. Aust - 1970; 2:846-51.

126. Crombie I K: Distribution of malignant melanoma on the body surface. 1981. Br.J. Cancer. 43:842.

127. Seldam R E J: Skin cancer in Australia. In Urbach F ed. Conference on biology of cutaneous cancer, Washington DC: US DHEW, 1963: 153. (N C I Monograph).

128. Crombie I K: Racial difference in melanoma incidence. 1979 Br. J. Cancer; 40:185.

129. Fitzpatrick T B and Queredo W C Jr. Albinism in: The metabolic basis of inherited disease. 2nd, 1966. New York; McGraw-Hill.

130. Witkop C J Jr. Albinism: In advances in Human Genetics, Vol II 1971. New York, Plenum Press.

131. Fould L: Neoplastic development. 1975. London Academic Press. Inc.: 1-108.

132. Farber E: The sequential analysis of liver cancer induction. 1980 Biochin Biophys. Acta; 605:149.

133. Berenblum I: Co-carcinogenic action of croton resin. 1941: Cancer Res: 1:44.

THE FOLLOWING HAVE BEEN USED AS CONSTANT REFERENCES ALONG THE STUDY:

Edmond Goblot: Traite de logique. 1952. Armand Colin, Paris.

H Rouviere: Anatomic Humaine, descriptive, topographique et fonctionnelle. 1970, Masson, Paris.

H Rouviere: Physiologie du systeme lymphatique. 1937, Masson, Paris.

Professor P Denoix: Soixante annees de l'Institut Gustave Roussy. 1982, Pfizer, Paris.

Le ganglion non envahi: N(-) Colloque tenu a l'Institut Gustave Roussy, Sept. 1981, Pfizer, Paris.