MALIGNANT MELANOMA

A REVIEW OF EXPERIENCE IN DIAGNOSIS AND TREATMENT AT THE WESTERN INFIRMARY, GLASGOW, AND OBSERVATIONS ON THE PATTERNS OF DISTRIBUTION OF THE CUTANEOUS MELANOCYTES

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BY

ALISTAIR J. COCHRAN

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"Up-on the cop right of his nose he hade
A verte, and thex-on stood a tuft of heres
Reed as the bristles of a sowes eres."

Geoffrey Chaucer,
Prologue to Canterbury Tales,
14th Century.

Hippocrates is credited with the first record of a pigmented cutaneous tumour, (de Cholnoky, 1941). Whether this was a malignant melanoma, a naevus or a pigmented tumour derived from cells other than the melanocytes is not clear. A skin tumour, particularly a pigmented one is an obvious blemish and the existence of such imperfections in their fellows did not escape the keen eye of observant lay persons such as Chaucer and Shakespeare. It seems likely that the contemporary medical profession was aware of the existence of these lesions, but written reports of such tumours are scanty prior to the early nineteenth century. The degree of acrimony felt in the debate as to whether Laennec or Dupuytren first described the disease entity is apparent from reading the contemporary literature, even after a lapse of more than one and a half centuries.

M. Laennec read a paper entitled "sur l'anatomie pathologique" to the Société de l'Ecole de Médécine de Paris in early 1805 (the 6th of Nivose in the 13th year of the Republic). In this, as part of a classification of tissue changes he included "les melanoses". In a footnote he acknowledged that part of the information on which the delineation of this category of tissue change was based was derived from work done by the author and M. Bayle, another member of the Société. This address was published in full in the Journal de Médécine, Chirugerie,/

Chirugerie, Pharmacie etc. of January/February 1805. In the subsequent issue of this Journal (Ventose of Anno 13) M. Dupuytren, in a lengthy article entitled "Observations sur la note..... par M. Laennec..." claimed that he had outlined a classification of pathological anatomy identical to that proposed by M. Laennec, in a series of four lectures given before the Société in the preceding two years. He claimed that a short note concerning these lectures had appeared in the second Bulletino of the Société, three months before Laennec's lecture. His classification, he stated, was based on six years study of pathological anatomy culminating in his doctorate thesis and the reports to the Société. He was sure that Laennec, who had attended his lectures on pathological anatomy in 1802 and had subsequently, in company with M. Bayle, been an assistant to him, must have been aware of these facts. This article was followed by a rejoinder from Laennec in a subsequent issue of the Journal. He stated that while he had doubtless learned from his contact with M. Dupuytren this gentleman might well have profited equally from their professional relationship. He strongly denied any suggestion of plagiarism. The Editors of the Journal terminated this unhappy correspondence after allowing Dupuytren to reiterate his views in more detail. I have had access to all these articles with the exception of that in the

second/

second Bulletin. The point at issue seems to have been the entire classification rather then the description of "les melanoses". Like Eiselt (1861) I am inclined to favour Laennec as the earliest author to use the noun "les melanoses".

There are a number of reports of cases prior to this time which sound remarkably like cases of melanoma and Eiselt quotes the reports of Highmore (1651), Bartholin (1677), Benot (1679) and Henrici and Nothangel (1757) which are strongly suggestive of malignant melanoma. I would add to these the case report by Crawford in 1791. In this report he describes the discharge of black material from a tumour and certain aspects of his report suggest that the tumour may well have been a malignant melanoma. It is noteable that as late as 1804 Abernethy makes no mention of the disease even under the name of "fungoid disease" in a fairly authoritative "Classification of Tumours".

In the Edinburgh Medical and Surgical Journal of October 1820 there is a most admirable report of a case of malignant melanoma by a physician named Norris from Stourbridge. The description is a truly remarkable one in which this observant physician notes most of the salient features of the disease as we know it today. The patient was a male aged 59 whose tumour was situated in the suprapubic area. Norris describes a pigmented /

pigmented halo, the development of satellite tumours, a recurrence after local excision, the development of enlarged groin glands and the all too familiar history of progressive dissemination of the disease. His comment on the distribution of secondary tumours in the abdomen, "tumours scattered in the utmost profusion in every direction" is a succinct comment on the metastatic potential of this tumour. He describes his patient's urine as "like porter", presumably a description of melanuria. His observations on the family history and on the death of the patient's father thirty years previously from a similar disease leads him to postulate an hereditary basis for the disease. He did not use the name melanoma, but described his case as one of "fungoid disease".

In 1833 Robert Carswell used the noun "melanoma" and differentiated melanosis (which name he attributes to Laennec) into two types: true melanosis which appears to be malignant melanoma and spurious melanosis which he describes as "resulting 1st, from the introduction of carbonaceous matter; 2nd, from the action of chemical agents on the blood; and, 3rd, from the stagnation of the blood". He goes on to describe very accurately and classify, on a morphological basis, the various manifestations of melanosis. It is obvious, however, that there was no appreciation of the true nature of the disease or of its cancerous nature at this time. Carswell states "Melanosis is more frequently combined/

FIGURES 1 - 4 These are reproductions of illustrations from Robert Carswell's book "Pathological Anatomy" published in 1833.

FIGURE 1 is an example of secondary melanoma in the lung.

FIGURE 2 is an example of secondary melanoma in the cerebrum.

FIGURE 3 appears to show secondary melanoma in the intestine.

FIGURE 4 is an example of "spurious melanosis", a lung and mediastinal lymph nodes conteining carbon pigment.

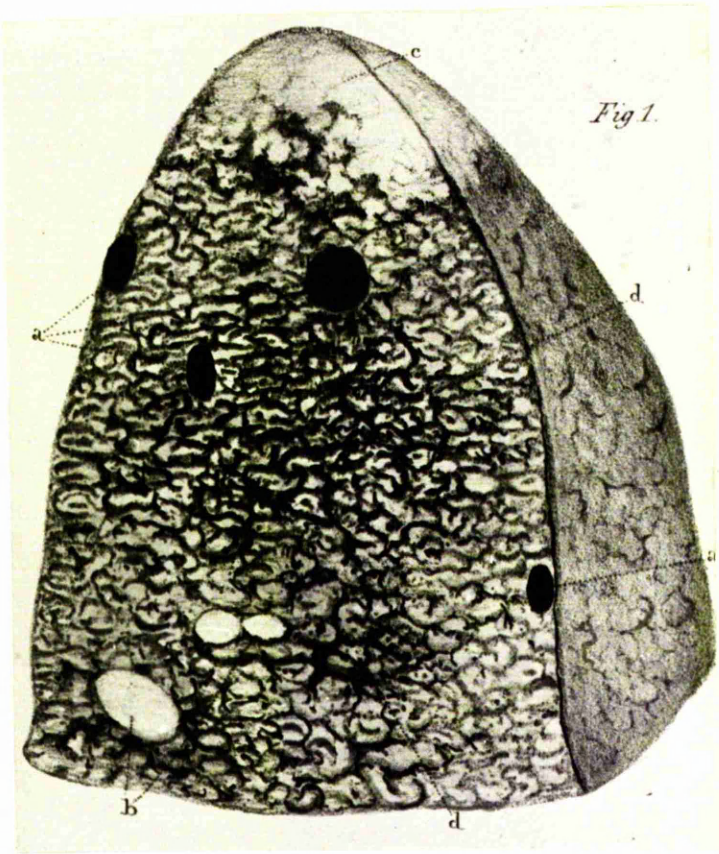

FIGURE 1

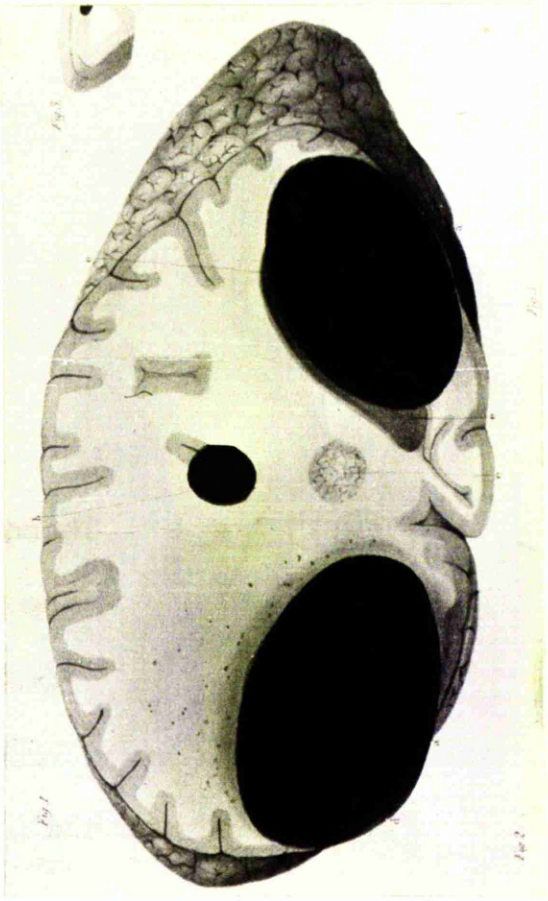

FIGURE 2

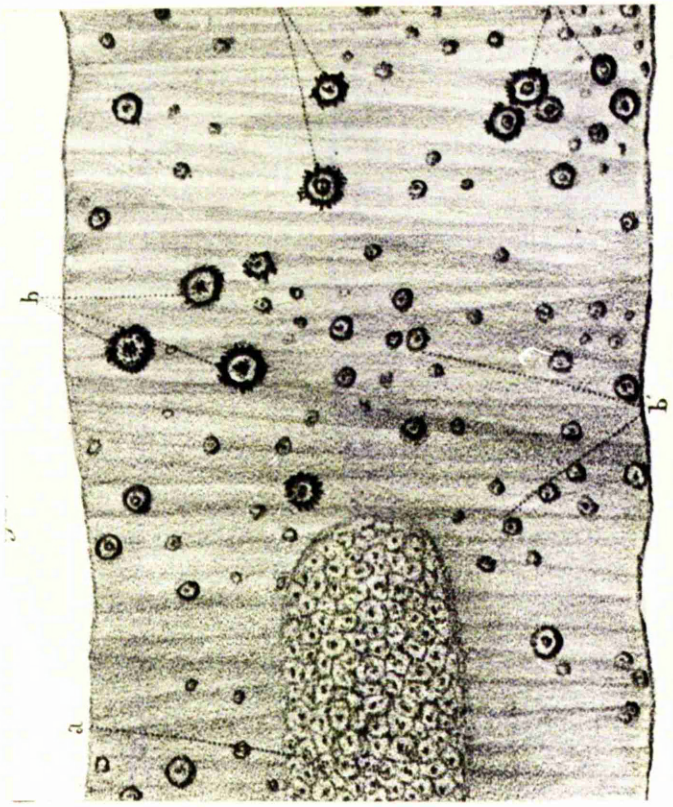

FIGURE 3

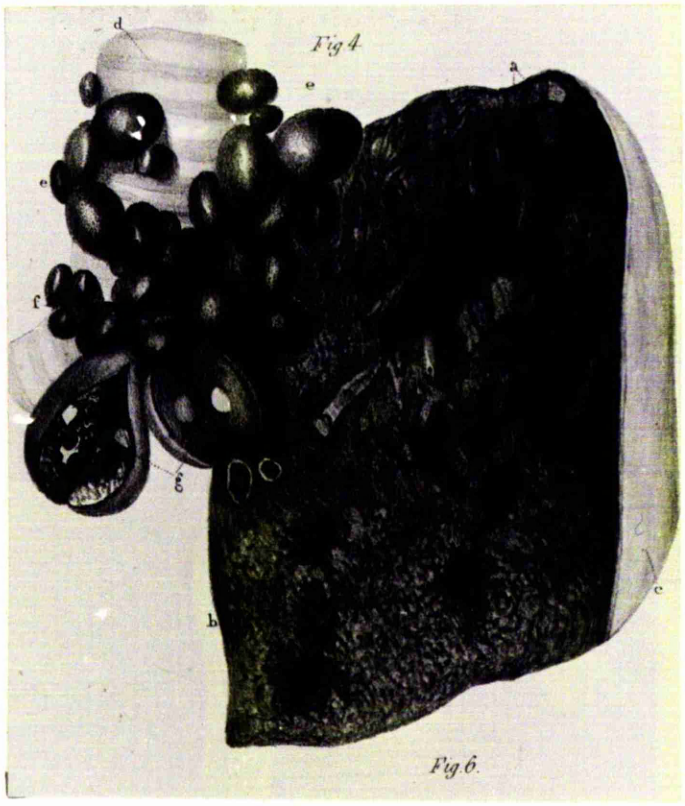

FIGURE 4

combined with carcinoma than with any other disease, but there is no similarity of nature in these two diseases. Their anatomical, physical and chemical characters being totally different". Figures 1-4 are examples of the beautiful illustrations in this book.

By 1858 the disease was sufficiently accepted as an entity that Pemberton in his "Observations on the History, Pathology and Treatment of Cancerous Conditions" was able to describe 25 cases. He described primary tumours in a wide variety of sites with and without secondary spread and one case of dissection of the groin glands. His criteria for truly wide excision of the primary tumour, "removal of the integument involved and of the fascia of the muscle under it" seem little different from those currently accepted.

Seven years later Paget, in another textbook "Lectures on Surgical Pathology", noted that the very typical colouration of these lesions was due to pigment in and around them and that they tended to arise in or beneath pigmented moles. He also noted and commented on the occurrence of secondary "melanoid formations" in numerous organs. Heusinger in 1823 appears to have been the earliest microscopist to note and accurately localise epidermal and dermal melanin.

The first decade of the twentieth century saw two significant advances in knowledge concerning this tumour and in the/

the surgical therapy of it. In 1907 Sampson Handley described the spread of the tumour via the deep as well as the superficial lymphatic channels and via the fascial planes. He suggested wide local excision of the primary tumour and excision of the regional lymph nodes and described the stigmata of malignant change in a naevus. One year later in Glasgow Hogarth Pringle (1908) advocated and practised the excision of the primary tumour, the regional lymph nodes and the intervening plexus of the lymphatic channels en bloc.

The years between 1890 and the middle of this century were notable for much fine observational study of the structure of naevi and malignant melanomas. Much has also been contributed by biochemists to the understanding of the chemical nature and method of biosynthesis of melanin in vivo (Lassaigne, Foy and Barruel and Henry quoted by Carswell , 1833; Bloch and Ryhiner 1917, Becker et al 1935, and Fitzpatrick et al 1950). Embryologists appear to have largely settled the much debated origin of the epidermal melanocytes (Eastlick, 1939, Ris, 1941, Rawles, 1947, 1953 and Zimmermann and Becker, 1959).

The main point at issue for many years (and in the opinion of some authorities still at issue) was the nature and site of origin of the component cells of the curious dermo-epidermal structures known as naevi. Three main schools of thought existed. One theory, originally proposed by Unna in

1896/

1896 and supported by, among others, Dawson in 1925 and more recently by Allen in 1949 suggests that the clear cells of the epidermis are modified cells of the stratum basale and that all epidermal basal cells are capable of melanin production per se. These workers believe that naevi and malignant melanomas are epidermogenetic. A second theory proposed by Soldan (1899) and Masson (1926) suggests that the clear cells of the epidermis, Masson's "cellules claires" have a neuro-receptor function and that common moles are dysontogenetic or neoplastic derivatives of cutaneous nerve endings. The wide variety of appearances in these lesions is explained by their derivation from different levels of the cutaneous nerves and from different types of nerve endings e.g. Wagner-Meissner corpuscles, Merkel-Ranvier nodes and Langerhans cells (which the epidermogenetic school regard as a form of effete basal cell with clear cytoplasm). A third theory supported by Virchow (1863, 1867), Demieville (1880), Recklinghausen (1882), Jadassohn (1888) and Ehrmann (1896), regards naevi as of mesodermal origin. These lesions have been variously considered by these authors to arise from lymphatic and vascular tissues. In view of the embryological evidence available today this latter theory is no longer tenable. The recent work of Rawles (1947, 1953) and others suggests that none of the classical theories of naeval origin are correct. There is, however, some evidence in the work of Nakai and Rappeport (1963) that blue naevi may be derived/

derived from the Schwann cells of cutaneous nerve sheaths.

The origin of the melanoblasts from the transient embryonic neural crest is now well established by Rawles (1947, 1953) using the tissues of embryonic mice in a manner similar to the technique employed by Eastlik (1939) and Ris (1941) in their work on fowl pigmentation. The reports of Zimmerman and Becker (1959) from their study of human negro foetuses are certainly highly suggestive that the melanocytes in humans are derived from the neural crest and reach their adult site by migration in early embryonic life. The melanomas can, therefore, be regarded as of neuroectodermal origin, although not in the sense postulated by Masson.

Further evidence that the melanocytes are different from the epidermal cells in structure and function has come from electron microscopy. Examination of the melanocyte at this level of magnification has revealed the existence of melanocyte specific structures known as melanosomes. These appear to be the site of action of tyrosinase and eventually when replete with melanin, become tyrosinase-negative and are, in fact, the melanin granules so long familar to light microscopists (Kennedy and Zelickson, 1963).

Since the early part of this century modes of treatment of malignant melanoma have altered from time to time and place to place depending on the experience and beliefs of individual/

individual clinicians and groups of clinicians interested in this condition. A variety of novel forms of treatment have been tried with varying degrees of success, but with the possible exception of isolated limb perfusion using phenylalanine mustard in combination with adequate and timely surgery (Creech et al, 1958, 1964), none of these modes of treatment has markedly influenced the course of the disease.

It is undoubtedly true that the survival and cure rates quoted by present day authors analysing recently treated groups of patients are better than those quoted by earlier authors. This progress, although slow, appears to be a continuing process. Such improvement is directly attributable to the analysis of numerous series of cases, both retrospective and prospective. This accumulation of experience and fact has allowed a more complete understanding of the disease, its modes of spread and of the forms of therapy apposite at the different stages of its progress.

Noteable contributions to the therapy of malignant melanoma in the past two decades include the reiteration of Pringle's principle of dissection in continuity of primary tumour, regional lymph nodes and the intervening lymphatic plexus by Pack et al. in 1945 and the concept of delaying regional nodal dissection to allow the passage of in-transit tumour lymphatic emboli to the nodal area (Stewart et al., 1953). By this/

this technique it is hoped that the development of secondary deposits of tumour between the primary site and the regional notes may be avoided. These latter authors believe that lymph stasis following lymphadenectomy is an important factor in the genesis of this type of metastasis. In 1952 Pack et al. advocated the routine dissection of the regional lymph nodes whether clinically enlarged or not. In support of this technique Pack sites a 27% improvement in the five year cure rate for a period in which this technique was employed, the existence of microscopic deposits of tumour in clinically uninvolved lymph nodes and the considerable number of patients, in whom the disease is clinically assessed as local, who subsequently develop regional nodal metastases.

Despite numerous reports and analyses of results in numbers of patients in the intervening twenty years, the value of delayed dissection of the regional lymph nodes and the value of prophylactic or elective dissection of clinically uninvolved lymph nodes is not yet proven.

AIMS OF STUDY

Although it would appear that advances in the understanding of the nature and control of malignant disease will come from experimental work, there is undoubtedly much information to be gained from the collation and analysis of significant groups of clinical and pathological material. Although such a study may not produce a spectacular advance in the understanding of the subject matter it is likely to be of value in showing clinicians and pathologists where the efficacy of their accepted modes of treatment and criteria of diagnosis stand in relation to comparable series undertaken in other centres. It will also provide information which will add to the sum total of knowledge available on the subject matter.

With these points in mind, the following study was undertaken. Its main aim was to assess, by reviewing the available histological material, how accurate the diagnostic criteria in use were in respect of malignant melanoma. An attempt was made to observe any clinical or histological features which would aid the assessment of prognosis. Of particular interest was the accuracy of prognosis based on a combination of the clinical and pathological features of the case.

In addition to reviewing malignant melanoma, particular attention was paid to the "borderline" cases which frequently present a considerable diagnostic problem;

1. Active/

1. Active compound and junctional naevi with marked activity in the superficial dermis. These lesions frequently raise suspicions of malignancy.
2. Juvenile melanomas in patients above the age of puberty.
3. Lentigo maligna.
4. Tumours in which the cytological and histological appearances raised the possibility of the diagnosis of malignant melanoma, but were not specific enough to allow a definite diagnosis to be made.

The aims of the study may, therefore, be stated shortly. An attempt was made to analyse the results of experience in diagnosis and treatment of malignant melanoma in the decade 1952-1961 and the value of appropriate clinical and pathological features in the prediction of prognosis assessed.

SOURCE OF MATERIAL

The greater part of the material on which this study of 192 cases of malignant melanoma of the skin, mucous membranes and eye is based consists of histological material removed at operation or postmortem. One hundred and ten of the cutaneous cases and 10 of the ocular cases were referred by general medical practitioners to the specialist clinics of this hospital during the decade 1952-1961. This is a busy teaching hospital associated with the Medical Faculty of the University of Glasgow.

At/

At the time of this study it had 670 inpatient beds and provided, in addition to general medical and surgical facilities, specialist Radiotherapy, Dermatology and Plastic surgical clinics and in-patient beds.

A second group of fourteen cutaneous cases were treated in hospitals other than the Western Infirmary and the excised tissues referred for histological examination.

A third group consists of patients referred for special examination and therapeutic techniques. These techniques include retinal photography, radiotherapy, pituitary ablation and the refined methods of cosmetic surgery.

A small group of 19 patients with ocular melanoma, treated elsewhere, but placed on the Cancer Register in this hospital is included to allow analysis of the intraocular group of cases.

The catchment area is large and ill-defined. Patients have attended from places as widely separated as Falkirk, Inverness, The Western Isles and the south of Ayrshire. It is impossible to ascertain, with any degree of accuracy, the population at risk. Estimation of the incidence of the disease must be based on its incidence relative to more common forms of cutaneous carcinoma of more accurately known incidence and on the figures of the Registrar General's report for the whole of Scotland.

METHODS

1. Malignant Melanomas

The histological reports on all melanocarcinomas which had been seen between 1952-1961 were traced and the histological material reviewed. Since it would be desirable to have prognostic criteria which could be ascertained from the routine histological stains no special stains (apart from that for melanin and occasionally van Gieson) were used. Details of the staining techniques used are given in appendix 1. The information obtained from this source was placed on edge punched cards. Particular points receiving attention were :-

1. Cell shape and size
2. Cell regularity.
3. The mitotic rate of the tumour.
4. Connective tissue architecture.
5. Tumour pattern.
6. Presence or absence of junctional activity over and adjacent to the tumour.
7. Epidermal invasion.
8. Pigment content.
9. Presence and pattern of field change.
10. Presence of a cellular reaction, its distribution and the nature of the cells composing it.
11. Relation of the tumour to the epidermal appendages.
12. Presence of lymphatic and/or vascular invasion.

13/

13. Presence of evidence of a previous intradermal naevus.

14. The presence and distribution of clear cells (melanocytes) in the stratum basale of the epidermis over and adjacent to the tumour.

15. Presence or absence of ulceration.

16. Degree of anaplasticity of tumour cells.

17. Overall tumour morphology.

Such of these points as were apposite were looked for in any tumour recurrences or secondary deposits examined.

Following the histological and cytological assessment of the tumours, the relevant case notes were obtained and abstracted. The main points of interest being :-

1. Age of the patient at onset of disease.

2. Sex of the patient.

3. Duration of symptoms prior to initial therapy.

4. Site of primary tumour.

5. Presence or absence of previous pigmented lesion at the site of the primary.

6. Presence or absence of a history of trauma.

7. Presenting clinical features.

8. Presence of local or extended disease when patient first seen.

9. Presence or absence of pregnancy.

10. History of unorthodox initial therapy - CO_2 snow, acetone etc. locally.

11./

11. Type of treatment.

12. Clinical diagnosis.

13. Site, type and time of origin of secondary disease.

14. Survival.

As far as possible all patients were followed up to death or the end of April 1965. This information was obtained from case sheets, follow-up letters sent to General Medical Practitioners and from the files of the Registrar General.

In addition to the specific histological details which were the main focus of interest in this series the opportunity was taken of examining the mass of clinical detail available and searching for any points which might shed light on the clinical estimation of prognosis, causal factors and the efficacy of the relevent varied therapeutic approaches to the problem. In this context it is worth stating that there was, during the period of the survey, no unified or standardised procedure adopted in this hospital for the treatment of this condition.

An interesting comparision is available in the paper of Wright, Clark and Milne (1953) which reviewed melanocarcinoma in this area during the decade 1939-1949. They included, however, hospitals other than the Western Infirmary, but nonetheless the paper is interesting from the comparative point/

point of view.

2. Simple tumours of Melanoblastic Origin

The histological material from all compound and junctional naevi, lentigos and blue naevi seen during the period under study was examined. Information as to the subsequent clinical course of such patients was obtained whenever possible. The clinical details of such tumours were gathered and analysed.

A random sample of simple intradermal naevi was gathered and examined in the same manner.

3. Cutaneous Tumours of Non-Melanoblastic Origin

The main importance of these tumours in the context of pigmented tumours is in the diagnostic difficulty which they can present. A close examination was, therefore, made of the symptomatology of such tumours to see in what manner they simulate and in what manner differ from the melanomas.

4. It became apparent at an early stage in the study that the incidence of melanocytes in the stratum basale is not constant from area to area and person to person. Szabo (1954) and Staricco and Pinkus (1957) have assessed the incidence of melanocytes in normal skin, but there appears to be little or no information available on the quantitative incidence of melanocytes/

melanocytes in relation to skin tumours. An attempt has been made to assess the effect of the tumours on this cell population.

ANALYSIS OF THE PATIENTS WITH MALIGNANT MELANOMA SEEN DURING THE SURVEY PERIOD

Histological preparations and clinical information are available from 192 patients with malignant melanoma seen during the period from 1st January 1952 to 31st December 1961. The primary tumour was situated on the skin or conjunctiva in 156 cases (81%), on the mucous membranes in 4 cases (2.1%), within the eyeball in 27 cases (14.2%) and no primary tumour was discovered in 5 cases (2.6%).

SEX INCIDENCE

There were 77 males (40%) and 115 females (60%) in the series. This represents a ratio of 2:3. This ratio, showing a preponderance of female patients with this condition is in agreement with many previous studies of groups of patients with malignant melanoma (Affleck, 1936, Wright, Clark and Milne, 1953, Lane, Lattes and Malm, 1958, Cade, 1961, James, 1961, Peterson, Bodenham and Lloyd, 1962). It is, however, at variance with the results reported by other authors, mainly from the North American continent (Gleeve, 1929, Raven, 1950, Catlin, 1954 and Teimourain and McCune, 1963). This disparity in the sex incidence between major series of cases from Britain and Sweden and North America has been noted previously by Peterson et al., 1962, and is certainly very striking. The report of Wright et al. (1953) is especially interesting since it is concerned/

TABLE 1. SHOWING THE AGE OF PATIENTS AT FIRST HOSPITAL ATTENDANCE

	AGE RANGE IN YEARS								
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Male	-	1	7	6	16	17	17	9	4
Female	-	2	11	15	21	17	22	16	10
TOTAL	-	3	18	21	37	34	39	25	4

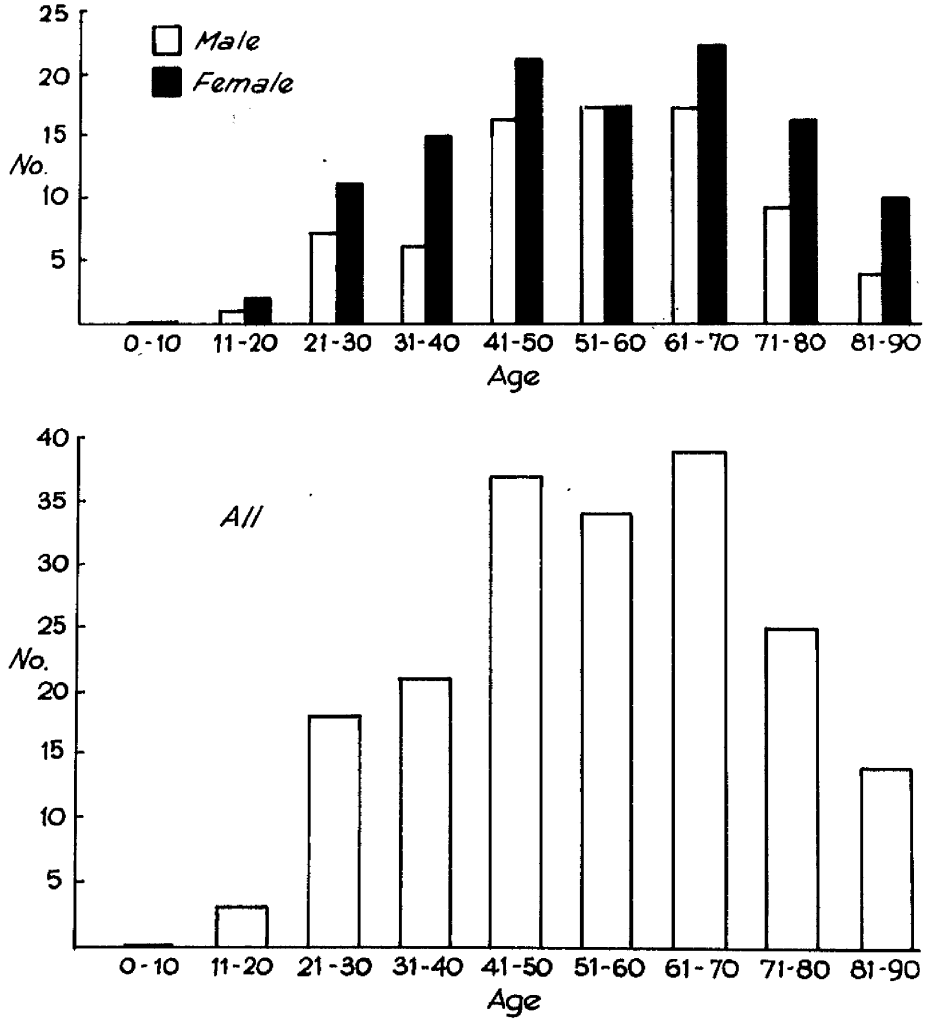

FIGURE 5

Showing the age of patients at first hospital attendance

concerned with the experience of an earlier decade in this region, at which time the plastic surgical facilities were less developed and for a part of the decade less readily available to the civilian population. The fact that the male:female ratio reported at that time 1:1.8, is higher than that noted in the present series, 1:1.5, suggests that the sex difference in incidence is not due to a selection of cases for cosmetic excision.

The sex ratio is remarkably constant in all age groups except the under 40 group in which the female preponderence is more marked, male:female ratio 1:2, and in the fifth decade when the disease occurs with equal frequency in both sexes.

Charalambidis and Patterson (1962), subdividing their figures for incidence by sex into subgroups by age, report that there is a preponderance of females under the age of 40 and males over the age of 60. The figures from the present series do not show this pattern.

AGE INCIDENCE

There were no prepubertal malignant melanomas in this series. Children under the age of 12 are not normally admitted to this hospital, there being a large paediatric hospital nearby.

The age of patients was available in all but 1 of the 192 cases. Table 1 shows that malignant melanoma occurs at/

at all ages (with the reservation made in the foregoing paragraph). The maximum incidence is in individuals over 40 years of age with a peak in the sixth decade (20% of all cases); 71% of all cases were in patients over 40 years of age. Buchanan (1961) found that 65% of his cases occurred in this group. Comparison of the mean age at onset of patients with cutaneous primaries (55.1 years) and of those with intraocular primaries (53.25 years) shows no significant difference.

It is of considerable interest to note that the mean age at onset for cutaneous cases (56.3 years) and ocular cases (58.4 years) reported by Gleave in 1929 are not dissimilar to the comparable figures noted in this series. This suggests that the increase in incidence of the disease (vide infra.) has occurred at all ages and is not purely a result of increasing longevity of the population. If the increased incidence of malignent melanoma were predominantly in the older sections of the population one would have expected the mean age at onset to have risen.

The rarity of true malignant melanoma prior to puberty is frequently related to the specific and unique hormonal climate of childhood which is undoubtedly very different from that obtaining in the sexually mature adult. While in no way disputing the truth of this, it seems surprising that, despite the frequent achievement of sexual maturity at a relatively early age/

age (11 - 13), the incidence of malignant melanoma remains relatively low up to the age of 20. Only 4.16% of the cases in this series occurred in patients under 25. This incidence agrees well with the figures of Affleck (1936), Raven (1950) and Lund and Ihnen (1955). It would seem that some secondary factor (or factors) is required in addition to hormonal maturity to allow the development of malignant characteristics in these tumours. This factor may be nothing more abstruse than time for development of malignancy. Most cutaneous carcinogens require a number of years to produce malignancy.

It has been argued that, as skeletal growth may continue until the age of 30, a truly mature hormonal milieu is not established until that age. Skeletal growth is primarily mediated by growth hormone and the consensus of opinion is that, on the basis of available clinical and experimental evidence, the melanocytes are influenced mainly by the sex hormones, the adrenocortical hormones and melanocyte stimulating hormones from the pars intermedia of the pituitary (and possibly from the placenta in the pregnant woman). The definitive pattern of these hormones is undoubtedly established well before the age of 30.

SITE OF PRIMARY TUMOURS

Table 2 shows that the commonest site of primary melanoma in this series is the lower limb with 26.6% of all primary/

TABLE 2. SHOWING THE SITE OF PRIMARY TUMOUR (192 CASES)

Site	Foot	Lower Leg	Thigh	Trunk	Ano-Genital	Hand	Arm	Head & Neck	Ocular	Occult	Mucous Membrane
Male	7	2	3	12	1	4	5	24	16	1	2
Female	11	24	4	13	6	5	10	25	11	4	2
TOTAL	18	26	7	25	7	9	15	49	27	5	4

TABLE 3. SHOWING THE DISTRIBUTION OF TUMOURS BY SITE IN RELATION TO AGE AND SEX

	Upper Limb (all)	Head & Neck	Trunk	Ocular	Ano-Genital	Sub-Ungual	Lower Limb (all)	Calf	Thigh	Foot	Hand	Occult
Males under 50 years	3	6	9	7	1	1	3	1	2	-	-	-
Females under 50 years	7	6	4	3	-	1	25	19	1	5	1	3
Males over 50 years	5	19	5	8	-	5	9	1	-	5	-	1
Females over 50 years	7	22	10	7	6	3	15	5	3	6	1	1
TOTAL	22	53	28	25	7	10	52	26	6	16	2	5

primary tumours. This is closely followed by the region of the head and neck (all areas above the clavicles exclusive of the mucous membranes and intraocular tumours), 25.5% of all primary tumours. Primary tumours within the eye (14.4%), on the trunk (13.0%) and on the upper limb (12.5%) are less common. Anogenital primaries (3.7%) and primary malignant melanoma of the mucous membranes of the upper alimentary and respiratory tracts and of the vagina are rare (2.1%). No primary tumour was discovered in 5 patients (2.6%).

The figure for intraocular primaries (14.4%) is artificially high since 19 additional intraocular malignant melanomas from other hospitals are included to increase the size of this group to allow statistical analysis.

SEX, AGE AND SITE

Subdivision of the site incidence figures by sex and age (Table 3) relative to an arbitrary female menopause at 50 yields certain interesting facts.

Tumours of the head and neck occur most frequently in individuals over the age of 50 regardless of sex. Of 53 primary tumours arising on this site, 41 (77%) were in patients in this older age group. Tumours in this region accounted for 40% of all malignant melanomas in males over 50 and 32% of all such tumours in females over 50.

Six of the seven anogenital tumours were in females over/

over 50.

Five of the 9 subungual tumours were in males over 50. In both these instances the numbers are too small to allow any form of analysis.

Certainly the most striking finding in the analysis of the sites of origin is the very high incidence of malignant melanoma on the lower limb in women younger than 50. Forty eight point one (48.1%) percent of all tumours arising on this site were in women of this age group. Tumours in this site accounted for 52% of all malignant melanomas in women of this age group. This remarkable incidence of tumours is mainly due to the frequent occurrence of primary tumours on the area between ankle and knee. Of the 25 primary malignant melanomas arising on the lower limb in females under 50, 19 (76%) were sited between knee and ankle. In males under 50 the most frequent sites of origin were the trunk, 9 cases and the eye, 7 cases. Thus 32% of all malignant melanomas arising on the trunk and 28% of those in the eye were in males younger than 50 years of age.

There is a close measure of agreement between these figures and the figures quoted by Raven (1950) in an analysis of 2,193 cases from the literature and the results of Allen and Spitz (1953). The latter authors do not include ocular primaries and Raven's figure of 8.3% for ocular primaries is rather lower than that found in this series (14%). This disparity is undoubtedly/

undoubtedly due to the inclusion of 19 additional ocular primaries from another centre, in this series. Exclusion of these extraneous cases reduces the incidence of ocular primaries to 5.8%. The only major changes in tumour distribution in this series as compared to that of Wright et al.(1953) are a higher proportion of tumours on the upper limb (12.5% in this series, 5.7% in the previous one), and fewer tumours arising on the lower limb (26.6% in this series as against 39.8% in the previous one).

LOWER LIMB

TABLE 4. SHOWING THE DISTRIBUTION OF TUMOURS WITHIN THE LOWER LIMB

	Thigh	Lower Leg	Foot	Sole	Dorsum	Sub-Ungual
Male	3	2	7	4	1	2
Female	4	24	11	7	3	1
TOTAL	7	26	18	11	4	3

From Table 4 it is apparent that there is a difference in site frequency between the sexes. The order of frequency in women is lower leg (excluding foot) 24 cases, foot 11 cases and thigh 4 cases. In men the order is foot, 7 cases, thigh, 3 cases and lower leg 2 cases. The preponderence of malignant melanomas of/

of the leg in women under the age of 50 has been noted by numerous previous authors, Clark and McDonald (1953), White (1959) and Petersen et al. (1962). It is difficult to account for these differences. Possible factors involved are :-

1. Protection of the male lower limb by the wearing of trousers.
2. Recurrent trauma to the female limb by cosmetic practices such as shaving.
3. The wearing by females of close fitting transparent stockings. This may act in two ways. The transparent hose will allow the passage of carcinogenic actinic rays and the close fitting synthetic fibremesh may produce recurrent trauma to an elevated lesion.
4. Although actinic rays do not present a major problem in this region, many women appear to expose their legs to the direct heat from electric, gas and open coal fires. The frequency of all degrees of erythema ab igne, locally known as "Tinker's Tartan" bears witness to the frequency of this practice. It seems not unreasonable that the heat and radiations emitted from these sources will effect the skin and in particular the melanocytes.

In this series malignant melanoma occurred more commonly on the sole of the foot, 11 cases, than on the dorsum, 7 cases./

cases. This latter group includes 2 subungual cases. The exact site within the foot was not stated in one case. This preponderance of tumours on the sole of the foot is in agreement with the findings of Hever (1953), whose patients were mainly Sudanese negroes. It is, however, at variance with the figures quoted by Boohor and Pack (1957). These authors in a very large series found 55.7% of pedal malignant melanomas on the dorsum of the foot and 44.3% on the sole.

Three pedal subungual melanomas were noted in this series. They all occurred on the hallux, a site predilection first noted by Handley (1907). This is a low incidence, representing 1.56% of all cases, but is not dissimilar to the figure of 1.8% quoted by Allen and Spitz (1953) in their very large series.

It is of interest to note that subungual tumours were noted more commonly on the hand in this series. Seven cases occurred on the hand, 3 on the foot. This finding is in agreement with the earlier series from this region by Wright et al. (1953) and with the figures reported by Womack (1927), and Gumport and Meyer (1959). It is, however, contrary to the experience of Boohor and Pack (1957).

UPPER LIMB/

UPPER LIMB

TABLE 5. SHOWING THE DISTRIBUTION OF TUMOURS WITHIN THE UPPER LIMB

	Hand including Subungual	Forearm	Upper Arm	Subungual	Total
Male	4	2	3	4	9
Female	5	7	3	3	15
Total	9	9	6	7	24

Primary malignant melanomas of this region accounted for 12.5% of all tumours. Tumours arising on the forearm and hand together account for 75% of all tumours on the upper limb. In the hand, the most frequent site is beneath the nails. Of the 7 subungual malignant melanomas arising on the hand in this series 4 were beneath the thumb nail, 2 beneath the nail of the fourth finger (dig. annularis) and 1 on an unspecified finger. Seven of the 9 tumours arising on the forearm were in females. This situation is of considerable interest since the forearm is the upper limb homologue of the calf and shin area in the lower limb. No specific age group is responsible for the cases in this site. The mean age at onset is 57 and there is a wide scatter around this, the youngest patient being 42, and oldest 81. Analysis of the ages of patients with melanomas on other sites in/

in the upper limb shows no significant variation in the mean age at onset.

There were no primary or secondary malignant melanomas on the palm of the hand in this series. In a parallel series of simple pigmented tumours, no naevi were noted on this site.

These results are in general agreement with the findings of Boeher and Pack (1957) and Peterson et al. (1962), but few authors have reported the sites of the tumours within the upper limb in this way.

HEAD AND NECK

TABLE 6. SHOWING THE DISTRIBUTION OF TUMOURS WITHIN THE REGION OF THE HEAD AND NECK

	Face(1)	Neck(2)	Scalp	Conjunctiva
Male	17	5	1	1
Female	22	0	0	3
TOTAL	39	5	1	4

NOTE:

1. "Face" included the ears, all areas anterior to the ears and between the hair line and lower jaw exclusive of the conjunctiva, eyes and mucosal surfaces.
2. "Neck" includes all areas above the level of the clavicles and inferior to hair bearing areas and lower jaw.

The/

The majority of malignant melanomas of the head and neck arose on the face in this material (79.5%). Primary tumours of the neck (10%) and conjunctiva (8%) are less common. Only one tumour arising on the scalp was noted.

This very low incidence of primary malignant melanoma, relative to the incidence predictable on the basis of surface area, on the major hair bearing area of the body is of considerable interest. The scalp is the remnant of the total body hair cover possessed by our primate ancestors. In hair bearing animals the melanocytes tend to be aggregated around the hair follicles, the primordia of which seem to demonstrate a tissue affinity for melanoblasts (Rawles 1947). The dermis and epidermis between hairs in such a hair-bearing area rarely contains melanocytes, which are confined to the developing hair. Conversely in areas with few hairs the melanocytes "appear in numbers in the surrounding tissues" (Rawles, 1953).

Examination of specimens of adult human scalp reveals a rather different disposition of melanocytes from that noted in hair bearing animals. In an examination of 16 specimens of skin from the human scalp 9% of the cells of the stratum basale in areas of epidermis between hair follicles were noted to be melanocytes. The melanocytes certainly occur in the hair follicles as non-pigmented cells in the deeper areas and pigmented ones in the upper portion (Staricco, 1960). No quantitative analysis of the incidence/

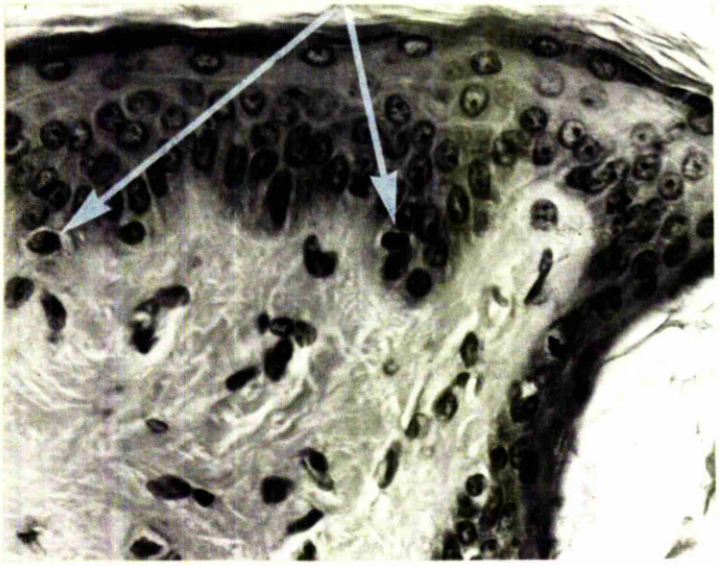

FIGURE 6(a) FIGURE 6(b)

FIGURE 6(a) Showing melanocytes in the stratum basale of the epidermis and in the hair follicles. H. and E. (x 450).

FIGURE 6(b) Showing "basal cells" of the hair follicles with clear cytoplasm simulating melanocytes. H. and E. (x350).

incidence of melanocytes in the hair follicles has been undertaken, but they do not appear to be present in especially high numbers. Towards the base of the hair follicle the basal cells often show a tendency to have a clear cytoplasm. The overall cell morphology is, however, quite different from that of a melanocyte and the nuclei tend to be larger and less basophilic. These various points are illustrated in Figure 6.

The only strikingly unusual feature of the scalp area, which has at least the same malignant potential in terms of melanocytes as other areas of the body is the (more or less) thick covering of hair which will serve to, at least partially, exclude carcinogenic actinic rays from the scalp.

These figures for incidence of tumours on the scalp and neck are very different from the results quoted by Gatlin (1954), Kragh and Erich (1960) and Conley and Peck (1963). Each of these series contained a much larger proportion of tumours on the extrafacial regions. It seems reasonable to assume that the apparent bias of the figures in this series in favour of lesions on the facial area is at least partly due to selection of cases referred for cosmetic surgery.

It is worth stressing that 77.3% of all malignant melanomas of the head and neck arise in individuals over the age of 50.

CONJUNCTIVA/

CONJUNCTIVA

Four malignant melanomas arose on the conjunctival surface. Three were in women aged 34, 35 and 38, the other in a male aged 53. The mean age at onset of this small group is 45. This suggests that conjunctival malignant melanoma may occur in a younger age group than the truly cutaneous form. The thinness and transparency of the conjunctival membrane may well be relative to this observation since the intraconjunctival melanocytes lack the medium of protection from actinic rays provided, in the skin, by the thickness of the epidermis, the keratin of the stratum corneum and the variable quantity of melanin interspersed through the layers of the epidermis. This observation, if confirmed on a statistically valid series of cases, could be adduced as supportive evidence for the role of actinic radiation in the genesis of malignant melanoma of the exposed areas.

TRUNK

Primary malignant melanoma of the trunk represents 13% of primary tumours in this series. This is a rather low incidence in view of the large surface area (38% of total body surface area) of this region of the body. These regions are equally affected in males and females, 12 tumours being in males and 13 in/

in females. Thus, 15.6% of all malignant melanomas in males were in this region; the comparable figure in females being 11.3%. The tumour was on the posterior aspect of the trunk in 15 cases and on the anterior aspect in 10 cases. Tumours arose on the upper, thoracic region of the trunk (16 cases) more frequently than on the lower, abdominal and dorsal below the thoraco-lumbar disc region (9 cases). Two tumours, one in a male, one in a female, arose in the pigmented areola of the breast.

This incidence is lower than those quoted by Allen and Spitz (1953), Cade (1961), Ochsner and Harpole (1962) and Wright et al. (1953) in the previous series from this region for tumours on the trunk. However, when allowance is made for ocular tumours, included in this study, but not in others, the incidence of malignant melanomas in this site is 15.2% of all cutaneous tumours. This figure approximates more closely to those quoted by the above named authors and is comparable to the figure of 14.72% quoted by Raven (1950) in an analysis of the site of 2,193 tumours drawn from the literature and the incidence quoted by Petersen et al., 1962 (14.2%).

The low incidence of malignant melanoma arising in this region is difficult to explain, especially since Block and Harbwell (1961) find the incidence of pigmented naevi in this site to be comparable to that predicted on the basis of surface area, i.e. 39.4% of total body moles arising in 38% of total body surface/

surface area. In an examination of 21 specimens of adult thoracic skin, 9.52% of the cells located in the stratum basale were found to be melanocytes. The comparable figure for 26 specimens of adult abdominal skin was found to be 8.04%. The incidence of melanocytes in the skin of the trunk is thus seen to be little different from that found in other areas of the body where malignant melanoma occurs more frequently e.g. foot, where the mean incidence of basal melanocytes in 21 specimens is 7.43%.

It seems that some factor or factors are active in protecting this area. The most obvious feature in this respect is that the trunk is generally covered by clothing which serves to exclude actinic rays and will reduce the amount of minor trauma to which the part is subjected. Authors who believe trauma and chronic irritation to be important in the genesis of malignant melanoma frequently cite the friction from tight fitting corsets, brassiere straps and braces as sufficient reason for the prophylactic excision of pigmented naevi in these sites. It would be of the greatest interest to examine the effect of continual exposure of these normally covered areas on the incidence of malignant melanoma.

ANOGENITAL AREA

This includes the regions of the external genitalia, the/

the anus and the perianal skin.

Seven primary malignant melanomas arose in this region. This represents 3.7% of all cases. Six were in women and one in a male.

In the solitary male case the primary was situated on the prepuce. In the female cases the tumour was on the labium majus in two cases, in the perianal skin in a further two cases, in the region of the clitoris in one and in the vaginal wall in one.

This incidence of 3.7% of all primary malignant melanomas arising in the anogenital region corresponds closely to the figure quoted by Allen and Spitz in 1953 (5.3%), but is lower than that quoted by Wright et al. in 1953 (9.2%), Scharnagel in 1953 (8.6%) and Raven in 1950 (11.1%). The preponderance of female cases noted in this series is reflected in the experience of most previous authors.

MALIGNANT MELANOMA OF THE VAGINA

Primary malignant melanoma of the vagina is rare. (Fricke, 1949, Ariel, 1961, and Katsakis and Dito, 1962). Some authorities believe that such a tumour is always secondary (Novak and Novak, 1955). In 1961, however, Mullaney revieved this subject and found 15 cases which she felt merited acceptance as primary tumours. Since that time Ariel (1961), Katsakis and Dito (1962)/

(1962) and Gupta et al. (1964) have added case reports making a total of 18 cases to date. In view of this rarity of reported cases a further example is reported below. A recent article reports that melanocytes are demonstrable in the vagina in 3% of women (Nigogeysan et al. 1964).

CASE REPORT

On 11:2:58, Mrs. I.G., a 79 year old woman presented with a four week history of vaginal bleeding. Vaginal examination revealed a neoplastic growth on the lateral wall of the cervix affixed to the descending pubic ramus. On 28:2:59 an incision biopsy was performed. This was reported (Histology report number P.580986) as "an anaplastic and very vascular carcinoma... the precise nature of the tumour is uncertain... but the possibility of a malignant melanoma has to be considered." On 18:3:58 radium needles were inserted into the tumour and some response was obtained. By 9:10:58, however, the condition had recurred and was adjudged beyong treatment. She died on 26:2:59 with extending disease. No necropsy was performed. No other primary site was discovered.

A review of the available histological material shows the tumour to consist of sheets of loosely aggregated polygonal and globular cells. The nuclei are circular or oval, moderately basophilic and contain basophilic or dark eosinophilic central nucleoli. The cytoplasm in a considerable proportion of cells is/

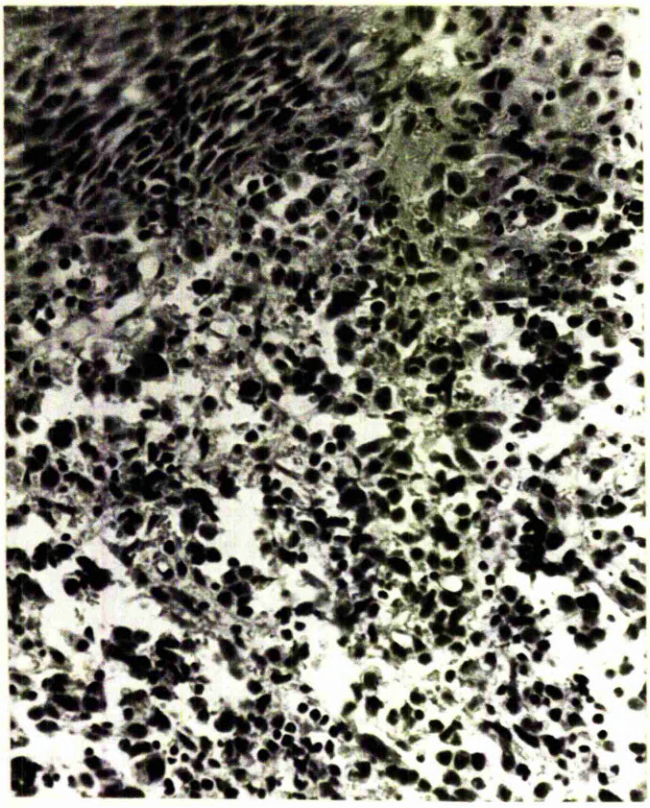

FIGURE 7

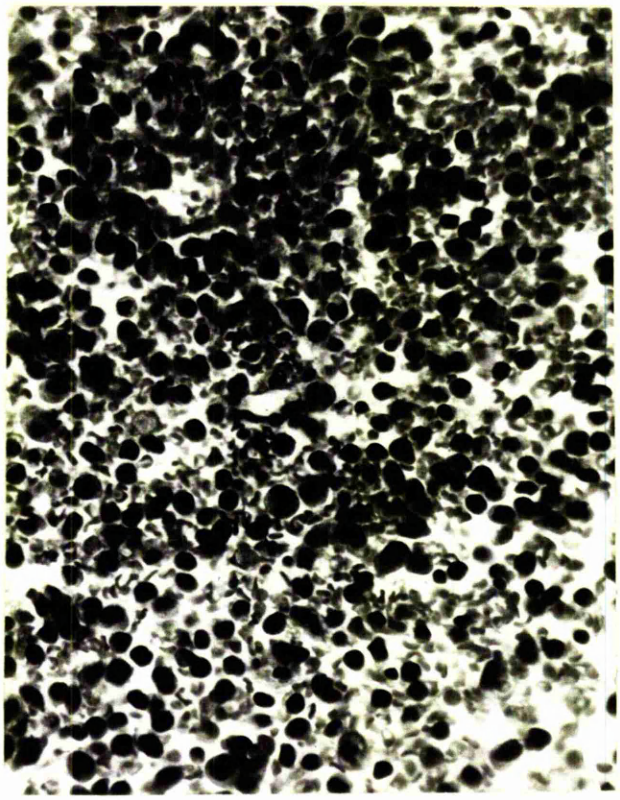

FIGURE 8

FIGURE 7 showing an appearance highly suggestive of junctional activity in the epithelium overlying a malignant melanoma. H. and E. (x 130).

FIGURE 8 showing the cytology and histology of a malignant melanoma of the vagina. H. and E. (x350).

is clear, in others it is of a delicate pink colour and amorphous structure. The strema is completely disrupted. Only fragments of epidermal vaginal epithelium are included. The amount of available epithelium is small, but there are clear cells in its deeper layers and their morphology suggests that seen in junctional change. There are a few areas of fine intracellular granules suggestive of melanin. Figures 7 and 8.

The cell morphology, presence of appearances highly suggestive of junctional activity, presence of melanin and absence of any other clinically detectable primary tumour make it likely that this is a primary malignant melanoma arising in the vaginal wall or portio vaginalis of the cervix uteri.

MALIGNANT MELANOMA OF THE FEMALE URETHRAL MEATUS

No examples of primary malignant melanoma of the urethral meatus occurred within the period of this survey. This is not surprising in view of the paucity of reports of cases of this kind in the literature. McBurney and Bale (1955) reported a single case of a tumour in this site as the seventeenth reported. They further state that there are no reports of malignant melanoma in the male in this site. Raven (1950), however, records such cases in his composite table of site distribution derived from the literature.

One/

One case of primary urethral malignant melanoma has been seen in this hospital recently and in view of the rarity of the condition a case report is appended.

CASE REPORT

M.D., a married woman aged 61, presented at a surgical clinic on 6:5:64 with a history of two episodes of "vaginal bleeding" in the preceding two months. Physical examination at that time revealed a urethral tumour and cystoscopy on 5:6:63 indicated that the tumour was confined to the area above the urethral meatus. Small lymph nodes were noted in the left groin. A biopsy was performed on 28:5:63 and the histology report (S.G.H. 1998-2007/63) stated "strong possibility of melanoma based on the pattern of the tumour tissues and the cytology. A few granules of brown pigment are seen in one or two cells. The patient was regarded as unfit for surgery and referred to this hospital for radiotherapy. On 16:7:63 a radium implant was placed around and in the tumour. Regression of the obvious tumour occurred and the patient remained well for twelve months. On 20:7:64 further vaginal bleeding was noted and examination under anaesthetic revealed a bluish tumour in the upper third of the vagina involving the whole of the right side of the cervix. A 3.0 cm. diameter lymph node was noted in the right groin. Biopsies were taken from the vaginal tumour and from the lymph node (P645265)./

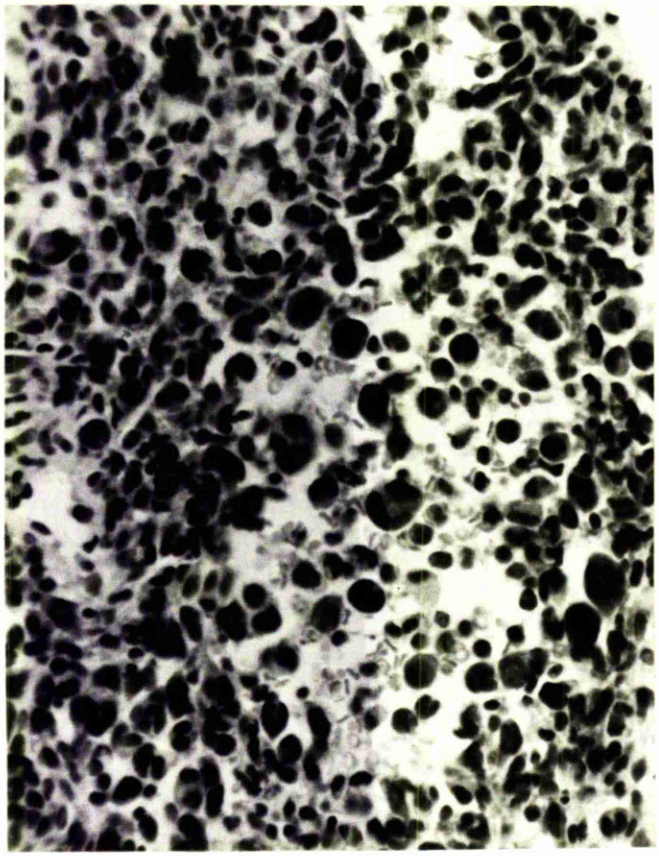

FIGURE 9 showing the cytology and histology of a malignant melanoma of the urethral meatus. H. and E. (x 350).

(P645265). The histological report on this material suggests that there is a "high probability that this is a melanoma, but it is so anaplastic that it is impossible to be absolutely certain". Melanin granules were noted in some cells. Figure 9. Between 3:9:64 and14:10:64 supervoltage radiotherapy was given using a linear accelerator and hyperbaric oxygen. (Details of doseage: 6,000 rads. given in 15 treatments over 6 weeks). A biopsy of the vaginal tumour taken on 14:10:64 (the last day of radiotherapy) showed little change in the tumour (P645806). However, on 26:11:64 the groin lymph node was noted to have become smaller, measuring 1.5 x 1.5 cms. A biopsy of the vaginal tumour and the excised lymph node removed on that date, (R.B.M.H. 2590/64) were reported as showing some radiation change in the tumour cells, an appearance less marked in the vaginal material than in the lymph node. A stain for melanin on this occasion was reported as inconclusive. On 18:3:65 no tumour was palpable on vaginal examination, but pulmonary metastases were noted in a chest radiograph. On 8:4:65 a necrotic recurrence was noted on the anterior vaginal wall involving the urethral meatus. The patient received "Melphalan" 5 mgm. twice daily up to 26:5:65 with little subjective or objective improvement. At the time of writing the patient is in poor health, the tumour remains in status quo and she is regarded as terminal.

MUCOUS/

MUCOUS MEMBRANES

Five malignant melanomas arose on the mucous membranes in this study. This figure represents 2.6% of all primary tumours. Two arose in the nose, one on the hard palate, one on the posterior pharyngeal wall at the level of the vallecula and one in the vagina (vide supra).

This incidence is very similar to that reported by Allen and Spitz (1953) (2.6%), Raven (1950) (3.54%), Pack, Gerber and Scharnagel (1952) (1.8%) and Charalambidis and Paterson (1962) (2.0%).

The existence of melanocytes in the wall of the upper alimentary and respiratory tract is accepted. The existence of reports of malignancy of this type is, therefore, not surprising.

MELANOMA OF THE NOSE AND ACCESSORY SINUSES

Malignant melanoma arising in this site is uncommon. Mason and Friedmann writing in 1955 found 82 cases in the literature and added 11 of their own. Sinclair-Stewart (1951) believes that the incidence of this tumour in the nose is not as low as generally reported. He believes that malignant melanoma constitutes 4% of treatable malignancies in the nose. Most of the cases in the literature, Wilkinson (1912), Collins (1930), Tweedie (1933), McKenzie (1939), Munro (1945), Grace (1947) and/

and Alexander (1954) are regarded as primary tumours, but Ringertz in 1938 described two cases of intranasal malignant melanoma secondary to skin tumours. Mason and Friedmann (1955) make the interesting comments that benign pigmented tumours do NOT occur in the nose and that the only pigmented area in the nose is around the olfactory area. By contrast most intranasal malignant melanomas arise just posterior to the muco-cutaneous junction in the anterior part of the nose, although they can occur in any area. The age of onset is most frequently in the sixth decade and the disease occurs with equal frequency in both sexes. The symptoms are most commonly nasal obstruction, nasal discharge, epistaxis and the passage of pieces of tissue from the nose. The prognosis is usually reported as poor due to late diagnosis and the technical difficulty of complete eradication of the primary tumour.

As mentioned above two such cases were encountered in this series and the case reports are included.

CASE REPORT

D.McK., a 67 year old male was first seen in early January 1956. His complaint at that time was of blockage of the right nostril for seven months and intermittent epistaxis and pain in the nose. He had recently discharged a small fragment of tissue/

FIGURE 10 showing the cytology and histology of a primary malignant melanoma of the nose. H. and E. (x 350).

FIGURE 11 showing an effete secondary malignant melanoma in a cervical lymph node. (Same case as Figure 10). H. and E. (x 130.

FIGURE 12 showing the cytology and histology of a recurrent malignant melanoma of the nose (Same case as Figures 10 and 11). H. and E. (x 350).

FIGURE 13 showing the cytology and histology of a malignant melanoma of the nose. H. and E. (x 350).

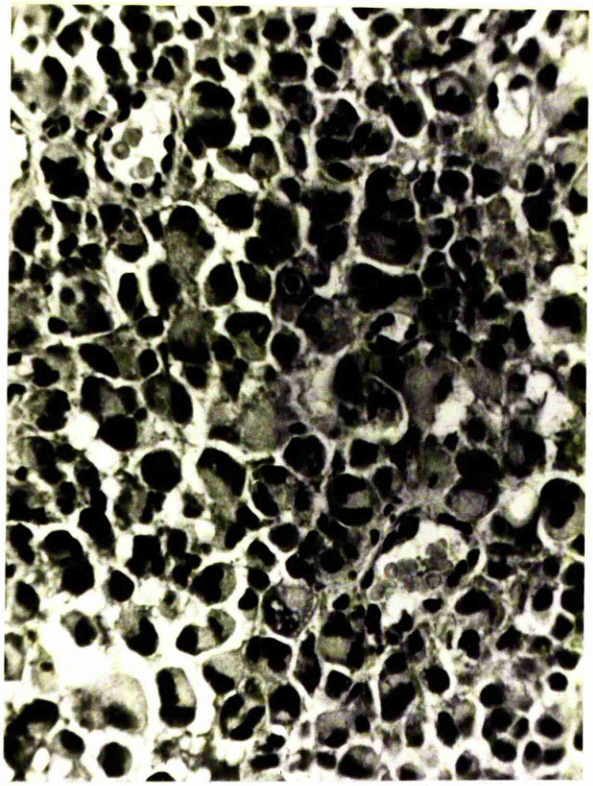

FIGURE 10

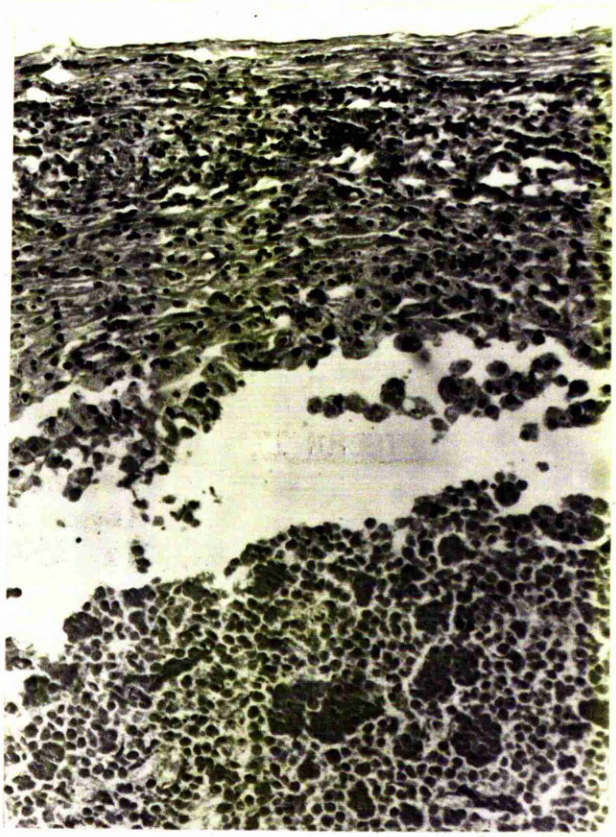

FIGURE 11

FIGURE 12

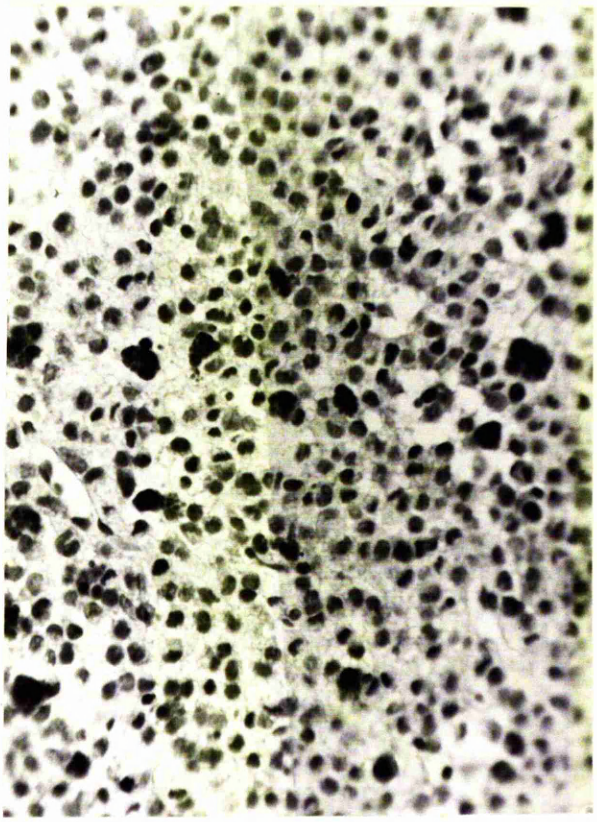

FIGURE 13

tissue. The tumour mass was biopsied and microscopic examination showed it to be a malignant melanoma (figure 10). On the basis of this diagnosis the tumour was excised on 13th February 1956 and radium implanted on 16th February 1956. he remained well until 19th February 1963 when a fixed swelling 2.5 cms. in diameter was noted in the right side of the neck below the angle of the mandible. This had initially been painful but, according to the patient, had decreased in size prior to his attendance at hospital. No therapy had been given in this period. He also complained at this time of a recurrence of the blockage of the right nostril. Examination of the nose showed no evidence of recurrence. The mass in the neck was excised on 23rd March 1963. Microscopic examination of this material showed two lymph nodes. One demonstrated the appearances of reactive hyperplasia, the other had a thick fibrous capsule surrounding cells compatible in appearance with an inactivated metastasis of melanoma (Figure 11). on 17th March 1964 he returned with a "blind boil" on the lateral wall of the right nostril. An excision biopsy was performed and on microscopic examination proved to be a recurrence of malignant melanoma (Figure 12). He remained well until June 1965 when a further two biopsies of the right nostril showed recurrent melanoma. At present his general condition is excellent and he is being kept under careful clinical observation.

CASE/

CASE REPORT

Mrs. M.H., a 64 year old woman was first seen on 21st October 1959 with a history of intermittent epistaxis over a period of several weeks. Two biopsies were performed. The first showed the appearances of a pyogenic granuloma, the second was reported as a malignant melanoma (Figure 13). The sinuses and chest were x-rayed at this time and the left antrum noted to be radio-opeque. There was no evidence of pulmonary involvement at this time. On the 2nd December 1959 a left Caldwell-Luc operation was performed and the surgeon reported: "Melanotic tumour was present on the floor of the antrum and had broken through the mucosa. There was a deficiency of the antro-nasal bony wall and the mucosa on the nasal side was infiltrated with melanoma. Further melanotic tumour was removed from the anterior meatus. The area was packed with radium." Radiotherapy was administered from 21st to 31st December 1959. On 22nd January 1960 hard nodes were noted in the cervical region. By September 1960 the patient had a mass arising from the pelvis and was regarded as terminal. Her own doctor states that she died on 25th October 1960 with a huge abdominal mass. There was no definite evidence of a local recurrence.

From the literature it is all too obvious that the latter case is more typical of the usual history of melanoma in this site; it is of interest to note that in the former case the/

the disease appears to have declared itself at a much earlier stage than in the latter.

MALIGNANT MELANOMA OF THE UPPER ALIMENTARY TRACT

Primary malignant melanoma of the mouth, pharynx and oesophagus is rare. From the literature it would appear to have much the same frequency as melanoma of the nose (vide supra). Baxter, writing in 1941, was able to find 54 case reports of oral tumours of this kind and added one of his own. Gotshalk, Tessner and Smith (1940) reporting a case of primary melanoma of the palate, state that this is an "infrequent" site and cite previous cases reported by Bernstein (1929), New et al. (1921), Patterson (1926) and Takezawa (1936). One case of primary malignant melanoma of the hard palate occurred in this series in a girl of 26. The tumour was situated on the right side of the hard palate and had been present since the age of 5. Unfortunately the case records of this most interesting case have been mislaid. It is known, however, that the patient died less than one year after developing new symptoms.

Malignant melanoma of the pharynx would appear to be very rare. Raven reported 27 rare pharyngeal tumours in 1964 and there were no melanomas within this group. One such case was encountered in this material. In view of the rarity of the/

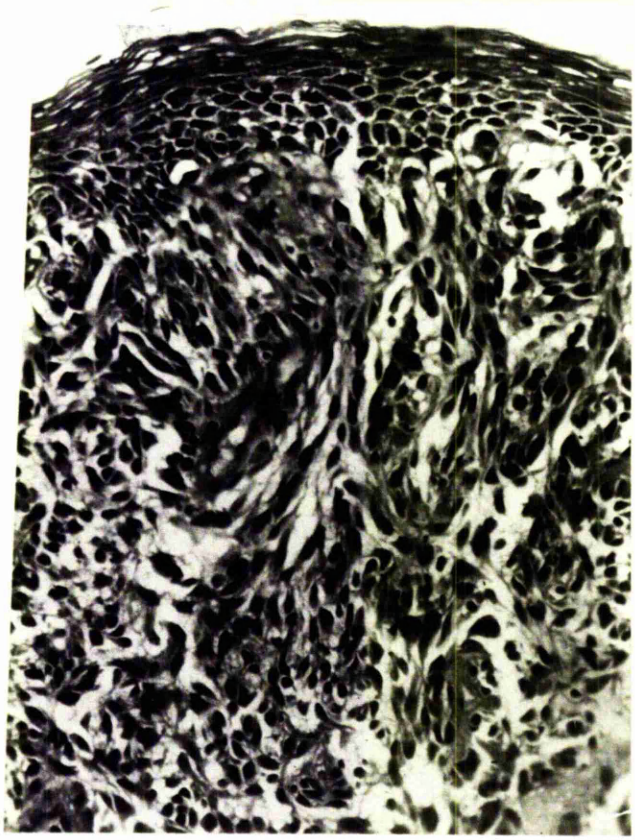

FIGURE 14 Showing the cytology and histology of a malignant melanoma of the pharynx. Masson. (x 130).

the condition a case report is appended.

CASE REPORT

J.McC., a male aged 54, was first seen on 11th May 1955 with a complaint of dysphagia for solids for two months. He made no complaint of dyspnoea, but following a direct examination required an emergency tracheotomy. Examination at that time revealed "black pigmentation in splotchy areas over the posterior pharyngeal wall with irregularity of the mucosa and a large granulating mass behind the epiglottis obscuring the larynx and extending into the vallecula and the root of the tongue where it is also noted to be pigmented. There is no evidence clinically of metastases." A biopsy of the mass on the vallecula was obtained. Microscopic examination of this showed the tumour to be a malignant melanoma (Figure 14). He had radiotherapy between 26th May and 22nd June 1955. This produced a good subjective remission, but objectively the tumour continued to grow. By 7th May 1956 a mass was palpable in the suprasternal notch and a second course of palliative radiotherapy was instituted. Despite this treatment, he deteriorated rapidly and died on 13th September 1956 with extending disease. No postmortem examination was permitted.

No example of malignant melanoma of the oesophagus was encountered during the period of this study, but Professor Cappell informs/

informs me that a case of this type did occur prior to 1950. That primary tumours of this type arise in the oesophagus is well documented and widely accepted. The histological evidence submitted in support of the claim that at least some of these tumours are primary is very convincing in several recent reports, particularly those of Garfinkle and Cahan (1952), Fowler and Sutherland (1952), Bullock, Thompson and Gregory (1953) and Raven (1964). Other case reports of melanoma in this site are relatively numerous, but lack histological evidence of their primary nature (Joliat, 1907), Baur (1904), Hofman (1920), Moersch (1927), Voss (1928), Jaleski (1935), Burnett and St. John (1951).

MALIGNANT MELANOMA ARISING WITHIN THE EYE

These are considered separately in view of their exceptional situation and tendency to metastasise later and less widely than cutaneous tumours.

There were 27 such tumours encountered in this series. Sixteen were in males and eleven in females. Twenty-five of the 27 tumours arose from the choroid in the posterior or posterolateral aspect of the globe. The remaining two tumours arose from the region of the ciliary body and iris. This tumour distribution is very similar to that found by Wright (1949) and by McKee (1941). Such a tumour distribution is not

surprising/

surprising in view of the relative surface area of regions involved.

MALIGNANT MELANOMA IN WHICH NO PRIMARY TUMOUR WAS DISCOVERED (OCCULT PRIMARY)

The primary tumour was not discovered in 5 cases, the diagnosis being made by examination of secondary deposits; this represents 2.6% of all cases. This figure is similar to that recorded by Pack et al. (1952), 2.4%, Royster and Baker (1957), 3.79% and James (1961), 3.84%. It is, however, lower that the figure quoted by Preston et al. (1954), 7.6% and Cook (1963), 13.1%.. This is an unpredictable group in which it is not possible to implement the first rule of cancer surgery - the excision or eradication of the primary tumour. The results of therapy on which such a limitation is imposed speak for themselves (vide infra.).

Of five such lesions in this series, three presented as lymphadenopathy, two in the cervical region, one in the inguinal area. Of the other two cases, one presented as an intracranial space-occupying lesion in a young woman who had been under almost continuous dermatological surveillance for an unrelated condition, the other presented with multiple disseminated skin nodules. A diligent search in these cases, including/

including examination of the eyes, ears, upper respiratory and alimentary tracts and the genitalia revealed no primary tumour.

MALIGNANT MELANOMA ARISING IN UNUSUAL SITES

Reports exist of malignant melanomas situated in a variety of unusual sites and in a number of cases the authors have claimed these tumours to be primary. Sometimes this is based on no more convincing evidence than a failure to demonstrate a primary tumour in any of the more usual areas. More convincing evidence does, however, exist in several instances in the shape of appearances suggestive of junctional activity in the overlying epithelium.

Sites of origin in this category include the central nervous system (Lence 1937), the meninges (Gibson, Burrows and Weir (1957) and Akelaitis, the small bowel (Gordon 1943), the gall bladder (Jones 1961, Lence 1937), the adrenal (Tuczek, MacLachlan), the ovary (Otken, 1942), the bladder (Wheelock 1942), an ovarian dermoid cyst (Jernstrom et al. 1959; Fruming 1963), the parotid gland (Heim), the liver (Paget 1863) and the breast (Affleck 1936).

No examples of this type of tumour were encountered in the present study.

THE/

THE EFFECT OF RACE ON THE INCIDENCE OF MALIGNANT MELANOMA

All patients in this series were Caucasian. A considerable proportion of the local population are of exactly the fair-sandy haired, pale-skinned type who are regarded by the American and Australian writers as more prone to develop melanoma. Unfortunately, since the study is a retrospective one information about the skin and hair colouring of the persons in the study group is not available. The coloured population of Great Britain and in particular of the West of Scotland was small during the period of the survey. With the recent increase in this element of the population it will be interesting to note how soon a report of a malignant melanoma arising in a coloured person domiciled in Great Britain appears.

The various reports of melanomas in negroes and Asiatics make it clear that a heavily pigmented skin is not an absolute prophylaxis against the development of tumours of the melanocytes. It would be surprising if this were the case since it has been shown that incidence of melanocytes in the skin of coloured persons is little different from that in the white races (Staricco and Pinkus, 1957). Hever (1935) has reported that naevi are of quite frequent occurrence in the natives of the Sudan. Pack (1959) and Morris et al. have recorded the occurrence of naevi in North American negroes. Oettle (1963), on the other hand/

hand has examined the skin of a group of Bantu and has not seen any junctional naevi. If malignant melanomas can develop in albinos (Rhende, 1952, Leonardi, 1958, Young, 1957, Kennedy et al., 1963, and Cottle, 1963) it would appear that it is the existence of melanocytes rather than their functional activity which is the critical factor in the genesis of this tumour.

The reports of melanoma in coloured races are of two types. Firstly, there are reports of the incidence of the disease in areas where the indigenous population is coloured. Secondly, there are reports from areas such as North America where considerable numbers of coloured persons live in climatic conditions of varying types. An interesting and early study of the second type exists in the report by Moreston in 1905 of a malignant melanoma arising in a negro resident in Paris. Morris and Horn, in their review of this facet of the subject in 1951 collected from the literature reports of 158 melanomas in North American negroes and 230 in African negroes.

The impression has existed for many years that melanoma is some three to four times as common in white persons as in negroes. Morris and Horn (1951) have suggested that this may not accurately reflect the true position. They suggest, on the basis of Muelling and Burdette's figures in 1950 that the relative incidence is nearer 2:1, whites predominating. Watson (1963)/

(1963) found melanoma to be twelve times commoner in New Zealanders of European stock than in Maoris.

National Cancer Institute Monograph, No. 10 (the report of a conference on cutaneous cancer) provides a most fruitful and fascinating source of information for anyone interested in skin cancer. Ten Seldam (1963) writing from Australia, an area where skin cancer is some ten times commoner in the European-derived element of the population than in a comparable group domiciled in Europe, notes that malignant melanoma forms a very high proportion of these skin cancers. He further notes that, whereas the disease occurs more commonly in women (1:0.68), it more frequently causes death in males, (1.35:1). This he attributes to women seeking medical advice at an earlier stage than men. This latter opinion is shared, to some extent, by Haenszel (1963) who regards "cosmetic awareness" as the reason for the apparently higher incidence of melanoma in women. Eastcott (1963) reporting from New Zealand, notes the incidence of melanoma in that country to be lower than that found in Australia, but higher than the incidence in Great Britain or the United States of America. His comments on the modus operandi of actinic rays in the genesis of skin cancer are novel and extremely interesting.

The comments on the incidence of malignant melanoma in the native peoples of New Guinea by Atkinson et al. (1963) of Hawaii/

Hawaii, by Quisenberry (1963), of Indonesia, by Priggoutoma and Pringgoutoma (1963), of Thailand, by Tansurat (1963), of Japan, by Miyaji (1963), of Ceylon, by Cooray (1944), of Malaya by Marsden (1958), of India, by Miley (1963), of South Vietnam, by Phan et al. (1963), of Taiwan, by Shu Yeh (1963), of the Phillipines by Pantangco et al. (1963) and of Singapore, by Shanmugaratnam and La'Brooy (1963) point out certain common trends. Malignant melanoma is not particularly common among the coloured native peoples of these regions. When it does occur there is a marked predilection for areas around the feet and ankles subjected to recurrent trauma in barefoot peoples, a point raised previously by Hewer (1935) in the Sudan. Where the wearing of shoes has become more common this predilection for primary melanomas on the feet has become less prominent. Those authors who have studied immigrant Europeans domiciled in their particular area without exception note a much higher incidence of malignant melanoma in those incomers.

From these observations certain inferences may be drawn. Two seperate groups of aetiological factors appear to be involved in the genesis of malignant melanoma. In the native peoples mechanical trauma of varying degrees and kinds would seem important. In the immigrant Europeans, on the other hand, actinic rays seem to be a highly significant factor.

SOCIAL/

SOCIAL CLASS AND OCCUPATION

Malignant melenoma, from the information available in this study appears to affect all classes of society and persons of all occupations. In particular, no tendency for the disease to affect outdoor workers was noted.

BLOOD GROUP OF PATIENTS WITH MALIGNANT MELANOMA

TABLE 7 SHOWING THE BLOOD GROUPS OF 28 PATIENTS WITH MALIGNANT MELANOMA

Blood Group	A	B	AB	O	Rh(D)+	Rh(D)-
Number	10	3	-	15	24	4

This information is available in 28 cases from this retrospective series. There is no obvious variation from the regional distribution of blood groups for the whole population. No information on this point has been noted in the literature.

TABLE 8 SHOWING REASONS FOR SEEKING MEDICAL ADVICE

First Symptom or Reason for First Attendance	No. of Patients with Symptoms	% of all Patients
Growth of Tumour	114	68.4
Bleeding from tumour	65	39.0
Ulceration of tumour	32	19.2
Pain in or around tumour	13	7.9
Irritation from tumour	15	9.0
Change of colour of tumour	10	6.0
Pigmented Halo	10	6.0
Satellites around tumour	5	3.0
Enlarged lymph nodes	7	4.2
Change in tumour surface	7	4.2
Development of new lesion on top of old one	6	3.6
Discharge from tumour	6	3.6
Itch	1	0.6
Crusting	1	0.6
Prophylactic excision	4	2.4
Cosmetic excision	1	0.6
Tumour noted	3	1.8
Tenderness	1	0.6
Remittent healing	2	1.2
Inflammation	3	1.8
"Trouble" with footwear	1	0.6
Disseminated skin tumours	1	0.6
Recurrence on site of previous treatment	1	0.6
Pain in back	1	0.6
Hemiparesis	1	0.6

THE DIAGNOSTIC PROBLEM OF MALIGNANT MELANOMA

1. Analysis of Presenting Symptoms of Patients with Cutaneous Malignant Melanoma

From Table 8 it is apparent that the majority of patients noted a change in character of a skin tumour or of an area of skin discolouration. In most cases (68.4%) this change was growth of the lesion, associated with bleeding in 39.0% of cases and with ulceration in 19.2%. Pain was noted in 13 cases (7.8%) and tenderness to touch in 1 case (0.6%). These latter complaints were usually associated with acute inflammation of the tumour or of the adjacent tissues. An alteration in the colour of a tumour was noted in 6% of cases. This took a variety of forms. Most frequently the change consisted of darkening of the tumour, but in a few cases the development of a lighter hue was noted. Ten patients recorded a change in colour in the skin around the tumour with the colour spreading centrifugally - this constitutes the so-called pigmented halo. Five patients had noted the development of minute new tumours around a pre-existing pigmented tumour - satellite nodules.
The primary tumour remained silent in 7 cases, enlargement of the regional lymph nodes leading the patient to seek advice (4.2% of cases). Other forms of change in character/

character of skin lesions which were noted by patients include; the development of a new tumour in, on or around a long standing previous one (6 cases - 3%); alteration in the character of the surface of a skin lesion (7 cases - 4.2%). In three cases the patients noted the development of a new tumour. In one case the development of a new tumour on the site where a mole had been excised some years previously caused the patient to seek attention. In two cases the mechanical sequela of enlargement of the tumour, itching in one case and "trouble" with footwear in the other, caused the patient to seek attention. Four of the primaries (2.4%) were excised prophylactically, being situated on areas where they were frequently traumatised. One tumour was excised for cosmetic reasons. Finally, two patients presented with disseminated disease, one with multiple skin nodules, the other with a hemiparesis due to haemorrhage into a cerebral secondary.

The symptomatology of malignant melenoma is well established. The relative frequency of the symptoms noted in this group of patients varies little from the experience recorded by previous observers e.g. Royster et al. (1957), Lane et al. (1958), Ochsner et al. (1962). Activation of and change in character of a more or less longstanding previously benign skin tumour are seen to be the most significant indicators of developing malignancy. Changes of this type in a pigmented area of skin or in a pigmented cutaneous tumour merit the greatest caution in the treatment of the tumour. Truly wide local excision/

excision and histological examination of paraffin sections of the material would appear essential in the management of these tumours.

The disturbing tendency of malignant melanoma to present with symptoms and signs attributable to metastatic deposits (the primary tumour remaining silent and inconspicious) is all too well known. This situation existed in 9 (5.4%) of the cases in this series. The frequency with which this form of presentation is encountered is the direct result of the facility with which these tumour cells spread. The size of the primary tumour has little bearing on the timing of metastatic spread. The most important factor appears to be the fortuitous invasion of blood vessels and/or of lymphatics.

The regional lymph nodes were palpably enlarged at the time of the initial clinical examination in 25 cases. This lymphadenopathy was the main complaint in 7 patients and was noted in the remaining 18 by the examining clinician. This incidence of nodal involvement at the time of initial clinical examination (15%) is lower than that recorded by James (1961) 45% and Ochsner and Harpole (1962) 30%.

2 Site/

TABLE 9 SHOWING THE SIZE OF THE PRIMARY TUMOUR IN 104 CUTANEOUS PRIMARY MELANOMAS

Size Range	Less than 0.5 cm.	0.5-0.99cm.	1.0-1.9cm.	2.0-2.99cm.	3.0-3.99cm.	Larger than 4.0cm.
Number of Cases	6	29	47	10	9	3
Percent of Group	5.8	27.9	45.2	9.6	8.7	2.9

2. Size of Primary Tumour on Initial Examination

Very large and very small tumours were exceptional in this series. Almost 75% were in the range 0.5 - 2.0 cm.

Comparison of these figures with the results reported in previous series reveals a rather higher proportion of small tumours less than 1.0cm. in diameter in this series (33.7%). De Cholnoky (1941) noted 15% of his tumours in this size range and Lane et al. (1958) 12.5%. The figure of 45.3% for tumours in the size range 1.0 - 2.0 cm. is very similar to the experience of most previous authors. In view of the relatively high proportion of small tumours in the study group, it is no surprise to find tumours longer than 2.0 cm. (21.2%) less frequent in this material than in previous series (Lund et al. (1955) 64%, Lane et al. (1958) 39%). Bowen and Walton (1961) in a small group of 32 cases found tumours ranging in size from 0.5 - 9.0 cm. with a mean of 2.4 cm.

3. Size/

3. Size of Primary Tumour in Relation to Duration of Symptoms

TABLE 10 Showing the size of Primary Tumours in Relation to Duration of Symptoms

Size of Tumour	Up to 1cm.	1-2cm.	2-3cm.	3-4cm.	Larger than 4cm.
Mean Duration of Symptoms	9 Months	11.5 Months	18 Months	20 Months	5.0 Months

With the exception of the group of tumours larger than 4.0 cms. diameter, this is the relationship which one would expect in a tumour, the main presenting feature of which is increase in size. If these figures are put into graph form the relationship is very nearly a linear one.

The exceptionally short duration of the large tumours is explicable in several ways :

1. These tumours may have a very high rate of growth.
2. The actual growth attributable to the development of malignancy may have been small if the tumour arose in relation to a large pre-existing naevus.
3. The number of cases of this type available for study is very small and the result may be entirely fortuitous.

4. The/

4. The presence or Absence of a Previous Pigmented Lesion at the Site of Origin of a Malignant Melanoma

After the recognition of a malignant melanoma as a distinct and separate clinical entity it was soon recognised that some of these tumours arose in relation to a pigmented lesion which had existed in a quiescent form for a variable period of time and had not hitherto shown any evidence of malignancy (Pagot, 1863).

More than a century after the recording of this very basic clinical observation there is still considerable debate as to whether all malignant melanomas arise from or in relation to pre-existing pigmented naevi, or whether some arise de novo from macroscopically normal skin. Allen and Spitz (1953) have advanced a strong case for the origin of most, if not all, melanomas from areas of junctional activity. If such an area of melanocyte activity lies in and beneath the epidermo-dermal junction with no intradermal naevus cells related to it, the tumour is termed a junctional naevus. If there are intradermal naevus cells it is known as a compound naevus. Junctional activity is also found in the rather immature looking compound naevi of children (and occasionally of adults) known as juvenile melanomas (Spitz, 1948), or epithelioid or spindle celled naevi (Kernen et al., 1960). This observation of Allen and Spitz is a highly significant one. It/

It emphasises the fact that malignant melanomas arise from the melanocytes intercalated in the stratum basale and lying in the epidermo-dermal area. It seems unlikely that anyone still believes that malignant melanomas arise from the intradermal naevus cells. Malignant blue naevi are, of course, a separate problem.

While the observations of Allen and Spitz are applicable to most melanomas it is rather difficult to explain the not inconsiderable number of such tumours in which the patient is unaware of or will not admit to the presence of a previous pigmented cutaneous tumour or blemish. Doubtless some of these cases are examples of the limited powers of observation of the individuals concerned. Others may be explicable on the basis of a minute lightly pigmented or totally amelanotic naevus. There does, however, remain a group of cases in which the tumour would appear to have arisen de novo from the melanocytes of normal skin. Such tumours can technically be made to fit into the Allen and Spitz scheme if it is considered that at some point, however transient, as the neoplastic melanocytes multiply the appearance of the tumour would be that of a junctional naevus, i.e. at a point before dermal invasion occurs. Sylven (1949) believes that the majority of malignant melanomas arise de novo from epidermal melanocytes.

Such/

Such a concept is not unreasonable. Despite the demonstration of morphologically distinct groups of melanocytes (Szabo (1954) no difference in their malignant potential has been demonstrated or even suggested. In an analysis of the patterns of melanocyte distribution, for the purposes of this survey, (vide infra), it has been noted that melanocytes occur almost twice as frequently in the epidermis in relation to simple intradermal naevi and even more frequently adjacent to junctional naevi, compound naevi, juvenile melanomas and lentigenes as compared to normal skin. On a purely quantitative basis it seems not unreasonable that a preponderence of tumours derived from these melanocytes arise in relation to pigmented naevi. In this series, of the 165 patients with primary malignant melanoma of the skin, 77 (46%) gave a definite history of a previous pigmented lesion on or adjacent to the site of origin of the malignant melanoma.

TABLE/

TABLE 11 Showing the Distribution of Malignant Melanomas Preceded by Pigmented Lesions

	MALE	FEMALE	ALL
HEAD AND NECK			
Total Number of Tumours	24	25	49
Number having Previous Pigmented Lesion	8	15	23
Percentage of Group	33	60	47
UPPER LIMBS			
Total Number of Tumours	9	15	24
Number having Previous Pigmented Lesion	3	7	10
Percentage of Group	33	47	42
TRUNK			
Total Number of Tumours	12	13	25
Number having Previous Pigmented Lesion	9	5	14
Percentage of Group	75	39	56
LOWER LIMBS			
Total Number of Tumours	12	39	51
Number having Previous Pigmented Lesion	4	25	29
Percentage of Group	33	64	57
ALL SITES			
Total Number of Tumours	61	104	165
Number having Previous Pigmented Lesion	25	52	77
Percentage of Group	41	50	46

In general the female patients reported a higher proportion of tumours arising on the basis of a previous pigmented lesion. This almost certainly reflects the greater attention paid by women to their personal appearance -

Haenszel's/

Haenszel's "cosmetic awareness". The overall percentage of 46.7% of cases in which a history of a previous pigmented lesion was obtained is probably rather low. Factors tending to make this figure low are :

1. Tumours existing on sites not visible to the individual and hidden from others by clothing.
2. Failure of the examining clinician, in the face of an obscure or an all too obvious diagnosis to inquire for, or record this information.

On a priori grounds it would seem reasonable to attempt to correlate the clinical history of a previous pigmented lesion with histological evidence of such a tumour. This subject is dealt with under the subject of histological appearances of melanomas.

The proportion of cases in which a history of a previous pigmented lesion was obtained in earlier series varies widely, but is usually higher than the figure obtained in this series (46.7%). High figures are recorded by Affleck 84% (1936), Lane et al. (1958) 71%, Lund and Ihnen (1955) 67% and Ochsner and Marpole (1962) 84%. The figures quoted by Wright et al. (1953) 39.3%, James (1961) 48.5% and Milton et al. (1963) 53% are more comparable with the figures from this material. Sylven (1949) notes that a history of a previous pigmented lesion is obtained in a higher proportion of melanotic tumours (40-50%)/

(40-50%) than in the amelanotic variety (23%).

In this series the pre-existing lesion had been present throughout the patient's life in 25 cases (38%) and for several years in 40 cases (62%). Some writers believe that a specific form of cutaneous pigmented blemish is recognisable clinically in older people which is usually a precursor to malignant melanoma. This is the "Melanotic freckle of Hutchison", a form of acquired lentigo. No example of this condition was recorded in the clinical material which forms the basis of this study.

TRAUMA IN THE GENESIS OF MALIGNANT MELANOMA

Thirty two patients (16.7%) in this series gave a history of trauma. The trauma was usually of mild degree and, in many instances, may merely have focused the patient's attention on a hitherto unnoticed tumour (traumatic determinism). Since a large projecting tumour is more prone to injury than a smaller, flatter one it is likely that any bleeding or trauma following the initial growth of melanoma will serve to attract attention to the tumour. In other cases the trauma involved was chronic irritation rather than of the form of an acute injury. There were, however, four cases in which the nature of the injury and its time relationship to the subsequent development of the tumour are worthy of comment.

CASE/

CASE 1

A malignant melanoma arose in a creosote burn scar on the neck. The time interval between burn and tumour development was twenty years. Norris and Horn (1951) cite a similar case in which a tumour arose on the site of an asphalt burn of foot.

CASE 2.

A malignant melanoma arose on the site of an area of static varicose pigmentation. Specific staining revealed much iron in the subjacent and surrounding dermis.

CASE 3

One patient noted a change in character of a mole following its being scratched by a dog.

CASE 4

A tumour of the sole of the foot arose following a penetrating injury of the site by a nail. Parallel cases to this one and Case 3 are quoted by Peterson et al. (1962).

Analysis of the time interval from injury to tumour development shows two clear groups of cases. In the first group are cases in which the injury antedated the observation of the tumour by only a short time or the two events were almost simultaneous./

simultaneous. These are probably examples of traumatic determinism.

The second group comprises eight cases in which there was a long period between the injury and the appearance of the tumour. The mean interval injury - tumour formation in this group was 9.5 years with a minimum of one year and a maximum of thirty years. This time leg is comperable with that recorded for skin carcinogens such as tar and tar products and it is possible that in this group the traumatic incident was contributory to the development of the cancer.

The problem of the place of trauma in the genesis of this tumour has been a vexed one since the late 19th Century. Most authors have confined themselves to recording the relevant facts as they have emerged from their series. A highly significant and very valid comment has recently come from the report of the Imperial Cancer Research Fund Report for 1964. This document reports a statistical analysis of the case notes of two large London hospitals with particular reference to the history of trauma given by patients with malignant melanoma. A comparable group of patients with basal celled carcinoma provided a control series. On the basis of this material they conclude, "the relationship of trauma to the production of malignant melanoma is regarded as established beyond any reasonable doubt". Unfortunately an analysis of this type can provide no information on the type, degree and modus operandi

of/

of the trauma involved.

Prior to the above publication Petersen et al. (1962) stated the viewpoint of many authoritative and experienced authors when they stated that, except in the case of melanomas of the feet trauma "is probably not a strong promoting factor". They did feel that trauma to an already established melanoma (including trauma occasioned by injudicious treatment, incision biopsy, cautery etc.) might worsen the prognosis by hastening haematogenous and/or lymphatic spread.

Attie and Khafif (1964) in their book "Melanotic tumours" state that they are impressed by the role of infection in the genesis of subungual melanoma. Of the 9 such tumours in this series there was a history of trauma in 5 (55.6%) and all had some degree of paronychia.

The incidence of a history of trauma in this material compares well with the figures quoted by other authors, Attie and Khafif (1964), less than 20%, Hall et al. (1956), 44%, Bickel et al. (1943), 18.7%, Charalambidis et al. (1962), 12%, McCune (1949), 58.3%. Watson (1963), 16.5%, Milton and Lewis (1963), 27%, de Cholnoky (1941), 25%, and Doland and Holmes (1939), 24.8%.

Authors who found no convincing evidence of trauma as an aetiological factor in malignant melanoma include Conley and Pack (1963), Catlin (1954) and the author of a leader in the Lancet of 9th September 1961. At the opposite extreme stand/

stand Howes and Birnkrant (1943), Sylven (1949) and McGuane (1949). This latter author regards trauma as an "important cause of malignant transformation of benign moles". Howes and Birnkrant (1943) regard moles as precancerous lesions which may become malignant on trauma, inflammation or endocrine stimulation.

IATROGENIC TRAUMA

Many authors, writing on this subject, have been seriously concerned that in some cases the treatment applied by medical practitioners to malignant melanomas was possibly harmful. The two most outspoken articles on this subject are those by Amadon (1939) and Tod (1944). There are in addition numerous reports of therapeutic disasters and tragedies included in general articles on malignant melanoma which, with the wisdom of hindsight, can be regarded as having been avoidable.

Most examples of injudicious therapy seem to result from an erroneous clinical diagnosis of which the clinician is so sure that he institutes the (to him) appropriate therapy without recourse to histological confirmation of the diagnosis. This leads to several highly undesirable consequences. Firstly there usually follows a long delay before the true nature of the disease is recognised and the appropriate therapy instituted. In the interim the tumour may well metastasise and the patient reach a stage beyond therapeutic aid. Secondly, in the opinion of some authors the use of electrocautery and chemical cautery may/

may actually accelerate the spread of the tumour by altering tissue pressures and opening up hitherto collapsed lymphatic channels. Amadon's article on this subject is very persuasive and makes sobering reading. Thirdly, the possibility exists that viable tumour cells may be implanted in the depths of the scar resulting from this treatment. Fourthly, the partial destruction of a primary melanoma by cautery destroys the invaluable histological evidence of the nature of the lesion and the evidence as to whether the tumour is primary or secondary. The evidence that the tumour is a malignant melanoma comes all too often from the development of small satellite tumours around the cautery scar shortly after treatment. Paget in 1863 cites three examples of this sinister sequence of events subsequent to thermal cautery of "angiektasie" reported by Pirogoff. Cautery without prior histological confirmation of a clinical diagnosis was performed in 6 cases in this series (3.6%).

Fortunately such tragedies are not very common, but significant delay in definitive treatment of these tumours is a common sequel of errors of clinical diagnosis.

TABLE 12/

TABLE 12 SHOWING THE FREQUENCY AND NATURE OF FACTORS CAUSING A DELAY IN DEFINITIVE TREATMENT OF MALIGNANT MELANOMA

Reason for Delay	Number of Patients Affected
Palliative or inappropriate therapy on basis of histologically unconfirmed clinical diagnosis	13
Incision Biopsy	23
Attempted ablation by cautery (electrical and chemical)	6**
Local excision with no histology	4
Period of observation to confirm clinical diagnosis	3
Radiotherapy on basis of erroneous clinical diagnosis	2
Delay due to economic factors	2
TOTAL	53

**This includes one patient who treated herself with a silver nitrate "pencil"

Table 12 shows the incidence of delay in definitive treatment in this material. The palliative treatment exhibited in these cases included the application of ointment and salves and the local treatment of supposed paronychia. In 3 cases (1.6%) definitive treatment was delayed while the progress of/

of the lesion was observed to provide clinical confirmation of the diagnosis. In a small cutaneous lesion a delay attributable to this course of action is certainly not acceptable and most authors would, in this situation, advise excision biopsy. In two cases the tumours were ocular and their progress assessed by frequent serial retinal photography. Since excision biopsy of a tumour in this site implies enucleation of the eye, a delay in definitive treatment of an ocular tumour for this reason seems logical and acceptable.

Four tumours were excised by the patient's family doctor and the resulting specimen discarded without histological examination. This practice cannot be too strongly condemned. In each of these four cases the tumour recurred on or adjacent to the site of the initial excision. In one of these examples the patient died of melanomatosis 33 months after definitive treatment. The tumour in this case had been excised initially some years previously. It seems very likely that, had this tumour been fully eradicated locally at the first attempt and the nature of the tumour appreciated, this man would not have died of melanomatosis.

Incision biopsy was performed in 23 cases in this series (12%). For a small lesion such a procedure seems irrational, but in dealing with a large lesion incision biopsy may occasionally be necessary to obviate an excessively large excision. Such a practice/

practice is certainly not without hazard. Increased lymphatic flow from the scar area, grossly altered intestitial fluid pressures consequent upon local oedema and the ever present danger of implantation of viable tumour cells are all factors to be reckoned with. The main advantage of this procedure is that in a relatively short period of time an accurate histological assessment of a paraffin section preparation of the tumour is available. This certainly avoids the sometimes considerable difficulty encountered by histologists of limited experience in interpreting frozen section material.

Economic circumstances caused a considerable delay in definitive treatment in two cases. The individuals concerned were resident outwith the British Isles when the diganosis of malignant melanoma was made and found themselves unable or unwilling to pay for the suggested line of therapy and its attendant period of hospitalisation. They subsequently returned to this country for treatment, their chances of survival diminished in proportion to the extended period between diagnosis and treatment.

It is regrettable that 26.5% of the patients in this series had definitive treatment delayed in one of the above ways. The mean delay suffered was 7.4 months, with a minimum of three weeks and a maximum of two years.

It is pleasant, by contrast, to record that no

undue/

undue delay was appreciable in the time from reference by the general medical practitioner to the first outpatient appointment. This averages just over one week, mean 8.9 days, range one to fourteen days. Excluding the group discussed in the foregoing paragraphs, little time was lost between outpatient examination and initial therapy. On average treatment followed outpatient consultation in 14 days with a maximum delay of one month and a minimum of one day. This information is particularly pleasing since the study period was one in which the hospital service was under criticism from the national press over the problems of long waiting lists and undue delays in allocation of outpatient appointments. It is obvious from the information recorded above that in respect of malignant melanoma a realistic system of priorities was operated in the allocation of outpatient appointments.

COLOUR OF THE PRIMARY TUMOUR

Classically a primary malignant melanoma is pigmented and the degree of pigmentation, the distribution of the pigment and the depth below the epidermis at which the pigment occurs produce clinical descriptions of black, brown, grey, dark and pigmented tumours. In this series 74.5% of the tumours were clinically pigmented. The remaining 25.5% were variously described as red, blue, purple and various combinations of these colours./

colours. These figures are not dissimilar to the findings of Lund and Ihnen (1955), 87% pigmented and Royster and Baker (1957), 86% pigmented.

TABLE 13 SHOWING THE INCIDENCE OF PIGMENTED AND NON-PIGMENTED MELANOMAS IN VARIOUS SITES

Site	Sex	Pigmented Tumours	%ge of Total	Non Pigmented Tumours	%ge of Total	Total
Head & Neck	Both	25	75.8	8	24.2	33
	Male	13	81.3	3	18.7	16
	Female	12	70.5	5	29.5	17
Upper Limb	Both	13	81.3	3	18.7	16
	Male	3	50.0	3	50.0	6
	Female	10	100.0	-	-	10
Trunk	Both	10	63.6	6	37.5	16
	Male	6	85.7	1	14.3	7
	Female	4	44.4	5	55.6	24
Lower Limb	Both	24	77.4	7	22.6	31
	Male	6	85.7	1	14.3	7
	Female	18	75.0	6	25.0	24
Ano-genital	Both	4	66.7	2	33.3	6
	Male	3	100.0	-	-	3
	Female	1	33.3	2	66.7	3
All Areas	Both	76	74.5	26	25.5	102
	Male	31	79.5	8	20.5	39
	Female	45	71.4	18	28.6	63

The proportion of pigmented and non-pigmented

tumours/

tumours was similar in all areas.

The existence of non-pigmented or unusually lightly coloured malignant melanomas presents a difficult diagnostic problem. The history of a pre-existing lesion, if available, may be of value in diagnosis. The accuracy of clinical diagnosis in the pigmented group is, not surprisingly, much higher than in the non-pigmented tumours.

STAGE OF DISEASE AT FIRST VISIT

De Cholnoky (1941) and others classify their cases on the basis of three stages based on the presence or absence of metastasis.

STAGE 1 Local disease only noted. There is no clinical evidence of spread to the regional lymph nodes, but primary tumours with halo formation, satellitosis and locally recurrent tumours are included.

STAGE 2 There is spread to one group of regional lymph nodes only.

STAGE 3 There is spread to more than one group of lymph nodes and/or evidence of haematogenous dissemination.

This classification is certainly of some value in assessing the results of treatment, but is open to criticism on the basis of the difficulty of accurate clinical assessment of/

of all but the grossest nodal involvement. In an examination of a group of patients with clinically involved lymph nodes Southwick et al. (1962) found that four of twenty five such patients had deposits of melanoma in the regional lymph nodes on microscopic examination. This finding has been noted by other authors - McCune et al. (1959) 5%, Gumport et al. (1959) 29%, Charalambidis et al. (1962) 14% and Fortner et al.(1964) 38%. The proportion of clinically unsuspected metastases noted on microscopic examination varies widely from series to series up to a maximum of 50%.

TABLE 14 SHOWING THE DISTRIBUTION OF CUTANEOUS MELANOMAS BY STAGE

STAGE	1	2	3
Number	122	38	4
%ge of Total	74.3	23.3	2.5

Analysis of the material from this series shows that, of the 164 cutaneous and mucosal primaries 122 (74.3%) were Stage 1 on initial clinical assessment, 38 (23.2%) were Stage 2 and 4 (2.5%) were Stage 3. The proportion of local and extended disease referred to general hospitals receiving unselected groups of patients should be similar. In the previous series from this region/

region, Wright et al (1953) noted that 80% of their cases had local disease only and that the remaining 20% had involvement of the regional nodes or wider dissemination. Rather higher proportions of patients with extended disease were reported by Bowen and Walton (1961) - Stage 1, 56.3%, Stage 2, 31.2% and Stage 3, 12.3%, Ochsner and Herpole (1962) - 30% of patients had nodal involvement and James (1961) - 45% of patients had nodal involvement.

Many factors operate to produce the proportions of patients with local and extended disease and such proportions are clearly reflected in the subsequent survival studies. The high proportion of patients with clinically limited disease in this series should, a priori, allow a reasonably good survival and cure rate.

The similarity between the figure for extended disease in this series and that quoted by Wright et al. (1953) in the previous report from this region is disappointing. This suggests that the public are either no more cancer conscious or at least no more willing to seek medical advice for this type of condition now than formerly. It appears too that the provision of "free" hospitalisation under the National Health Service, with the consequent removal of the major economic problems attendent upon admission to hospital in some countries, has not lead to a greater number of patients seeking earlier attention.

AIDS/

AIDS TO DIAGNOSIS

In Stage 1 histological examination is essential for the accurate diagnosis of a malignant melanoma, but even this presents many difficulties of interpretation and assessment. This should, ideally, be the examination of several sections taken at different levels through a totally excised tumour. The best results are undoubtedly obtained by examining paraffin block sections but, under certain circumstances, the examination of high quality frozen sections prepared by an experienced technician and examined by a pathologist with wide experience of skin tumours will provide very acceptable results within certain well defined limits.

In this Department it is held that the advent of the "Cryostat" has much improved the quality of sections available. Sections as thin as 4 microns are now obtainable whereas formerly sections were in the range 15-20 microns. This improvement and the great reduction in the degree of distortion of the tissue allow greater accuracy of diagnosis. Two special techniques are employed when an opinion is requested in this manner on a pigmented tumour. One section is stained with haemalum alone and another is stained by the prussian blue method in order to identify haemosiderin, if present. With these two refinements it is felt that an increased level of accuracy has been attained.

Frozen/

Frozen section examination was not widely employed in the material of this series.

Milton and Jelihovsky (1962) reported a series of 39 cases in which they examined biopsy material from pigmented tumours in this manner. An accurate and correct diagnosis was made in 28 out of the 39 tumours and was suggested in a further 4 cases. Of the remainder, 2 malignant melanomas were diagnosed as rodent ulcers and a juvenile melanoma diagnosed as a compound naevus. No simple tumour was diagnosed as malignant. The authors conclude that the diagnosis is made on the overall tumour pattern rather than on the detailed histology. They believe that, provided the limitations of the techniques are clearly understood by the surgeons and pathologists concerned, it may well prove of considerable value.

The impression of the present author is that in the hands of experienced technicians and histologists, using modern equipment it is a technique which could well be more widely employed.

Two further techniques claimed as aids to the diagnosis of malignant melanoma have been described recently. Neither technique was employed in this series, but their interest is considerable to all dealing with pigmented tumours.

Venkei and Bakos (1964) describe a technique whereby the skin temperature over skin tumours and over the adjacent/

adjacent apparently unaffected skin is measured. This is an application of the technique orriginally described by Lawson (1956) and Lawson et al. (1963) in reports on breast carcinoma. The technique has subsequently been applied to breast cancer by Lloyd-Williams et al. (1961) and by Kuemmerle (1958), Kleine-Natrop and Venkei (1963) to cutaneous cancer.

Venkei et al. (1964) define an average temperature difference of more than 1°C between tumour and adjacent skin as positive and a difference of less than 0.8°C as negative. In a series of 176 naevi and basal cell papillomas they found no significant temperature difference in 96%. In a group of malignant melanomas they found a significant average thermo-difference (A.T.D.) in 76.3% with a mean A.T.D. of 1.6°C. They further noted that 4 of the malignant melanomas with negative A.T.D. became positive while under observation.

No significant A.T.D. was found in 14 of 16 subepidermal secondary deposits of malignant melanoma. As a form of control they employed the P^{32} uptake test and found an accumulation of P^{32} of the order of 6-7 times in the positive cases, of the order of 3-4 times in the pseudonegative cases and no accumulation of P^{32} in the negative cases.

In 1955, Bauer and Steffen described the cumulation of radioactive phosphorus, P^{32}, in the tissue of malignant melanomas. Lazarov-Ikonopisov (1965) has recently confirmed this finding/

TABLE 15 THE CLINICAL DIAGNOSIS OF (a) DISPENSARY CLINICIANS (b) GENERAL MEDICAL PRACTITIONERS IN LESIONS DIAGNOSED MICROSCOPICALLY AS MALIGNANT MELANOMA

Diagnosis	No. of Patients Diagnosed at Outpatient Department	No. of Patients diagnosed by General Practitioners
Malignant melanoma	58	6
Mole	10	14
Squamous carcinoma	9	3
Angioma	8	6
Simple papilloma	6	-
Pyogenic granuloma	6	1
Granuloma	5	1
Rodent ulcer	5	3
Wart	4	7
Basal cell papilloma	2	-
Molluscum sebaceum	2	-
Sebaceous cyst	1	-
Mixed parotid tumour	1	-
Epulis	1	-
Neurofibroma	1	-
Foreign body	1	-
Thrombosed pile	1	-
T.B. cutis	1	-
Keratoma	1	-
Lipoma	1	-
Chancre	1	-
Rhadbomyosarcoma	1	-
Anthrax	1	-
No firm diagnosis	7	-
Tumour	-	8
Cyst	-	3
Fibroma	-	1
Ungual sequestrum	-	1
Parotid duct stone	-	1
Suspicious papilloma	-	1
Pigmented skin	-	1
Malignant wart	-	1
TOTAL	134	61

finding and, on the basis of careful examination of the skin around the tumour with a Geiger counter claims that this technique allows assessment of the clinically inapparent zone of field change so frequently seen on histological examination. If confirmed this would be a technique of the greatest value, allowing a more rational and exact approach to the problem of the extent and adequacy of local excision.

THE ACCURACY OF THE CLINICAL DIAGNOSIS OF MALIGNANT MELANOMA

The clinical diagnosis of malignant melanoma has long been accepted as a difficult one to make. This unfortunate fact is evident in an analysis of the results of this series. The patients were examined by experienced specialist dermatologists and general surgeons. Despite this the true nature of the condition was appreciated in less than half the cases.

A firm provisional clinical diagnosis was made at an outpatient clinic in 134 cases subsequently diagnosed microscopically as malignant melanoma. Table 15 shows that the clinical diagnosis was correct in 58 of these tumours (43.3%) and wrong in 76 instances (56.7%). The malignant nature of the tumour was suspected in 88 cases (65.6%), unsuspected in 41 (30.6%) and no firm opinion on this was given in 5 cases (3.8%).

A/

TABLE 16 HISTOLOGICAL DIAGNOSIS IN 372 CASES DIAGNOSED CLINICALLY AS MALIGNANT MELANOMA

Histological Diagnosis	Number	Percentage of Total
Malignant melanoma	65	49.5
Basal cell papilloma	27	25.7
Nevus (all types)	16	6.8
Angioma	11	6.4
Rodent ulcer	10	5.8
Subungual haematoma	4	2.3
Squamous carcinoma	3	1.8
Histiocytoma	2	1.2
Fibroma	2	1.2
Lipomyoma	2	1.2
Keratoma	1	0.6
Pigmented epidermis	1	0.6
Hidradenoma	1	0.6
Epidermal cyst	1	0.6
Molluscum sebaceum	1	0.6
Squamous papilloma	1	0.6
Hyperkeratosis	1	0.6
Venous thrombosis	1	0.6
Lentigo maligna	1	0.6
Carcinoma in situ	1	0.6
TOTAL	372	100.0

A firm provisional clinical diagnosis was recorded in the accompanying letter from the patient's general practitioner in 61 cases. The nature of the condition was correctly diagnosed by the general medical practitioner in 6 cases (9.9%). Malignancy was suspected in 22 cases (36%). It is felt that if more general practitioners had committed themselves to a firm provisional diagnosis the proportion of correct diagnosis by them might well have been higher.

The figure 43.3% for the incidence of correct clinical diagnosis is very similar to those quoted by Becker (1948) 48%, Swerdlow (1952) 59%, McMullen and Hulmer (1956) 50% and Bowen and Walton (1961) 45%. The latter report is of considerable interest since it was prompted by the surprise felt in dermatological circles after Becker's paper in 1954 which focussed attention on this problem. McMullen and Hulmer (1956) conclude that although only one out of two malignant melanomas is diagnosed clinically, it seems unlikely that this level of accuracy could be much improved without the use of ancillary technical diagnostic techniques.

A similar situation is apparent when the group of patients diagnosed as malignant melanoma at the Outpatient Department is analysed. This diagnosis was suggested on the histopathology request forms in 172 cases during the decade 1952-61. (Table 16). The diagnosis was confirmed histologically

85/

85 times. This represents a diagnostic accuracy of 49.5%. Malignancy was suspected on 109 occasions (63.5%).

TABLE 17 SHOWING THE ACCURACY OF CLINICAL DIAGNOSIS AND ASSESSMENT OF MALIGNANCY IN SEVERAL COMMON SKIN TUMOURS DIAGNOSED HISTOLOGICALLY

	Total	Correct Diagnosis	%ge of Total	Malignancy Suspect.	%ge of Total
Malignant Melanoma	134	58	43.3	88	68.2
Rodent Ulcer	383	278	72.5	349	91.0
Squamous Carcinoma	307	182	59.3	248	71.0
Naevi	176	93	52.9	-	-
Basal Cell Papilloma	177	-	-	-	-
TOTAL	1,117	611	54.6	685	83

The level of diagnostic accuracy recorded above, although predictable on the basis of the experience of other countries, is the more disappointing when comparison is made with the situation in other skin tumours. (Table 17). In a comparable group of rodent ulcers 72.5% were diagnosed clinically and the malignant nature of the lesion suspected in 91.0%. In the case of squamous carcinoma 59.3% were diagnosed correctly and malignancy suspected in 71.0%. Naevi (of all kinds) were diagnosed as naevi or moles in 52.9%. This is a rather lower figure/

figure than that recorded by McMullen and Hulmer (1956), but is very similar to Becker's figure for the clinical diagnosis of naevi (1948). It is difficult to account for the very varied accuracy of diagnosis of the different skin tumours. It may well be that, since rodent ulcer and squamous carcinoma are much commoner than malignant melanoma, familiarity and a constant awareness of these latter tumours may allow of their more frequent recognition.

CLINICAL DIFFERENTIAL DIAGNOSIS

The variety of cutaneous lesions liable to be confused clinically with malignant melanoma are legion. Tables 15 and 16 show the main conditions so confused in this series. It is noteable that the most frequent source of error was the basal cell papilloma (syn. verruca senilis, seborrhoeic wart, senile wart). This diagnosis accounted for 15.7% of the group of tumours subsequently discovered to be malignant melanomas on histological examination. Naevi of all histological types, tumours of the blood vessels and pigmented rodent ulcers all were frequent diagnostic problems.

The subungual melanoma seems to be even more difficult to recognise clinically than its cutaneous counterpart. As far as can be assessed from the case material none of these were recognised on first clinical examination. In two cases, however/

however, the clinician observed that there might be a more sinister pathology underlying an ungual paronychia. The usual clinical pitfalls are to regard subungual discolouration as haemorrhage or a foreign body and to regard inflammation as primary rather than secondary and of subsidiary importance to an unsuspected underlying tumour.

The frequency with which other cutaneous tumours are confused with malignant melanoma appears to depend largely on their content of pigment. Amelanotic malignant melanomas are very seldom diagnosed clinically. Table 18 shows the frequency with which the various common skin tumours seen during the decade under survey were pigmented. It will be seen that there is a close measure of agreement between the frequency of confusion with malignant melanoma and the frequency of pigmentation.

TABLE 18 SHOWING THE PERCENTAGE OF VARIOUS COMMON SKIN TUMOURS WHICH SHOW CLINICAL PIGMENTATION

Tumour Type	Total	Pigmented	%ge of Total
Naevi (all types)	176	143	81.0
Basal Cell Papilloma	117	54	46.0
Rodent Ulcer	383	15	3.9
Squamous Carcinoma	307	1	0.3

Since the differentiation of the various naevi

and/

and pigmented skin tumours from malignent melanoma on the basis of clinical features requires something more than can be provided by the most experienced and discriminatingobserver, it is to be hoped that clinicians will increasingly recognise and use excision biopsy of these tumours as the only truly reliable means of diagnosis. Routine adoption of this practice would greatly reduce the number of cases treated by cautery etc. on the basis of an erroneous clinical diagnosis.

A COMPARISON OF THE CLINICAL FEATURES OF MALIGNANT MELANOMA ARISING ON EXPOSED AND COVERED AREAS.

Eastcott (1963), in a report on skin cancer in New Zealand, divides such tumours into those arising on exposed and covered areas. He reports that tumours arising on exposed areas increase in frequency in both sexes as the population ages. He believes that this is evidence in favour of an actinic influence on these tumours. He notes that the mean age at onset of patients with melanomas on covered sites is earlier that in those with melanomas of exposed areas and notes an inverted U-shaped distribution for these cases. The mean age at onset of women with tumours on covered areas is noted to be 15 years earlier than in men. On the basis of these latter findings he suggests that a hormonal factor may be important in the patients with covered tumours.

Division/

Division of the cases composing this series shows that, overall, 76 (54.5%) tumours were on exposed sites and 64 (45.5%) on covered sites. In men the tumours were equally divided between the two types of area while in women rather more tumours arose on the exposed areas (56.8). The mean age at onset of men with tumours on exposed areas was 60.96 years and of men with tumours on covered area 49.38 years. The difference between these two figures is statistically significant. It thus appears that malignant melanoma occurring on covered areas in men occurs in a younger group than does malignant melanoma arising on exposed areas. No statistically significant difference in mean ages at onset was noted between women with tumours on exposed and covered areas.

TABLE 19 SHOWING THE MEAN AGE AT ONSET AND INCIDENCE OF MALIGNANT MELANOMAS ON EXPOSED AND COVERED SITES

Group	Sex	No.	%ge of Total	Mean Age at Onset	Range of Ages
Exposed Site	Male	26	50%	60.96	24-89
Covered Site	Male	26	50%	49.34	23-84
Exposed Site	Female	50	56.8%	52.34	19-88
Covered Site	Female	38	43.2%	59.15	26-85

Eastcott (1963), as noted above, reported that the mean age at onset of women with tumours on covered areas was

15/

TABLE 20 SHOWING THE DISTRIBUTION OF CLINICS TO WHICH PATIENTS WITH MALIGNANT MELANOMA WERE INITIALLY REFERRED (173 CASES)

Clinic	Surgery	Dermatology	Ophthalmic	Radiotherapy	Plastic Surgery	Gynaecology	ENT	Medical	Orthopaedic	Armed Services
No. of Patients	80	33	34	8	4	4	3	1	4	2
%ge of Total	46.3	19.1	19.7	4.6	2.3	2.3	1.7	0.6	2.3	1.7

15 years less than the comparable figures in males. Analysis of the figures from this series does not repeat this observation. The opposite situation appears to exist with a mean age at onset of 49.38 years for men with tumours on covered sites and a comparable figure of 59.15 years for women.

The effect of these factors on survival is considered in the section on follow up studies.

CLINICS TO WHICH PATIENTS WERE REFERRED

The ubiquity of site and protean symptoms of malignant melanoma means that, although an individual clinician may see relatively few cases of this kind during his professional life, all clinicians in virtually every speciality may be required to diagnose this condition, often presenting in a bizarre manner. Table 20 shows the outpatient clinics to which the patients in this series were referred. This information is not accurately available in 19 cases which are excluded from consideration in this respect. It is obvious that the majority of patients are referred by their general practitioners to general surgical outpatient clinics (46.4%). The next most frequent speciality to see these patients initially is dermatology (19.1%). In view of the large number of patients referred to the plastic surgeons for cosmetic removal of pigmented lesions of exposed surfaces, it is interesting to note that only

2.3%/

TABLE 21 SHOWING THE INCIDENCE OF DEATH FROM MALIGNANT MELANOMA IN SCOTLAND 1952-1961

(FIGURES EXTRACTED AND ADAPTED FROM THE ANNUAL REPORT OF THE REGISTRAR GENERAL FOR SCOTLAND NO. 107, 1961)

	1952	1953	1954	1955	1956	1957	1958	1959	1960	1961
No. of Deaths from Melanoma	25	36	34	42	42	41	49	49	45	62
No. of Deaths from all forms of Malignancy	10,119	10,125	10,505	10,585	10,754	10,747	10,691	10,032	11,033	11,221
Age of Deaths from Malignancy due to Melanoma	0.24	0.35	0.32	0.38	0.39	0.38	0.45	0.44	0.40	0.55
Deaths per 100,000 head of Population from all forms of Malignancy	198	199	206	207	210	210	211	214	223	216
Deaths per 100,000 head of Population from Melanoma	0.47	0.69	0.65	0.78	1.81	0.79	0.94	0.94	0.85	1.18

2.3% of tumours in this series were seen there initially. The small number of such tumours seen initially by the gynaecologists (2.3%) and the otolaryngologists (1.7%), merely reflects the low incidence of these tumours in the regions peculiar to these specialities.

THE INCIDENCE OF MALIGNANT MELANOMA

While malignant melanoma is certainly not a common condition it is the third commonest cutaneous malignant neoplasm seen in this department. As previously noted it is impossible to assess even approximately, the population at risk from which the cases of this series are drawn. Two methods of estimating the incidence of malignant melanoma are, however, available despite the absence of an accurately known catchment population. Firstly, since no major environmental variations occur within the boundaries of Scotland it seems acceptable to adopt the figures produced by the Registrar General for Scotland for the country as a whole. Secondly, the frequency of occurrence of malignant melanoma *vis a vis* other forms of cutaneous cancer can be calculated. This latter figure has been reported previously by other authors and allows comparison between their results and the relevent figures from this material.

Table 21 can be derived from the Annual Report

of/

of the Registrar General for Scotland, No. 107, 1961. It shows very clearly that the number of deaths attributable to malignant melanoma has increased sharply in the decade under consideration. This increase is certainly a part of the overall increase in deaths from malignant disease of all kinds, but the rate of increase in the incidence of death from malignant melanoma is higher, over the decade, than that noted in other malignant diseases. The difference in the death rate per hundred thousand head of the population from malignant melanoma in 1952 (0.47/100,000) and the comparable figure for 1961 is statistically highly significant ($Chi^2 = 12.2$ at $P = 0.05$). This increase in incidence is also noted in the figures reported by Lancaster (1956 and personal communication 1965). It is of considerable import that a comparable increase in incidence has been noted in two areas of very widely differing climate. Petersen et al. (1962) reporting from the South West of England and Clemmensen et al. (1960) from Denmark have also commented recently on the rising incidence of this disease.

The peak figure for deaths from melanoma in Scotland, 1.18/100,000 obtained from the 1961 Report of the Registrar General for Scotland is lower than the figure quoted by Petersen et al. (1962) 1.7/100,000 and much lower than that quoted by Clemmensen et al. (1960), 25/100,000 from Denmark in 1960.

Table/

TABLE 22 ANALYSIS OF CASES OF CUTANEOUS MALIGNANCY SEEN IN THE WESTERN INFIRMARY, GLASGOW, BETWEEN 1952-1961

Histological Diagnosis	Number	%ge of all Tumours
Rodent Ulcer	1,385	65.5
Squamous Carcinoma	772	28.3
Malignant Melanoma	140	5.12
Hidradenocarcinoma	12	0.44
Reticulosis	77	2.83
Carcinoma - in - Situ	203	7.45
Secondary Tumours	84	3.08
Sarcoma	24	0.88
Anaplastic Carcinoma	18	0.66
Blood Vessel Tumours (Malignant)	16	0.59
Sebaceous Tumour (Malignant)	1	0.04
TOTAL	2,732	100

Table 22 shows the proportions of the various forms of cutaneous malignant disease diagnosed histologically during the decade 1952/61 in this department. Malignant melanoma is seen to be the third commonest tumour and represents 5.12% of all cutaneous malignant disease. This figure is comparable to the incidence quoted by Peller (1941), 4.1% and Ackerman et al. (1947) 2.85%. It is considerably lower than that quoted by Pack and Livingstone (1940) which is 20% of cutaneous tumours. These latter authors found malignant melanoma to constitute 2% of all malignant tumours, but Rowen and Walton (1961), dividing their figures in a similar manner, find this tumour to constitute only 0.83% of all malignancy seen by them. These four reports were all based on North American populations.

THE TREATMENT OF MALIGNANT MELANOMA

The form of treatment applicable in malignant melanoma depends on the stage of disease as assessed on clinical grounds. If the disease is entirely confined to the immediate vicinity of the primary tumour, excision of the primary tumour with a three dimensional margin of tissue will eradicate the disease. Once the tumour has spread the problem of eradication becomes technically more difficult. Tumour spread may be via the lymphatics to the regional lymph nodes or via the blood stream to a wide variety of organs. In the former situation current surgical opinion appears to favour wide excision of the primary tumour and the lymph nodes including, where technically feasible, the intervening lymphatic plexus and the lymph nodes above the highest group clinically involved. With a tumour of this type situated on a limb some surgeons favour radical amputation as the only means of excising adequately the affected tissues (Cage and Dawson, 1951, Pack, 1959 and James 1961). If the tumour has spread via the blood stream to multiple widely separated sites no therapy at present available offers real hope of successful arrest of the tumour; it remains to be seen whether selective uptake of radioactive amino-acids will make a worth while contribution to this problem.

One of the most difficult current therapeutic problems in the management of malignent melanoma is occasioned by/

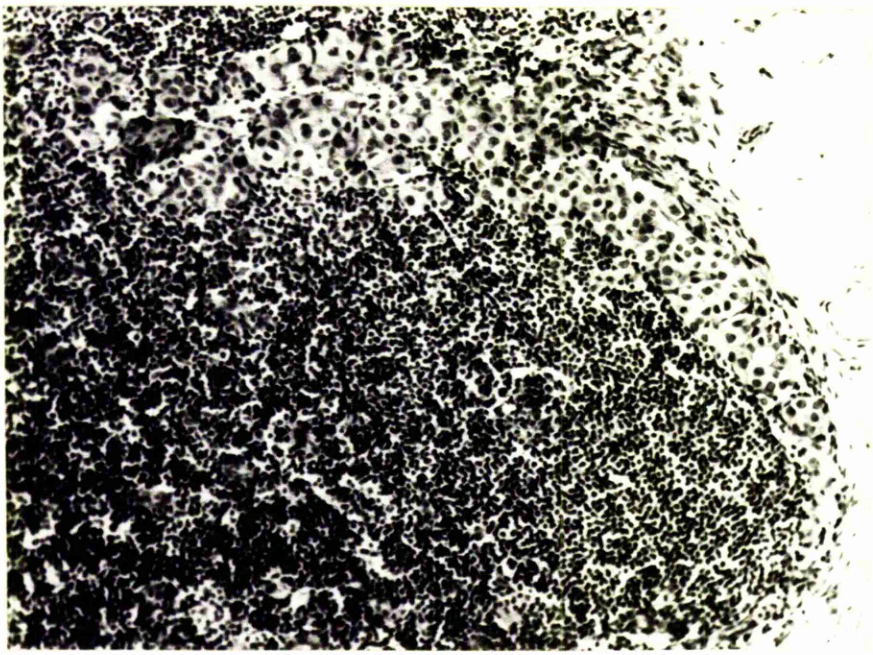

FIGURE 15 (a) showing a cord of malignant cells in the peripheral sinus of a lymph node. The clinical assessment regarded the node as tumour free. H. and E. (x 130).

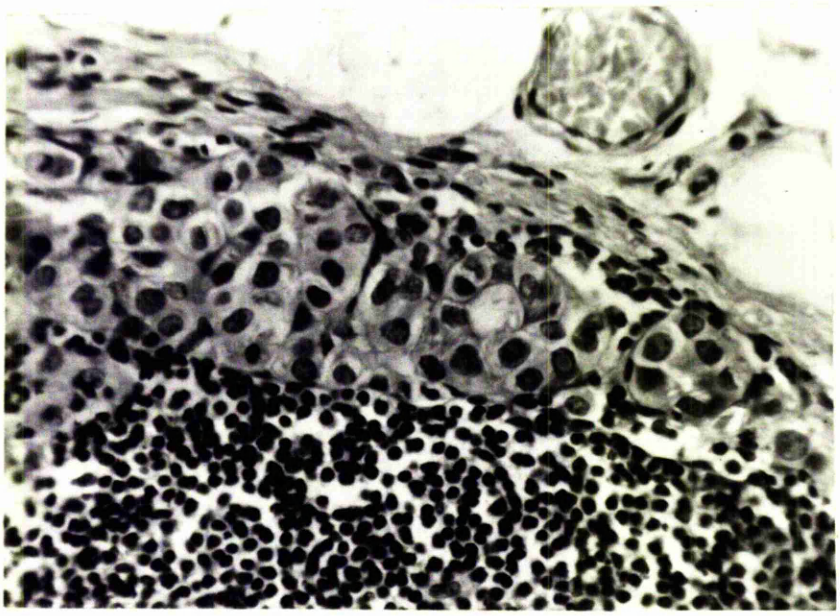

FIGURE 15 (b) A high power detail of the tumour cells in Figure 15 (a) H. and E. (x350).

by the difficulty of assessing clinically whether or not lymph nodes are involved by the tumour. Such a clinical assessment is notoriously difficult and errors are frequent. In this series 2 of 11 patients (18.3%) undergoing excision of lymph nodes believed on clinical grounds to contain no tumour had microscopically evident tumour deposits in their lymph nodes. The comparable figure quoted by previous authors varies widely. Meyer (1957) quotes a figure of 28%, Royster and Baker (1957) 20%, Stewart et al. (1953) 50%, Charalambidis and Patterson (1962) 14%, McCune (1949) 58% and Johnson (1957) 12.5%. Southwick et al. (1962) believe that a more thorough microscopic examination of all lymph nodes removed prophylactically would reveal an increased proportion of tumour-containing lymph nodes. It may well be that it is this very variation in the techniques of examination of lymph nodes which is at least partly responsible for the wide discrepancy in the proportion of tumour-containing lymph nodes. Some histologists examine serial or near serial sections while others merely examine representative random sections of the material submitted. Figure 15 shows an example of minimal nodal invasion. Certain of the lymph nodes examined in this study showed marked melanin pigmentation and the histology was occasionally such that meticulous examination of bleached sections was necessary before the presence of tumour cells could be excluded. This difficulty has been appreciated for/

for many years. Harding and Passey (1930) experienced just this difficulty in their work on a transmissable mouse tumour. Different interpretations of this situation may also contribute to variations in results. The inescapable fact is that clinical and even microscopic assessment of nodal status in malignant melanoma is highly fallible.

A similar error exists in the case of patients alleged to have nodal metastases on the basis of clinical examination. Of 36 cases regarded as having nodal involvement in this study 5 (13.9%) had no recognisable tumour on histological examination of the lymph nodes. In the assessment of clinically positive lymph nodes, Fortner et al. (1964) report an error of 2.6%, Preston et al. (1954) 2.1%. McCune and Letterman (1955) 9% and Royster and Baker (1957) 33.3%. The last quoted figure is from a small series of 9 cases.

In order to prevent the subsequent development of nodal metastasis in patients erroneously assessed clinically as having local disease, the concept of elective or prophylactic nodal dissection was introduced. The protagonists of this technique recommend that the regional lymph nodes should be excised whether or not they are clinically enlarged. Papers in favour of this form of therapy have come from Pack et al. (1952) Hall et al. (1952), Meyer (1957), McCune and Lettermann (1955), Royster and Baker (1957) and Tolmourtian and McCune (1963).

In/

In support of this technique these authors quote the number of clinically unsuspected foci of disease discovered on microscopic examination of lymph nodes removed in this manner. The occurrence of subsequent lymphatic metastases in patients initially regarded as having local disease is also regarded as evidence in favour of the technique of elective nodal dissection. In this series 107 patients were clinically assessed as having local disease and were treated accordingly. Of these 107 patients 29 (27%) subsequently developed nodal metastases. It is certainly true that the routine use of elective nodal dissection will submit a certain number of patients to relatively major surgical procedures unnecessarily. This is highly undesirable, but in the absence of accurate methods of forecasting which patients will develop extended disease seems justified.

The results of all forms of treatment used in this series are presented in the following portion of the thesis. Certain therapeutic techniques not actually used during the study period, but considered of interest, are discussed.

LOCAL EXCISION

What constitutes "wide local excision"? This is a problem to which no absolute answer exists. Certain authors have attempted to qualitate the margin of excision which should be aimed at for tumours of varying sizes in different sites.

This/

This seems an impossible task in view of the accepted inability to assess the degree of malignant change. In the material of this study the surgeons who were most successful at locally eradicating the disease usually excised the tumour with a margin of apparently healthy adjacent skin. If the histological report raised even the slightest doubt as to the adequacy of the excision, re-excision was performed with as little delay as possible. In 39% of cases the second wound resulting from this two stage procedure required the provision of a graft. In the remainder primary closure was possible.

It is to be hoped that the use of the thermo-difference test (Page 78) and the P^{32} uptake test may allow a more rational approach to the assessment of the extent of local excision necessary for these tumours. From studies on the distribution of melanocytes in relation to the tumours presented in this paper (vide infra) it seems possible that the assessment of adequacy of excision may have been hitherto based on rather narrow criteria.

In 115 of the patients of this series the initial surgical therapy provided was local excision of the primary tumour. In 6 cases the excision was palliative or diagnostic in patients so riddled with malignant disease that radical curative treatment was not possible. In the remaining 109 patients local treatment was considered appropriate since the disease was adjudged/

TABLE 29 SHOWING THE FATE OF PATIENTS AS INFLUENCED BY TYPE OF TREATMENT

Type of Treatment	No. of Cases	Deaths from Melanoma	%	Deaths from other Causes	%	Alive	%	Available for 5 year Study	Alive at 5 years	% alive at 5 years
Excision and re-excision	23	8	34.7	5	21.7	10	43.4	14	8	57.1
One excision only	92	44	47.8	22	23.9	26	28.2	75	35	46.6
Local treatment (all)	115	52	45.2	27	23.4	36	31.3	89	43	48.3
Elective Nodal dissection	11	4	36.4	3	27.3	4	36.4	11	10	91.0
Therapeutic Nodal dissection	36	28	78.3	2	5.4	6	16.2	24	5	14.7
Radiotherapy	22	13	59.0	4	18.1	4	18.1	16	3	18.7
Pituitary Ablation	5	5	100.0	-	-	-	-	-	-	-
Chemotherapy	2	2	100.0	-	-	-	-	-	-	-
Untreatable	5	5	100.0	-	-	-	-	-	-	-

adjudged clinically to be confined to the local manifestations of the patient's physical condition was regarded as too poor through age or disease to allow more extensive surgery. The 115 patients are subdivided into two groups on the basis of the type of local treatment employed. Ninety two had one total local excision of the primary tumour. Twenty three had wide re-excision of the scar area of the first excision after the histological diagnosis became known. In 18 of the 115 patients (15.6%) the local excision was sufficiently wide to preclude primary closure and a skin graft was necessary.

Examination of Figure 23 shows that there is little difference in the survival patterns of the single and double excision groups. It seems that, if the initial excision is well clear of microscopically evident epidermal alteration, re-excision of the primary excision scar area does not materially alter the prognosis. Comparison of the 5 year survival figures, corrected for deaths from unrelated causes prior to five years and patients alive, but followed for less than five years shows no significant difference. Of the 89 patients treated by local excision alone and available for five year consideration, 43 (48.3%) were alive on the fifth anniversary of their initial treatment. The proportion of patients dying eventually of melanoma is similar whether the local treatment was confined to a single excision or whether re-excision was performed.

When/

TABLE 24 SHOWING PATTERNS OF METASTATIC DISEASE FOLLOWING VARIOUS FORMS OF SURGICAL TREATMENT

Type of Treatment	No.	Free of Further Disease	%	Local Recurrence	%	Nodal Secondary	%	In transit Secondary	%	Disseminated Disease	%
Excision and re-excision	21	13	62	1	4.75	5	23.8	1	4.75	7	33.3
Excision once locally	86	37	43	23	26.7	24	27.9	4	4.7	37	44.0
All local Excisions	107	50	46.5	24	22.4	29	27.0	5	4.65	44	41.0
Elective nodal Excision	11	6	54.5	3	27.3	1	9.1	1	9.1	4	36.4
Therapeutic nodal Excision	30	3	10.0	3	10.0	8	26.7	3	10	34	80.0

When the incidence and type of metastasis occurring in the two groups of patients who received local treatment is examined, certain interesting differences become apparent. (Figure 2%). Thirteen of the 21 patients who had a re-excision have remained free of disease to date (62%), whereas 37 of the 86 patients who had one excision are free of disease (43%). This difference is not statistically significant (Chi squared = 2.39 and P lies between 0.2 and 0.1). There is, however, a significant difference between the incidence of local recurrence in the two groups. Only one of 21 patients who had re-excision of the scar developed a local recurrence (4.75%). The comparable figure for patients having a single local excision is 26.7%. The difference between these two figures is significant (Chi squared = 4.67 and P lies between 0.05 and 0.02).

The incidence of subsequent regional nodal metastases in the two groups is very similar. Following re-excision of the primary tumour area 23.8% of patients developed regional nodal metastases and following a single local excision 27.9% of patients developed this type of metastasis. These figures are of particular interest, since they suggest that the residual tumour cells which produce the subsequent nodal involvement must be located at a distance from the primary tumour. They may lie in the lymphatic plexus between the primary site and the regional lymph nodes or within/

TABLE 25 SHOWING THE PATTERN OF METASTASIS IN PATIENTS HAVING A SINGLE CONVENTIONAL LOCAL EXCISION AND THOSE HAVING EXTRA-WIDE EXCISION

	No.	Recurrence (Local)	%ge	Nodal Metastasis	%ge	In transit Metastasis	%ge	Dissem-ination	%ge
Conventional Local Excision	76	22	29.0	20	26.3	4	5.25	32	42
*Extra-Wide Local Excision	32	3	9.4	11	34.4	2	6.25	14	44

* Patients with skin deficiences requiring grafting and those having re-excision of the primary scar.

within the lymph node itself at the time of the initial treatment. If these cells were located in the proximity to the primary tumour it would be reasonable to expect a lower incidence of nodal metastasis following re-excision of the primary site.

If the patients who had re-excision of the primary scar area and those requiring a skin graft are considered together they form a group of patients who had a more then usually wide local excision. Table 25 compares this group with patients who had a single excision of the tumour of a magnitude allowing primary skin closure. From these figures it is apparent that exceptionally wide excision of the primary site is an effective means of preventing the development of locally recurrent disease, but has no influence on the development of secondaries at a point remote from the primary site or on the ultimate prognosis of the patient. The difference between the incidence of local recurrences is statistically significant ($Chi^2 = 4.8$; P less than 0.05).

THE TREATMENT OF PATIENTS WITH CLINICALLY INVOLVED LYMPH NODES

The occurrence of subsequent nodal metastasis in more than one quarter of patients regarded clinically as having local disease is highly disturbing. This fact, considered with the discovery of microscopic deposits of tumour in 18.3% of lymph nodes clinically assessed as tumour free and the failure of truly/

truly wide local excisions to reduce the incidence of this type of metastasis, is considered to lend support to the view that the regional lymph nodes should be dissected out regardless of their clinical status. The only alternative to this procedure, which will subject three patients out of four to an unnecessary major surgical procedure, would be some means of more accurately assessing the involvement of the regional lymph nodes. The only reasonable available technique which might provide some assistance in this respect is lymphangiography. Recent articles by Norman and Wilder (1963) and McFeak and Constantinides (1964) present a far from encouraging picture of the accuracy of this technique in its present form.

The problem of "occult metastasis" has been carefully reviewed by Johnson (1957). In a group of 65 cases he notes this type of metastasis in 21 (36.5%). In this category he included satellitosis and in transit metastases as well as subsequent nodal involvement. There was a relatively high incidence of satellites and in transit metastases in the lower limbs. This was attributed by the author to the long lymphatic plexuses of the lower limb and to lymph stasis after dissection of the lymph nodes. He also suggested that earlier treatment of this tumour occurring on visible areas, the older age group of patients who had these tumours on the head and neck and possibly some inherent quality in the tumours of the head and neck which militated against early metastasis might explain the low incidence of occult metastases/

metastases in the region of the head and neck.

The percentage of patients reported initially as Stage I who subsequently develop metastatic manifestations of disease (27% in this series) varies widely in the literature. Lund and Ihnen (1955) noted that 23% of their patients who were assessed initially as having local disease only subsequently developed nodal metastasis. Other comparable figures are Preston et al. (1954) 42%. Southwick et al. (1962) 40.8% and Sylven (1949) 45%.

The number of patients undergoing excision of clinically uninvolved lymph nodes in this series is small. The procedure was adopted in only 11 cases. The results are not susceptible to statistical analysis, but they are of considerable interest. Of these 11 patients all but one survived for five years after initial treatment. This is a five year survival rate of 91%. Four died of melanomatosis, one in the third, one in the fifth, one in the seventh and one in the eighth year after initial treatment. Three patients died of unrelated causes. The remainder are alive and free of disease at periods of 8 to 12 years after treatment. Of the two patients with microscopic evidence of tumour in the lymph nodes, one died of melanomatosis in the fifth year after treatment, the other is alive and free of disease 12 years after treatment. The five year survival figure for this group, 91%, compares favourably with the figures reported by others, Lane et al. (1958) 71%. Southwick et al. (1962) 80%, Conley and

Peck/

Pack (1963) 70.5% and Meyer and Gumport (1959) 52%.

The main arguments against elective nodal dissection appear to be a reluctance to subject 75% of patients to an unnecessary operation and the possibility of lymph stasis subsequent to dissection of the regional nodes (Stehlin et al., 1963).

Troublesomelymphoedema of the affected limb is not uncommon and it is suggested that the lymph stasis may increase the incidence of in transit metastases. Stehlin et al. (1963) note that 60% of patients developing such metastases have had a previous nodal excision.

In transit metastases did not occur frequently in this series. Of the 9 patients who did develop this type of metastasis 5 had had no previous nodal surgery. Of the remaining 4, 3 had had therapeutic nodal dissection and 1 an elective dissection of the regional lymph nodes. On the basis of the admittedly small number of cases available for study it seems that in view of :-

1. The fallibility of clinical assessment of nodal status,
2. The number of patients developing metastasis subsequent to local treatment,
3. The rather higher five year survival figures achieved by most authors using this technique,
4. The failure of even very wide local excisions to reduce the incidence of subsequent nodal metastases,

it is felt that elective nodal dissection should be performed where technically possible. If technically feasible the intervening lymphatic/

lymphatic plexus should be either excised or exposed to a cytotoxic agent.

Following elective nodal dissection only 1 of the 11 (9.1%) patients so treated developed a recurrence in the nodal area. This compares very favourably with the comparable situation when therapeutic excision is performed. After therapeutic excision of lymph nodes 8 of the 30 patients so treated (26.7%) developed recurrence in the nodal area. This shows that the hazards of lymphadenectomy rise with the degree of involvement. Such local recurrences in the region of the lymph node area can have their origin in three ways.

1. From melanomatous tissue inadvertantly missed at operation. The possibility of this happening obviously is proportional to the degree of involvement of the regional lymph nodes.
2. From cells implanted in the wound at the time of the operation. Such cells appear to come from ruptured or traumatised tumour containing lymphatics or lymph nodes.
3. From tumour emboli in the lymphatic plexus distal to the nodal area. Dissection of this tissue in continuity or <u>en bloc</u> with the lymph nodes will serve to reduce this source of recurrence.

The proportion of patients who develop subsequent disseminated melanomatosis following elective nodal dissection is 36.4%. This figure/

figure is very similar to the comparable one following local treatment alone. This suggests that this form of treatment is still not sufficiently extensive since viable tumour tissue is obviously left *in situ* in a considerable number of patients.

THERAPEUTIC NODAL DISSECTION

If the regional lymph nodes are clinically enlarged by tumour infiltration the already grave outlook in this disease becomes infinitely worse. Of 36 patients who had the disease advanced to this stage 28 (78.3%) have died of melanomatosis to date. This compares with 52 of 115 patients with localised disease (45.2%). The five year survival rate corrected for deaths from other causes prior to five years and individuals alive, but followed up for less than five years is 14.7%. The comparable figure for patients with localised disease treated by local treatment is 48.3%. Since it has been shown that malignant cells can be demonstrated in the peripheral blood before there is any evidence of disseminated disease, (Romsdahl *et al.* 1960), it is not surprising that, despite apparent complete eradication of the local and nodal manifestations of the disease, 80.0% of these patients subsequently develop disseminated disease.

It was noted previously that 5 of the 36 cases in this series which were regarded clinically as having evidence of nodal tumour deposits had no tumour in the lymph nodes when these were examined histologically. Despite this negative histological examination/

examination of the lymph nodes 2 of the 5 patients died of malignant melanoma, 1 in the first and 1 in the second year after treatment. The remaining 3 are alive and free of disease two, five and seven years after treatment.

The results reported by the other authors for treatment of disease advanced to this stage are equally poor. Catlin (1954), discussing tumours of the head and neck, reports a 5 year control rate of 10% after the development of secondaries. Meyer (1954) reports an excellent 39% 5 years survival rate, 14 of his 36 patients with nodal spread of tumour survived 5 or more years. In a group of 47 patients Preston et al. (1954) found that 12.8% were alive 5 years after treatment. The comparable figures reported by Lane et al. (1958), 20%, by Southwick et al. (1962), 22.6% and by Conley and Pack (1963), 10.6% are more comparable to the results reported here. Peterson et al. (1962) do not record 5 year results in this context, but noted a 3 year cure rate of 9.5% in patients presenting initially with nodal involvement and of 22.2% in patients with initially local disease who subsequently developed nodal metastasis.

It appears that the current standard treatment of malignant melanoma which has spread to the regional lymph nodes offers little hope of cure. There are, as always, exceptions to the rule. A few patients in this series survived for periods up to 8 years with no evidence of disease. Even assuming that no general dissemination of the disease has taken place the technical difficulties/

difficulties of surgical eradication of the tumour at this stage are considerable. The lymphatic plexus between primary site and nodal area may be long, especially in the lower limbs. The difficulty of assessing clinically whether or not a lymph node contains tumour makes the planning, execution and limitation of dissection of a chain of lymph nodes an almost impossible task. The decision, on clinical grounds that a group of lymph nodes does not contain tumour, must always be arbitrary, even in the hands of the most skilled operators. The ability of this tumour to implant itself is well known. The rupture of tumour filled lymphatics cannot be a rare occurrence in this type of operation. As previously discussed, it has been shown that the tumour cells circulate freely in the systemic blood stream long before clinical dissemination has occurred. On the basis of these observations it seems likely that some potent systemic agent is required to complement present day modes of surgical treatment. The techniques of isolated regional perfusion, as described by Creech et al. (1958, 1964) go some way to filling this hiatus, but as yet the chemotherapeutic agents available are neither specific enough nor lethal enough in subtoxic doses.

RADIOTHERAPY

No case of malignant melanoma was treated by radiotherapy alone during the period of this series. In a few instances radiotherapy was administered as initial therapy, usually/

usually on the basis of an erroneous clinical diagnosis of squamous carcinoma. As soon as it was appreciated that the tumour was not responding to irradiation (which was invariably the case), further radiation was withheld and a diagnostic excision biopsy performed.

Radiotherapy was used as part of the treatment of 22 patients. In 11 cases the aim of the treatment was palliation and this limited objective was at least partly achieved in most instances. The majority of patients so treated felt better after irradiation and pain, if present, tended to be alleviated. Little objective change was reported in the patient's local or general condition. The remaining individuals include those treated on an erroneous clinical diagnosis, some in whom the histological diagnosis was in doubt and the radiotherapy was of the nature of a therapeutic trial, and a group of patients with tumours in inaccessible sites where the radical techniques of cancer surgery were not applicable. In the last mentioned group of cases radiotherapy was usually an adjuvant to surgery. Some temporary remissions were noted, but no permanent cures were seen.

A review of the literature on the use of radiotherapy in malignant melanoma reveals an interesting situation. The majority of authors (who are usually surgeons or pathologists) do not favour the use of radiotherapy except in the limited role of palliation. There are, however, a minority of/

of reports which record a more favourable experience with this form of therapy and suggest its wider use at least as an adjuvant to surgery. Nivinskaya (1964), in a review of 525 patients gathered from various Moscow clinics and diagnosed as having malignant melanoma, reports as his best results, a five year survival rate of 24.3% in a group of patients treated by radiotherapy alone. This author notes that there is a wide variation in individual tumour response and that there is no obvious relationship between dosage and response. This report is of particular value in presenting a group of patients, apparently with early localised disease, treated ab initio by radiotherapy alone. Sylven (1949) reported that radiotherapy was useful in the palliation of metastatic disease. He also felt that "hypermassive" irradiation might control some cases, but was of the opinion that the experiment was not justified. Scharnagel (1933) reported a 5 year survival rate of 28.7% in 49 cases treated by radiotherapy alone or in combination with electroendo-therny. Hellreigel (1961) seems also to favour radiotherapy.

Most other reports indicate that radiotherapy has no real place in the management of malignant melanoma, except in palliation. Daland and Holmes (1939) state baldly that radiotherapy is of "no value" in the management of malignant melanoma. Webster et al. (1944) state that radiotherapy is "as a rule ineffective". Adair (1936) summarised the experience and sentiments of most authors when he stated that only 2.5% of tumours/

tumours respond to radiotherapy which is a "disappointing mode of treatment".

The introduction of more accurately controllable and more powerful sources of medical radiation and increasingly refined techniques of administration of radiotherapy may, however, alter the situation and allow radiotherapy to take its place as a significant factor in the treatment for cure of malignant melanoma.

CYTOTOXIC CHEMOTHERAPY

One of the comparatively recent advances in the treatment of malignant disease has been the introduction of potent cytotoxic drugs. These drugs, from the earliest alkylating agents, used as long ago as 1946, to the more potent preparations now available have one basic property in common. This is their ability to destroy living cells. This ability is proportional to the proliferative activity of the tissues exposed to their action. Tumours with a high mitotic rate are, therefore, very susceptible to the action of these drugs. The potentialities of this form of treatment did not escape those interested in the control of malignant melanoma. The effect of these agents on melanomas has been carefully examined in experimental animals and in man.

Two basic factors control the applicability of any chemotherapeutic agent to a diseased patient. These are the effectiveness/

effectiveness of that agent in controlling the disease and the incidence of undesirable side effects attributable to it. From the examination of a host of different chemotherapeutic agents, p-di(chloroethyl) aminophenylalanine (phenylalenine mustard, P.A.M.) would appear to be the most efficacious compound available for the treatment of human malignant melanoma at this time. The side effects following administration of these compounds are serious, bone marrow depression being the most sinister. This is a particularly difficult problem since the optimum therapeutic dose of these compounds is frequently only marginally less than the toxic dose. The sophisticated techniques now available (vide infra.) allow the application of a very high dose to the target organs and tissues without exposing the bone marrow. It is possible with the techniques now available for removal and storage of bone marrow that, after removal of marrow, whole body perfusion with high concentration cytotoxic agents in disseminated malignant disease may be feasible.

A number of different techniques have emerged for the administration of these drugs. The most obvious route of administration is the time-honoured oral one. The drugs available at this time have either not proved suitable for administration in this way or have not shown much effect when administered by mouth. The incidence of side effects, gastrointestinal upsets, liver upsets, oedema, erythema, blistering, vascular damage and above all bone marrow depression limits the usefullness of this technique./

technique. The drugs have also been administered parenterally. Creech et al. (1964) state that parenteral chemotherapy does not affect the natural course of melanoma. There is, however, some room for slight optimism since these authors have noted an evanescent 3 - 4 month response of varying (usually minimal) degree in 25% of cases.

In an effort to obtain a high concentration of drug at the tumour site without endangering the bone marrow, Klopp (1950) used intra-arterial administration of mustine hydrochloride while attempting to isolate the part by venous occlusion. The isolation so obtained was relatively poor and this limited the use of this technique. The dosage and concentration of drug used was also limited by the occurrence of arterial thrombosis. The concept was nonetheless an original and highly valuable one. The subsequent introduction of extra-corporeal circulation techniques allowed a more complete isolation of limited areas of the body. This meant that the main limit to dosage was the resistance of the normal tissues exposed to the drug. Creech et al. (1958) reported an objective regression of 18 out of 19 malignant melanomas treated by phenylalanine mustard. A more recent report by Creech and Krementz (1964) indicated that this technique is particularly valuable as an adjuvant to surgery. Some surgeons actually perfuse the tumour area before, during and after operative techniques. Irvine and Noon (1961) have also reported some tumour regressions after perfusion with phenylalanine mustard/

mustard. Stehlin et al. (1963) in a report on a series of 194 perfusions in 142 patients, using phenylalanine mustard, record an impressive clinical and histological response in one third of their patients. Fifteen percent showed no response. Although this group of authors see the main role of this technique as an adjunct to surgical treatment they do report striking responses in the treatment of primary tumours. Westbury et al. (1959) using a different compound nunomustine hydrochloride, B.C.M., known as Degranol, reported a striking clinical response in the treatment of a malignant melanoma of the scapular area. Christlieb et al. (1964) have reported the successful use of phenylalanine mustard as a palliative agent and suggest that perfusion prior to conventional surgery may well improve the survival figures.

Triethylene thiophosphoramide (T.S.P.A.), another alkylating agent has produced some response according to Gumport et al. (1958, 1959), Tullis (1958) and Brindley et al. (1964). The last mentioned authors report no response to methyl-bis (chloroethyl) amine hydrochloride (HN_2). Host et al. (1964), in a preliminary report from a series of 145 cases of stage I and II malignant melanoma treated for 6 days post-operatively with cyclophosphamide, report no significant effect on survival and recurrence rates as against a control group receiving no chemotherapy. It is stressed that this is a preliminary report and follow up studies over a longer period may show a different picture./

picture. Negative results have also been reported by Colsky et al. (1952) using Guanaseloin and by Whitelaw et al. (1964) using Vinkaleukoblastine. These reports concern only two and one patient respectively.

New compounds are continuing to become available and laboratory reports on animal experiments and animal and human tissue culture experiments are of considerable interest. Cobb and Walker (1964), using tissue cultures from human malignant melanomas, found that Thiotepa and Actinomycin D damaged a significant percentage of the tissue culture cells. Methotrexate and phenylalanine mustard were generally ineffective and the results with Chlorambucil were equivocal. They noted that cultures derived from patients who had received previous *in vivo* chemotherapy were more sensitive *in vitro*.

The effect of hyperbaric oxygen on the efficacy of chemotherapeutic agents is also receiving attention. The results of this work are at present somewhat ambivalent. Kinsey (1964), in a study of the effect of hyperbaric oxygen and 5-Fluorouracil on the Cloudman S91 melanoma in DBA/2 mice thought the results suggested some potentiation of the antitumour effect of 5-Fluorouracil by hyperbaric oxygen. De Cosse and Rogers (1964) using hyperbaric oxygen alone and in combination with mechlorethamine and methotrexate found no prolongation of survival following the addition of hyperbaric oxygen to these chemotherapeutic agents in the treatment of the A Mel.4 hamster melanoma.

These/

These authors noted that hyperbaric oxygen alone produced a prolongation of survival. They suggest that this may be due to "preferential suppression of pulmonary metastases by the hyperbaric oxygen". This review of some of the relevent literature shows that this technique is still crude and limited in its application and effect. There have been striking advances since its introduction in 1946 and it is to be hoped that the introduction of more potent and specific agents, the refinement of existing techniques and the introduction of new ones will increase the value of chemotherapy in the treatment of malignant melanoma.

A rather disturbing report has recently come from Mehta and Riddell (1965). These authors have noted a significant increase in the content of free melanoma cells in the oxygenator used in isolated perfusion. Their attention was drawn to this fact by the occasional occurrence of rapid dissemination of melanomatosis following isolated regional perfusion. They comment that great care would be necessary if this technique is used in the treatment of potentially curable patients.

Two patients in the present series received cytotoxic chemotherapy. One was given cyclophosphamide followed by mustine hydrochloride, the other had systemic Degranol concurrently with supervoltage radiotherapy followed by Leukeran orally and finally he had a course of Triethylene Melamine. In the first case the patient is reported as showing some clinical improvement, in the second/

second the clinicians concerned felt that they had "halted the progress of disease temporarily". The prolongation of survival obtained was short in both instances and both patients died of melanomatosis shortly after treatment.

TREATMENT OF MALIGNANT MELANOMA BY ATTEMPTED ALTERATION OF THE HORMONAL MILIEU

It has been suggested for many years that malignant melanoma is to some extent hormone dependent. Factors suggestive of such a relationship include:

1. The low incidence of truly malignant melanoma in prepubertal children.
2. The apparent increase in incidence of this tumour during pregnancy (George et al. 1960).
3. The occasional spontaneous regression of a malignant melanoma following parturition (Sumner, 1953 and Allen, 1955) with subsequent recrudescence of activity during subsequent pregnancies, Folner (1961). This author suggests the increase of melanocyte stimulating hormone with pregnancy (Shizume and Lerner, 1954) as significant in this context. Pegum (1955) has also considered this factor as possibly significant. Varon (1959) has suggested that the excess M.S.H. in pregnancy may come from the placenta.
4. The relatively favourable prognosis in premenopausal women as compared with postmenopausal women and men of all ages. This fact has been noted in this series and in previous ones./

ones.

5. The occurrence of a malignant melanoma in a neonatal infant, transplacental spread having occurred *in utero* while the foetus was under the influence of maternal hormones, Weber *et al.* (1930).

The exact nature of this relationship, which does not appear to be a simple one, is not at present apparent. The hormones involved have not been identified, but it seems likely that they must be closely related to the gonad-derived sex hormones or to the adrenocortical hormones which show sexual activity. On the basis of this rather tenuous evidence of hormone control various authors have, from time to time, felt that a profound alteration in the hormonal milieu might have a significant effect on these tumours. Initially a direct technique, excising the adrenals and the ovaries was considered. The precedent for oophorectomy is considerable. Sir George Beatson used this technique for carcinoma of the breast in 1896. West *et al.* (1952) reported a case of malignant melanoma treated by bilateral adrenalectomy. There was some temporary relief of pain, but no objective improvement. Pack and Scharnagel (1951) regard the results of adrenalectomy as inconclusive. Adrenalectomy was attempted in 1 case in this series. Infiltration of both adrenals by tumour was found at operation and the attempt abandoned.

An indirect attack can be made on the adrenals and ovaries by destroying the pituitary. This removes the trophic hormones normally secreted by this endocrine gland. Forrest *et al.* (1959)/

(1959) examined the effect of pituitary ablation in a number of cases of malignant disease. Pituitary ablation was achieved by the transnasal implantation of radioactive Radon or Yttrium seeds directly into the gland. Five cases of malignant melanoma were treated. All were individuals with widely disseminated disease, regarded as beyond the aid of conventional therapy. None of the patients showed any real improvement and death occurred in periods between three weeks and eight months. Histological examination of the pituitary after this type of treatment showed marked necrosis. No real advantage was gained from this form of therapy and its use has now been discontinued. Peck and Scharnagel (1951) report a similar experience using pituitary irradiation.

Methyltestosterone was given to 2 patients in the terminal steges of this disease. Both reported some subjective improvement in their symptoms, but no objective improvement. Mioduszewska (1964) has examined the effect of several hormones on tissue cultures of human melanoma. He reports that A.C.T.H. and M.S.H. stimulate the growth and maintain the life of human malignant melanoma in vitro. Progesterone and oestrogen have a similar, but weaker effect. Testosterone has no effect on or slightly inhibits the growth of malignant melanoma in vitro. Hydrocortisone markedly inhibits the growth of malignant melanoma in tissue culture and causes diffuse cell death. The effect of testosterone in vivo would appear to be possibly rather

contrary/

contrary to the above. Kekst (1943) reported some objective regression of a metastatic melanoma following removal of the secretory tissues of the testis.

TRANSFUSION OF IMMUNE SERUM

A number of very striking reports of the use of "immune" serum exist. These sera are obtained from patients showing an apparent spontaneous regression of a malignant melanoma or with long periods free of recurrent disease after treatment. In the earliest of these accounts Sumner (1953) reported the case of a young man who developed an apparently spontaneous regression of a histologically proven malignant melanoma. Two hundred and fifty mls. of this patient's blood were administered to a second patient with disseminated melanomatosis. A regression of the second patient's disease followed which has remained complete, apart from one small cutaneous deposit, for 8 years. Teincourain and McCune (1963) reported two further cases where transfusion with blood from patients with apparent cure of malignant melanoma produced objective regression of similar tumours in the recipients. This procedure is by no means always successful and the last mentioned authors report in the same paper two unsuccessful attempts to utilise this technique. In a recent article Scanlon et al. (1965) report a further unsuccessful attempt to produce a regression of malignant melanoma by immune transfusion. This article contains a rather salutory account/

account of fatal metastasis from a homo-transplented melanoma. The unfortunate volunteer recipient of the tumour homograft was the patient's mother. She died of melanomatosis 451 days after implantation of the tumour. In view of the reports of circulating melanoma cells in the blood of patients with malignant melanoma (Mehta and Riddell, 1965) it would appear highly desirable that potential donors of immune serum should be carefully screened to exclude circulating viable tumour cells.

Teimourain and McCune (1963) report that Dr. Fert, an immunochemist working at the American Red Cross Laboratories, using immunoelectrophoresis has demonstrated an absorption band between a water soluble protein extracted from a melanoma and an alleged "immune serum".

ONCOLYTIC VIRUSES.

Southam et al. (1952) reported experimental studies with Oncolytic viruses in patients with terminal stages of various malignant disease. In this study the authors used a variety of viruses, vaccinia virus, Newcastle disease virus, West Nile virus, Ilheus virus, Egypt 101 virus and Bunyamwera virus. These all display some degree of oncotropism. This is defined as the selective localisation of a virus in tumour tissues. Ideally a virus used therapeutically in this way would localise selectively in the tumour, multiply in it causing death of the tumour tissues and, at the same time, exhibit a low virulence for the normal tissues/

tissues of the human host.

Two malignant melanomas were treated in the series using Egypt 101 virus. Both showed titre assessed evidence of oncotropism. Neither showed any evidence of tumour regression. This technique is obviously at a very early stage of development. It may well produce significant results if viruses can be adapted to have a high oncotropism, a high antitumour virulence and a low anti-host virulence.

LASERS (Light Amplification by the Stimulated Emmision of Radiation)

Lasers are optical instruments which produce monochromatic coherent light of a single wave length (6943 degrees Ångström in the case of ruby lasers) arranged in near perfect parallel rays. They release their energy with incredible rapidity, can be focussed and their depth of tissue penetration is more readily controllable than is the case with gamma and x-rays. McGuff et al. (1963) noted some regression in the Pitt 4A melanoma in a hamster after laser exposure. Founds et al. (1964) noted that the pigmented cells of the rabbit retina were readily destroyed by the laser beam while nonpigmented cells withstood such exposure well. Goldman et al. (1963) also noted the difference in response of pigmented and non-pigmented tissues to the laser beam. Helsper et al. (1964) found that the area of necrosis produced by a laser beam in a pigmented naevus stopped short at the pigmented - non-pigmented interface at the basement membrane. They further found that

25-100%/

25-100% of the tissue of human malignant melanoma secondaries was destroyed by variable exposures to laser beams. These authors believe that the effect produced by a laser beam is in excess of that attributable purely to the effect of the total energy released. They postulate that the beam may release some cytotoxic agent from the tumour tissues and report that early results from tissue culture studies suggest that such a substance may exist. They conclude that no significant therapeutic effect has yet been demonstrated. Minton et al. (1964a, b) using the Cloudman S-91 melanoma in CDBA/2F, hybrid mice have also noted a definite oncolytic effect. They are of the opinion that this is directly due to the laser energy and in support of this describe a motion picture of a laser strike which shows the emergence of a vapour plume, and the swollen "burst" cells left in the path of the laser beam. They believe that the effect of a fixed dose varies with the size of the tumour and are of the opinion that if doses can be calculated on the basis of tumour size better ablation would be possible.

"SPECIFIC" CHEMOTHERAPY

Mois and Kallman (1964) have reported the selective uptake of C^{14} labelled dihydroxyphenylalanine by mouse melanomas. They related the degree of uptake of this precursor of melanin to the pigment-forming activity of the tumour. Previous studies of/

of this type by Fimian (1959) and Robertson et al. (1955) using C^{14} labelled tyrosine showed no selective uptake of this compound by mouse tumours. Blois and Kalman (1964) believe that these negative results were due to the incorporation of tyrosine into numerous compounds other than melanin. Hempel and Detmel (1963) conducted similar studies on melanomas in mice using tritiated dihydroxyphenylalanine (D.O.P.A.H_3). These authors found that while there was some evidence of selective concentration of this compound in melanomas, a more specific concentration occurred in the adrenals. They concluded that to obtain a therapeutic dosage of D.O.P.A.H_3 in a melanoma the gut would have to be exposed to excessive irradiation.

This type of technique is obviously still in its infancy, but may yet add a sensitive and effective weapon to the therapeutic armamentarium.

Just prior to the completion of this thesis a patient with recurrent melanoma has been given a therapeutic dose of H_3 tagged dihydroxyphenylalanine (Kerr, 1965). It is as yet too early to make any comment on the efficacy of this regime in this instance.

RESULTS

The presentation of the results of treatment of malignant disease and the analysis of the manifold clinical and pathological features which may influence such results pose certain problems. In the past there has been a wide variation in the methods and parameters used to assess such results. Such variation introduces certain obvious disadvantages. The main problem resulting from this situation is that results from different series are difficult, if not impossible to compare and the compilation of large volumes of quantitative information so necessary for a true understanding of the potentialities of diseases and of the effect of separate forms of treatment is hindered.

In the analysis of this material the survival information is presented in three ways.

1. The five year survival figures have been calculated in the manner suggested by MacDonald (1948). In broad terms the definitive population at risk for five year studies, the column headed "available five year follow-up" in subsequent tables, is calculated by subtracting patients dying of other diseases with no evidence of melanoma, patients alive, but not followed for five years after definitive treatment and patients lost to follow up from the total study population. The last mentioned group are included by some authors in the group of patients dying of melanoma. MacDonald (1948) is of the opinion that this produces a definite bias in result reporting and that a

more/

more accurate method is to exclude this group from consideration.

2. Five year survival figures are at best a random sample of the population under consideration. It has been shown repeatedly that a not inconsiderable number of patients with this disease die of the disease after five years. In order to present a true picture of the fate of groups of patients it has been considered necessary to compare graphically the proportion of patients surviving against the time from initial treatment. In preparing these graphs patients lost to follow up, patients dying of other diseases and followed up for relatively short periods of time are included in the population at risk for the period for which accurate information concerning their fate is available.

3. The three possible fates of patients, death from melanomatosis, death from unrelated disease and survival have been recorded according to the latest known status of the individual concerned at the time of writing.

Almost as important as the absolute survival figures are the patterns of metastasis exhibited by the patients under consideration. This information has been recorded where opposite.

Statistical analysis of the results has been carried out where the populations were considered large enough to warrant this. Populations were compared using the Chi-squared test and means compared using the t-test. Differences showing

a/

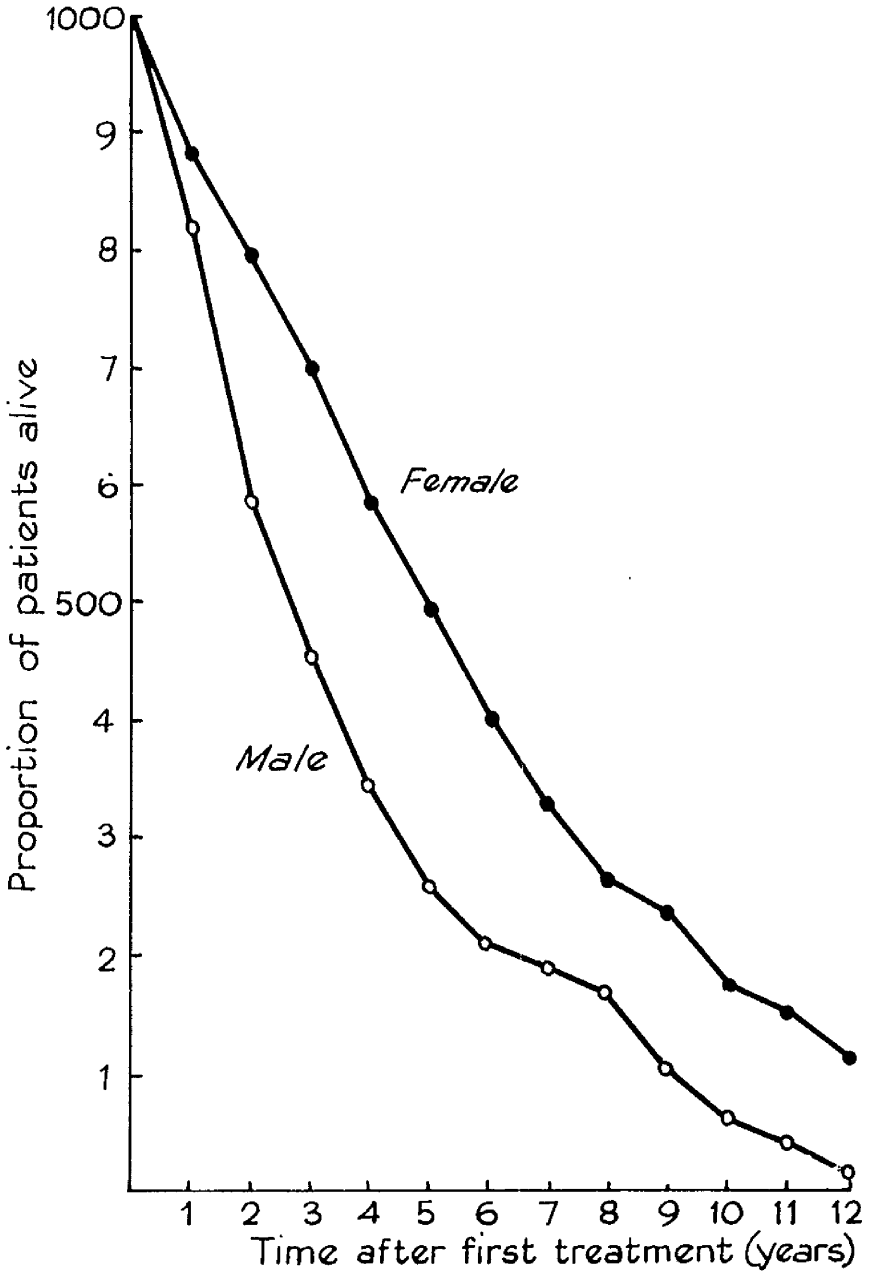

TABLE 16 showing the proportion of patients alive at varying periods after treatment. (Subdivided by sex.)

TABLE 26 SHOWING THE FATE OF PATIENTS WITH MALIGNANT MELANOMA AND THE INCIDENCE OF METASTASES (SUBDIVIDED BY SEX)

Sex	Total	Dead Melanoma		Dead Other Causes		Alive		Available 5 Year Follow up	Alive at 5 Years		Local Recurrence		Nodal Secondary		In transit Secondary		Disseminated	
		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Male	62	43	69.3	10	6.1	9	4.5	56	16	28.5	11	18.7	20	34.8	1	1.7	37	61.6
Female	104	42	40	24	23	38	37	80	48	60	30	29.4	26	25.5	7	6.85	41	40.0
Both	166	85	51.1	34	20	45	27	136	64	47.0	41	25.5	46	28.6	8	4.97	78	48.5

a value of P = 0.05 or less were considered statistically significant.

CLINICAL FACTOR AFFECTING SURVIVAL AND METASTASIS

1. SEX

Examination of Figure 16 and Table 26 reveals a very striking difference in the survival pattern and in particular in the 5 year survival rate of men and women with malignant melanoma. The 5 year survival rate for men is 26.5%, for women it is 60.0%. This difference is highly significant (P is less then 0.001).

There is no statistically significant difference in the incidence of regional nodal metastases between men and women. Disseminated disease developed in 61.6% of male cases and 40.0% of female cases. The difference between these two figures is statistically significant (P lies between 0.05 and 0.02). The number of cases in which in transit metastasis developed is too small for statistical analysis.

Examination of the literature on the effect of sex on prognosis reveals 2 groups of reports. Pack et al. (1952), Wright et al. (1959), Catlin (1954), Ochsner and Harpole (1959), Cade (1961), Charalambidis et al. (1962), Watson (1963) and Fortner et al. (1964) report that the survival rate of female patients is better than that in males. On the other hand Sylven (1949), Reven (1950), Lund and Ihmen (1955), Lane et al. (1958), and Block/

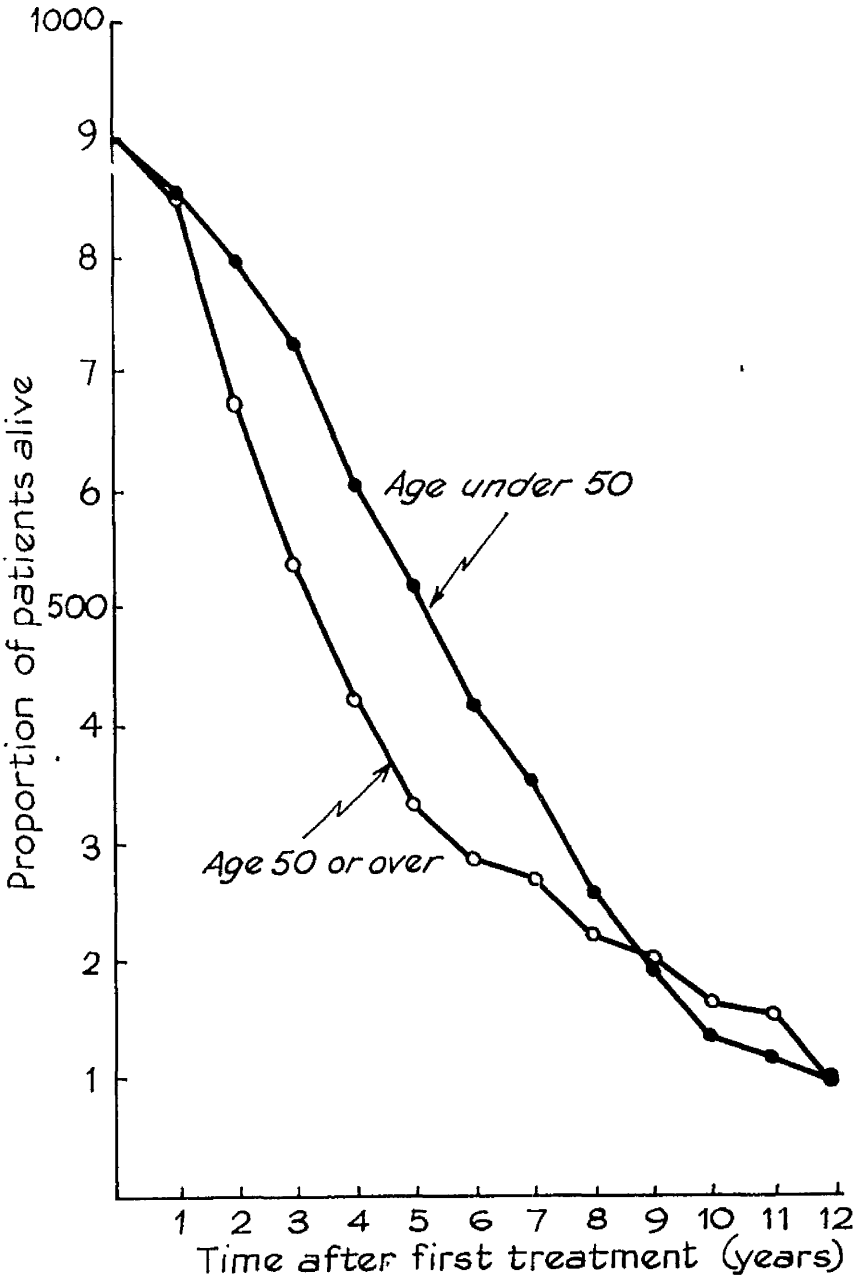

TABLE 17 showing the proportion of patients alive at varying periods after treatment (subdivided by age).

TABLE 27 SHOWING THE FATE, 5 YEAR SURVIVAL RATE AND THE INCIDENCE OF METASTASES IN PATIENTS (SUBDIVIDED BY AGE)

Age	Total	Dead Melanoma		Dead Other Causes		Alive		Available 5 Year Follow up	Alive at 5 Years		Local Recurrence		Nodal Secondary		In transit Secondary		Dissem-inated	
Group		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Under 50	68	34	50	5	7.4	29	42.7	61	39	59	16	25	17	26.6	3	4.7	32	50.
Over 50	98	51	52	29	29.6	18	18.3	75	28	37.4	24	24.8	29	29.9	5	5.15	44	45.4

Block et al. (1961), found no significant difference between the survival of men and women with this disease.

2. AGE

There is a statistically significant difference between the five year survival figure for patients under the age of 50 (59%) and that for patients over 50 (37.5%). Figure 17 and Table 27. P lies between 0.05 and 0.01. When the figures are further examined it is seen that there is a statistically significant difference between women under and over 50. P lies between 0.05 and 0.02. Women under 50 have a five year survival rate of 72%. The comparable figure for women over 50 is 42.8%. No significant difference in survival was demonstrated between men under 50 and men over 50.

Not surprisingly intercurrent deaths were more frequent in the older age group (29.6%) than in the younger patients (7.35%).

The incidence and pa tern of metastatic spread is similar in both groups.

TABLE 28/

TABLE 23 SHOWING THE FIVE YEAR SURVIVAL OF PATIENTS DIVIDED INTO DECADES

Age Range	Total	Indeterminate at 5 Years	Determinate Group	Alive at 5 Years	%ge Alive at 5 Years
Up to 29	14	1	13	8	61.5
30 - 39	21	1	20	10	50.0
40 - 49	33	5	28	18	64.2
50 - 59	25	-	25	7	28.6
60 - 69	37	7	30	13	43.3
70 - 79	18	9	9	3	33.3
80 - 89	18	7	11	5	45.5

When the patients are grouped by decades and their survival examined it is apparent that the 5 year survival rate decreases with increasing age. The increasingly unfavourable prognosis with advancing years had been noted previously by Wright (1949), Ochsner and Harpole (1959), Block and Shattuck (1961). Sylven (1949), Pack et al. (1952) and Lund and Ihnen (1955) noted no statistically significant difference in the survival of patients of different ages. Raven (1950) reported that the young die more rapidly than the old. This statement was not confirmed by the results from this series. The mean time from treatment to death was similar in all age groups. The value of this figure for women was 3.2 years and for men 2.2 years. In the previous series from this centre Wright et al. (1953) reported that the prognosis for women under the age of 50 was more favourable/

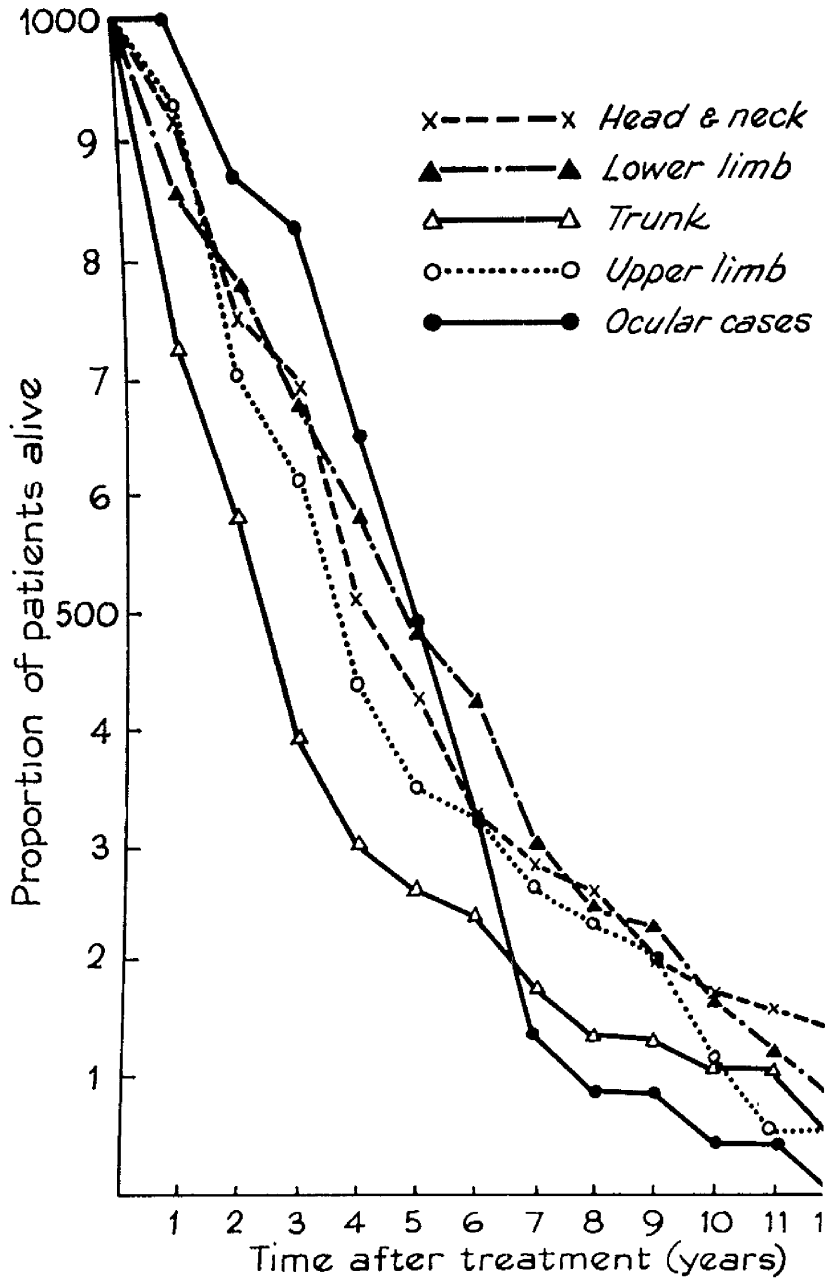

FIGURE 18 showing the proportion of patients alive at varying periods after treatment. (subdivided by site of primary tumours).

TABLE 29 SHOWING THE FATE, 5 YEAR SURVIVAL RATE AND INCIDENCE OF METASTASIS IN PATIENTS WITH TUMOURS IN VARIOUS SITES

Site	Total	Dead Melanoma		Dead Other Causes		Alive		Available 5 Year Follow up	Alive at 5 Years		Local Recurrence		Nodal Secondary		Intransit Secondary		Disseminated	
		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Head & Neck	53	22	41.5	18	34.0	13	24.6	38	20	52.5	14	26.5	9	17	2	3.8	22	41.5
Lower Limb	51	28	55.0	3	5.9	20	39.1	46	24	52.2	12	24.0	21	42	6	12.0	24	48.0
Trunk	27	19	70.5	6	22.2	2	7.4	24	7	29.2	7	26.0	9	33.3	-	-	19	70.0
Upper Limb	29	13	45.0	3	10.7	13	45.0	24	12	50.0	8	27.6	9	31.0	1	3.4	11	38.0
Ano-Genital	7	5	71.5	1	14.3	1	14.3	5	1	20.0	-	-	-	-	-	-	-	-
Occult	5	4	80.0	1	20.0	-	-	4	-	-	-	-	-	-	-	-	-	-
Sub-Ungual	10	6	60.0	1	10.0	3	30.0	9	3	33.3	-	-	-	-	-	-	-	-
Mucosal	5	4	80.0	-	-	1	20.0	5	1	26.0	-	-	-	-	-	-	-	-

favourable than that for other age groups. The results from this material confirm this statement.

3. SITE

From these figures, Table 29 and Figure 18, it seems likely that the site of the primary tumour is important in a consideration of prognosis. The 5 year survival rate for patients with tumours on the limbs or head and neck is very similar. The 5 year survival rate for patients with tumours arising on the trunk is considerably lower, but the difference between this value and the value for the limbs or head and neck is not statistically significant (P lies between 0.10 and 0.05). The number of patients with tumours on the anogenital area, mucosal surfaces, in the subungual tissues or with an untraced primary tumour is too low to allow statistical analysis. The 5 year survival figures available for tumours in these sites seem poor.

The incidence of local recurrences is similar in all regions. Metastatic spread to the regional lymph nodes occurs in a significally smaller number of cases with the primary tumour on the head and neck than in other areas. (P lies between 0.02 and 0.01). The overall incidence of nodal metastasis, 17%, is lower than those reported by Gerlin (1954), 45% and Krogh and Frich (1960), 49.6%. The former author noted that 44% of his patients with melanoma of the head and neck developed and died of haematogenous/

haematogenous spread melanoma. This figure is very similar to the 41.5% of patients in this material with head and neck tumours who developed disseminated melanomatosis. It seems likely that the visibility of these tumours and their cosmetic effects cause patients to seek earlier treatment than is the case with tumours on less obvious areas.

The number of examples of in transit metastases available for study is small. This type of secondary does occur significantly more often on the lower limb then elsewhere. (P lies between 0.02 and 0.01). It seems likely that the long lymphatic plexus which often exists between the primary site and regional lymph nodes in the lower limbs, the relatively sluggish lymphatic flow from these dependent parts and the lymph stasis following interruption of the lymphatic pathway by tumour in the regional lymph nodes or surgical excision of the lymph nodes are important factors in this context.

A significantly higher proportion (70%) of patients with primary tumours on the trunk developed disseminated melanomatosis than patients with tumours on other sites (41.5 - 45%). (P lies between 0.01 and 0.001). Factors concerned in this may be the relatively late presentation of patients with tumours on the trunk and the less predictable pathways of lymphatic spread.

The reported experience of previous authors shows some variation in regard to the prognosis of tumours arising on different/

different sites. Certain trends are apparent. The majority of authors regard the prognosis for tumours arising on the head and neck as relatively good, but Allen (1949) found this to be an unfavourable site. The trunk is generally regarded as an unfavourable site, but Charalambidis and Patterson (1962) found the prognosis of tumours on this site to be better than average. Tumours arising on the mucous membranes, external genitalia and occult primary tumours are generally regarded to have a very poor prognosis. This experience was borne out by the results in the small number of tumours on these sites in this series.

The prognosis of tumours arising in the lower and upper limbs was found to be relatively good in this series. There is considerable variation in opinion in the literature on this subject. Wright (1949), Lund and Ihnen (1955) and Rodenham and Lloyd (1963) found the upper limb to be a favourable site, but Catlin (1954) found the prognosis of tumours in this site to be relatively poor. Lund and Ihnen (1955) and Pack (1959) found the lower limb to be a favourable site while Catlin (1954) again found this to be an unfavourable area. Fortner et al. (1964) have subdivided the lower limb and report that tumours of the thigh and leg have a better prognosis than tumours of the toes, buttocks and flanks.

The prognosis for patients with subungual melanomas is generally regarded as quite good, Pack et al. (1952), Catlin (1954) and Lane et al. (1958). The number of patients available for study with tumours in this site is small. Of these 10 patients

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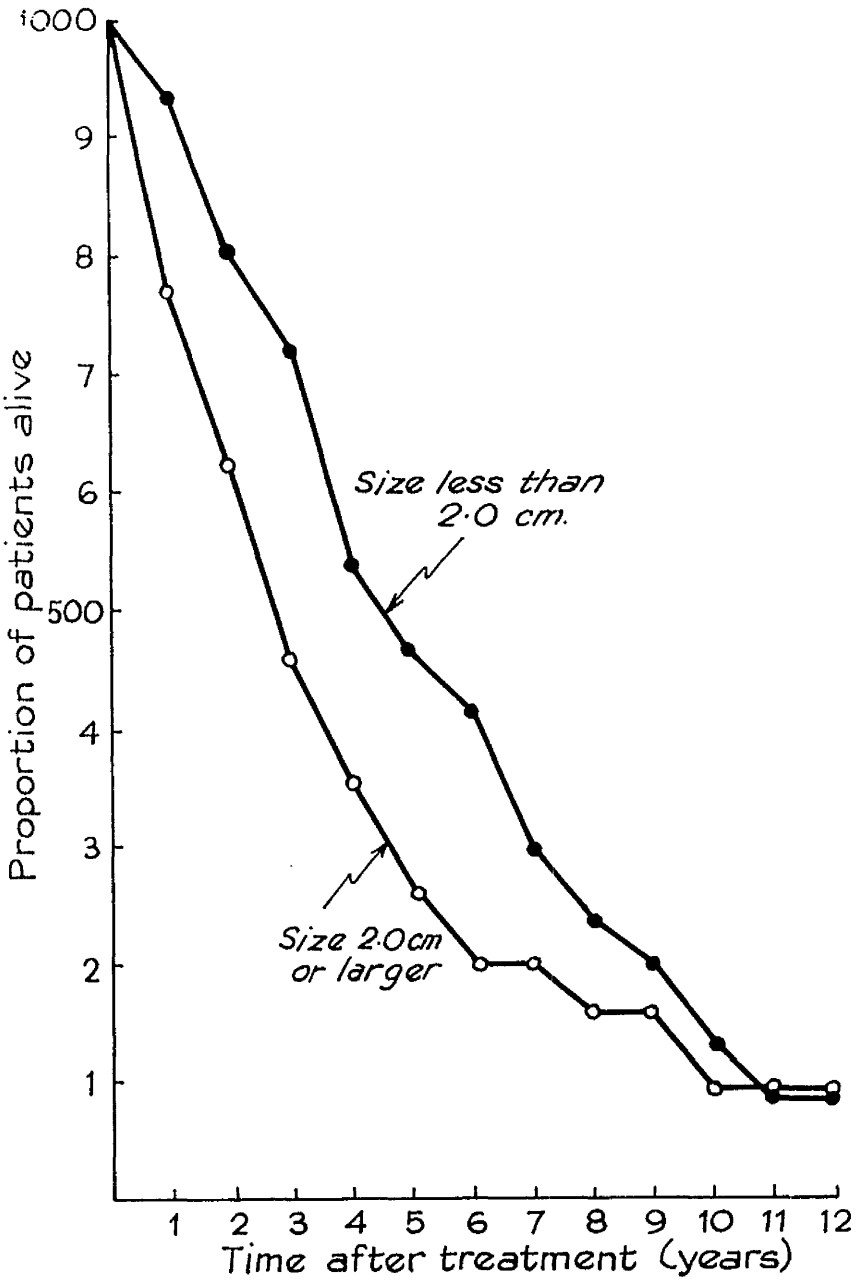


FIGURE 19, showing the proportion of patients alive at varying periods after treatment (subdivided by size of primary tumours).

TABLE 30 SHOWING THE FATE, 5 YEAR SURVIVAL RATE AND METASTASES OF PATIENTS GROUPED BY SIZE RELATIVE TO 2.0 cm.

Group	Total	Dead Melanoma		Died Other Causes		Alive		Available for 5 Year Follow up	Alive		Local Recurrence		Nodal Secondary		In transit Secondary		Disseminated	
		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Less than 2.0 cm.	70	27	38.5	14	20.0	29	41.5	52	31	59.6	16	22.8	15	21.5	5	7.15	27	38.5
Greater than 2.0 cm.	33	19	57.5	10	33.3	4	12.1	25	7	28.0	3	28.0	14	42.5	1	3.04	18	54.5

6 died of melanoma, 1 died of an unrelated condition with no evidence of melanoma and 3 are alive and free of disease. The determinate 5 year survival rate is 33.3% This compares unfavourably with tumours on other sites.

SUMMARY ON THE EFFECT OF SITE ON PROGNOSIS

1. Tumours on the head and neck and limbs have a similar relatively favourable prognosis.
2. Nodal metastasis occurs less frequently in the region of the head and neck.
3. In transit metastases occur most frequently in the lower limb.
4. The prognosis for tumours arising on the trunk is bad. A higher proportion of patients with tumours on this site develop disseminated disease and die of melanomatosis.
5. Tumours arising on the anogenital region, the mucous membranes, beneath the nail and occult primaries have a relatively poor prognosis

4. SIZE OF PRIMARY TUMOUR

The 5 year survival of patients with tumours less than 2.0cm. in diameter is 59.6%, Figure 19 and Table 30. This compares very favourably with the comparable figure for patients with tumours more than 2.0cm. in diameter, 28.0%. The difference between these figures is statistically significant (P lies between 0.01 and 0.001). There is also a statistically significant difference/

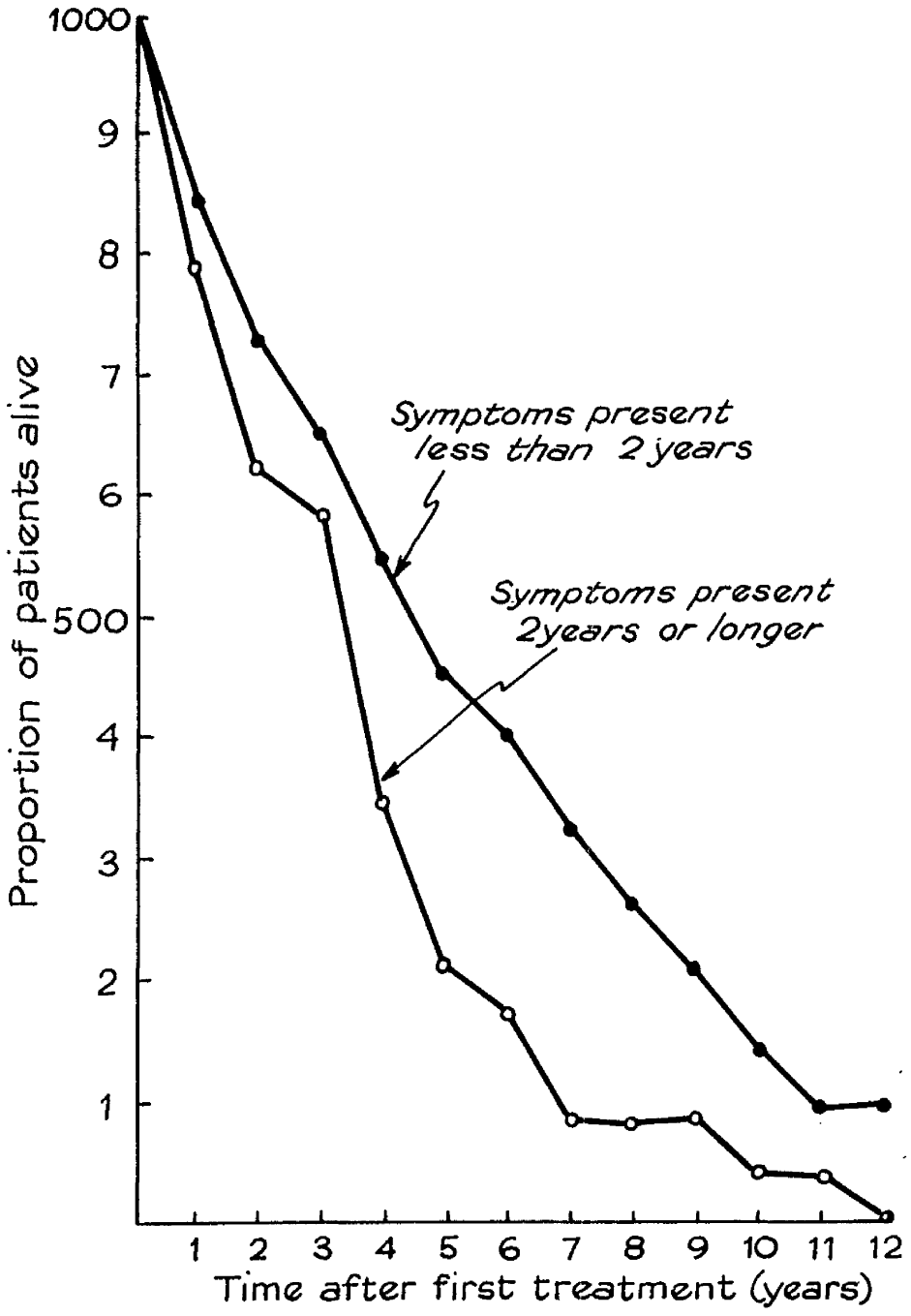


FIGURE 20 showing the proportion of patients alive at varying periods after treatment (subdivided by duration of symptoms prior to treatment).

TABLE 31 SHOWING THE FATE, 5 YEAR SURVIVAL RATE AND INCIDENCE OF METASTASES IN PATIENTS WITH SYMPTOMS OF VARYING DURATION

Group	Total	Died Melanoma		Died Other Causes		Alive		Available 5 Year Follow Up	Alive at 5 Years		Local Recurrence		Nodal Secondary		Intransit Secondary		Disseminated	
		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Less than 2 years	99	48	48.5	24	24.3	27	27.3	80	41	51.3	10	10.1	27	27.3	2	2.02	46	46.5
More than 2 Years	24	15	62.5	1	4.2	8	33.3	20	5	25.0	6	25.0	7	29.2	-	-	15	62.5

difference between the incidence of lymph node metastasis in these two groups, 21.4% of patients with the smaller tumours developed nodal involvement at some stage as against 42.3% of patients with the larger tumours. (P lies between 0.05 and 0.02). The apparent difference in the frequency of occurrence of local recurrences and disseminatedmelanomatosis are not significant. (P is greater than 0.05 in each case).

The effect of the size of the primary tumour on prognosis has been noted previously. Cade (1961) stated that larger tumours had a worse prognosis. Tompkins (1953), Lund and Ipnen (1955), Lane et al. (1958), Charalambidis and Patterson (1962) and Allen and Spitz (1953) were more specific and noted that tumours smaller than 2.0cms. have a better prognosis than those larger than this.

5. DURATION OF SYMPTOMS PRIOR TO FIRST HOSPITAL VISIT

Patients whose symptoms have been present for more than two years have a significantly worse 5 year survival from first treatment than patients whose symptoms are of shorter duration (P lies between 0.05 and 0.02), Figure 20 and Table 31. Local recurrences appear to be less common in patients with symptoms of relatively short duration, but the difference in incidence falls just short of statistical significance. (P is slightly greater than 0.05). Similarly there is an apparently lower incidence of disseminated melanomatosis in the patients with symptoms/

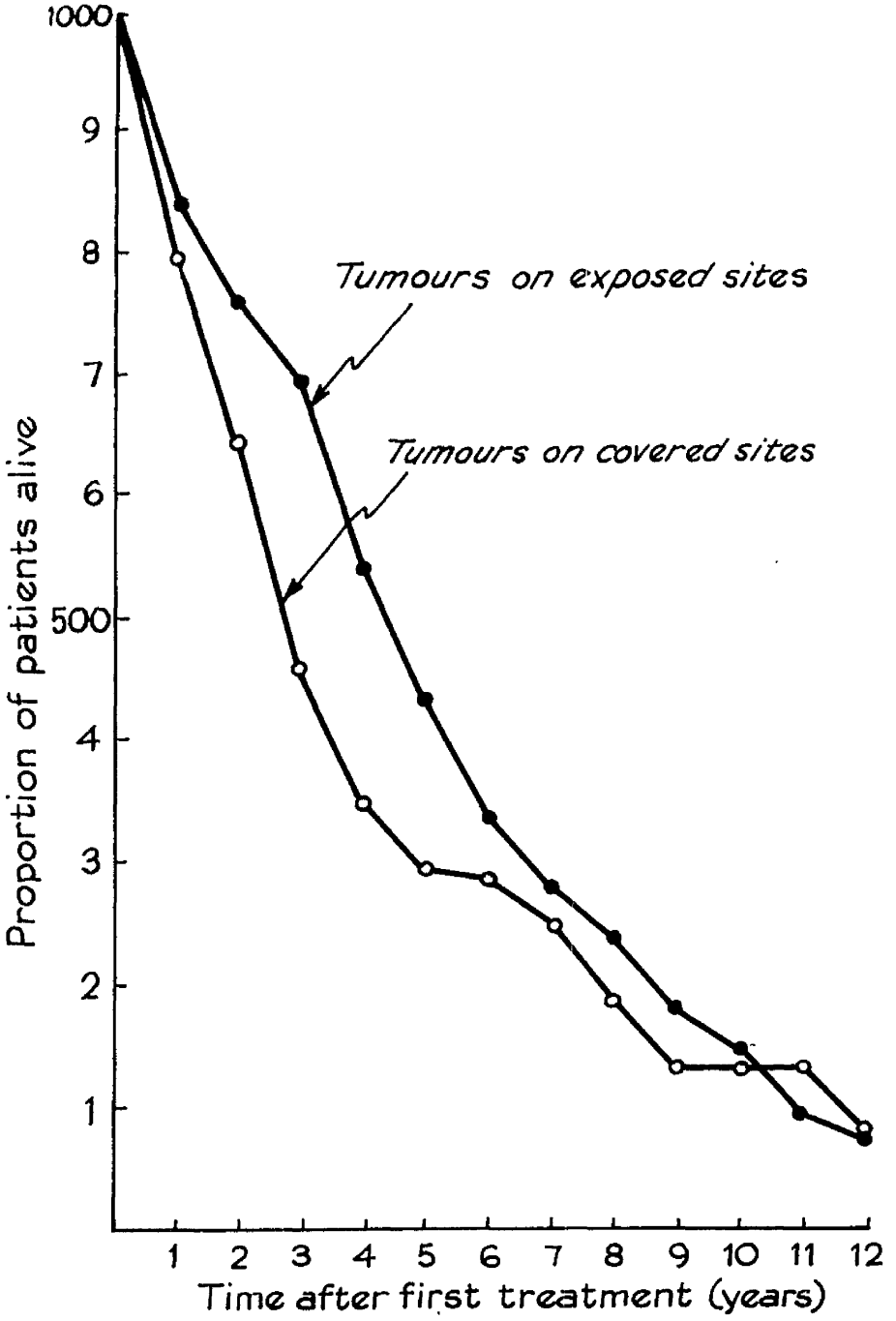


FIGURE 21 showing the proportion of patients with tumours on exposed and non-exposed sites alive at varying periods after treatment.

TABLE 32 SHOWING THE FATE, 5 YEAR SURVIVAL AND INCIDENCE OF METASTASES IN PATIENTS WITH TUMOURS ON EXPOSED AND NON-EXPOSED SITES

Group	Total	Dead Melanoma		Dead Other Causes		Alive		Available 5 Year Follow up	Alive at 5 Years		Local Recurrence		Nodal Secondary		In transit Secondary		Disseminited	
		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Exposed	76	29	38.3	21	27.6	26	34.2	57	32	56.1	17	22.4	20	26.6	4	5.3	31	41.4
Non-Exposed	61	40	65.5	9	14.8	12	19.7	53	17	32.0	10	16.4	24	39.4	2	3.2	39	64.0

symptoms of short duration, but the difference is certainly not significant (P lies between 0.2 and 0.1). Lund and Ibnen (1955) have also related the duration of symptoms and prognosis. They noted that patients whose symptoms had been present more than 6 months had a worse prognosis than those with symptoms of shorter duration.

6. SITUATION OF PRIMARY TUMOUR ON EXPOSED AND NON-EXPOSED SITES

It has been previously noted that there are certain differences in the mean age at tumour onset of patients with tumours on exposed and non-exposed (clothing covered sites), Watson (1963). It has been suggested that different aetiological factors may be concerned in the genesis of these two groups of tumours. Comparison of the 5 year survival rates of the two groups of patients shows a statistically significant difference. The 5 year survival rate of patients with tumours on exposed sites is 56.1%, that of patients with covered tumours, 32.0%. (P lies between 0.01 and 0.001). A smaller number of patients with tumours on exposed sites appear to develop disseminated melanomatosis. The incidence of dissemination in these patients (41.4%) is significantly different from that for patients with tumours on covered sites (64.0%). (P less than 0.05).

7. PATIENTS WITH AND WITHOUT A HISTORY OF A PREVIOUS PIGMENTED LESION AT THE SITE OF THE PRIMARY TUMOUR

The/

The 5 year survival and incidence of metastasis in these 2 groups of patients were noted to be similar. It must be concluded that the biological characteristics of tumours arising in proximity to a pigmented cutaneous lesion and those arising de novo from apparently unblemished skin are similar.

8. SURVIVAL OF PATIENTS WITH PIGMENTED AND NON-PIGMENTED PRIMARIES

No significant difference was noted in the 5 year survival or incidence of metastases in tumours noted clinically to be pigmented when compared with non-pigmented tumours. The biological characteristics of these 2 groups of tumours are noted to be similar.

9. SURVIVAL OF PATIENTS PREGNANT CONCURRENT WITH OR SUBSEQUENT TO THE DEVELOPMENT OF A MALIGNANT MELANOMA

Seven patients were pregnant at or around the time of development of a malignant melanoma in this series. The tumour was noted during the pregnancy by three patients and the pregnancy followed the excision of the primary tumour in four cases. The time interval between pregnancy and tumour development was from 1-5 years. The number of patients concerned is too small to allow any form of statistical analysis. Three of the 7 patients died of melanomatosis at periods varying from 4-7 years after initial treatment. The remaining 4 are still alive at periods from 3-9 years after treatment. Five of the 6 patients available for

5/

5 year study were alive on the fifth anniversary of their initial treatment. The incidence of metastasis is apparently similar to that of the whole study group. Three patients developed locally recurrent disease, 1 at least had lymph nodal involvement, 1 had intransit metastasis and 3 developed disseminated disease.

Up to the late 1950s it was generally held that the prognosis for a pregnant woman with malignant melanoma was worse than that for a non-pregnant woman and that the disease was more rapidly progressive in a pregnant woman. (Meyer and Gumport, 1953 and Pack and Scharnagel, 1951). George et al. (1960) reviewed a group of 115 patients with malignant melanoma associated with pregnancy. They concluded on the basis of this material that the prognosis for a woman with malignant melanoma coexisting with a pregnancy was no different from that for a non-pregnant woman. They also noted that melanomas in pregnant patients tended to be more advanced when first seen. White et al. (1961) in an examination of a smaller group of patients with melanoma and pregnancy reported that "No deleterious effect of pregnancy on the survival of a group of women with melanoma was demonstrated". Pelner (1961) in discussing this problem believed that "pregnancy acted as a growth stimulus for melanoma". He also noted "that more than an occasional instance of regression" had been seen after pregnancy. Allen (1955) reported an interesting example of regression after pregnancy. Watson (1963) reported no increase in malignancy of melanomas in pregnant women.

No/

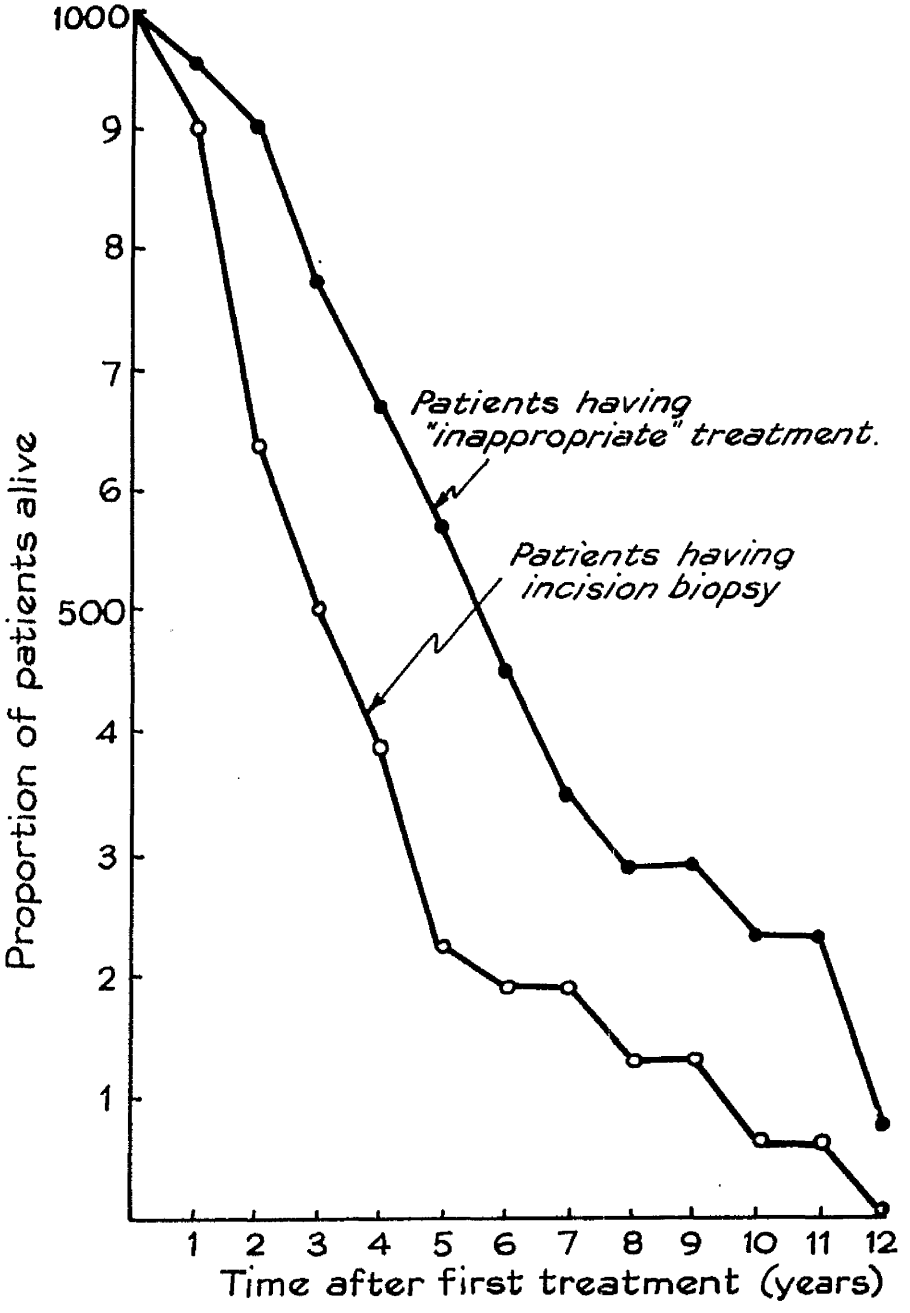


TABLE 22 showing the proportion of patients alive at varying times after inappropriate therapy or incision biopsy.

TABLE 33 SHOWING THE FATE, 5 YEAR SURVIVAL AND INCIDENCE OF METASTASIS IN PATIENTS HAVING INAPPROPRIATE THERAPY AND INCISION BIOPSY

Group	Total	Dead Melanoma		Dead Other Causes		Alive		Alive at 5 Years		Local Recurrence		Nodal Secondary		In transit Secondary		Disseminated	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Inappropriate Therapy	32	12	37.5	8	25	12	37.5	17	68.0	8	30.8	6	23.1	3	11.6	9	34.6
Incision Biopsy	20	12	60.0	4	20.0	4	20.0	4	27.0	8	40.0	8	40.0	-	-	10	50.0

No examples of spread from the mother to the foetus or placenta were noted in this material. At least 2 examples of the spread of maternal malignant melanoma to the foetus are recorded in the literature (Weber et al., 1930 and Dargeon et al., 1950). Placental involvement is almost equally rare (Bender, 1950).

Retik (1962) examined the effect of pregnancy on mice with Cloudman S91 melanoma. He reported that some inhibition of secondary tumour growth was noted. The same author (Retik et al., 1962) has noted that maternal tumour cells can pass through the intact placenta.

The impression gained from the patients in this study is that malignant melanoma is no more frequent in pregnant women than in the population as a whole. The prognosis appears to be essentially the same as that noted in the whole study group.

10. THE EFFECT ON SURVIVAL OF INAPPROPRIATE THERAPY AND INCISION BIOPSY

The delay and local trauma attributable to initially inappropriate therapy does not appear to have altered the prognosis of the group of patients concerned. Figure 22 and Table 33. The proportion of patients dying of melanoma, the incidence of metastases and the 5 year survival rate (68%), compare well with the results from groups of patients treated expeditiously by the currently/

currently accepted optimum modes of therapy. This finding is markedly at variance with the results reported by Tod (1944). This author reported that many (34%) of the deaths from malignant melanoma in her series were attributable to incorrect treatment. Pack et al. (1952) reported that a delay in treatment of more than 4 weeks was important. Preston et al. (1954) reported that failure to control the primary tumour lead to a worsening of the prognosis.

Patients who had an incision biopsy in this series did badly. Of 15 who had this form of treatment only 4 survived 5 years. This is a 5 year survival rate of 27%. It is not immediately apparent why this procedure, which was usually followed rapidly by more definitive treatment, should be associated with such a poor prognosis. Analysis of the cases concerned provides at least part of the answer. Fourteen of the 20 patients concerned were male. Fifteen of the patients had the primary tumours on relatively unfavourable sites, 3 on a mucous membrane, 5 subungually, 4 on the sole of the foot and 1 on the external genitalia. In 6 cases the regional lymph nodes were enlarged at the time of first treatment. The mean age of the patients was 65.7 years. The mean size of the primary tumour was 2.32cms. It appears from these figures that the group of patients having incision biopsy performed was composed of individuals whose prognosis was poor regardless of the form of therapy employed. It is possible, however, that local hyperaemia, altered tissue pressures and the increased lymphatic flow consequent upon operative trauma may well hasten/

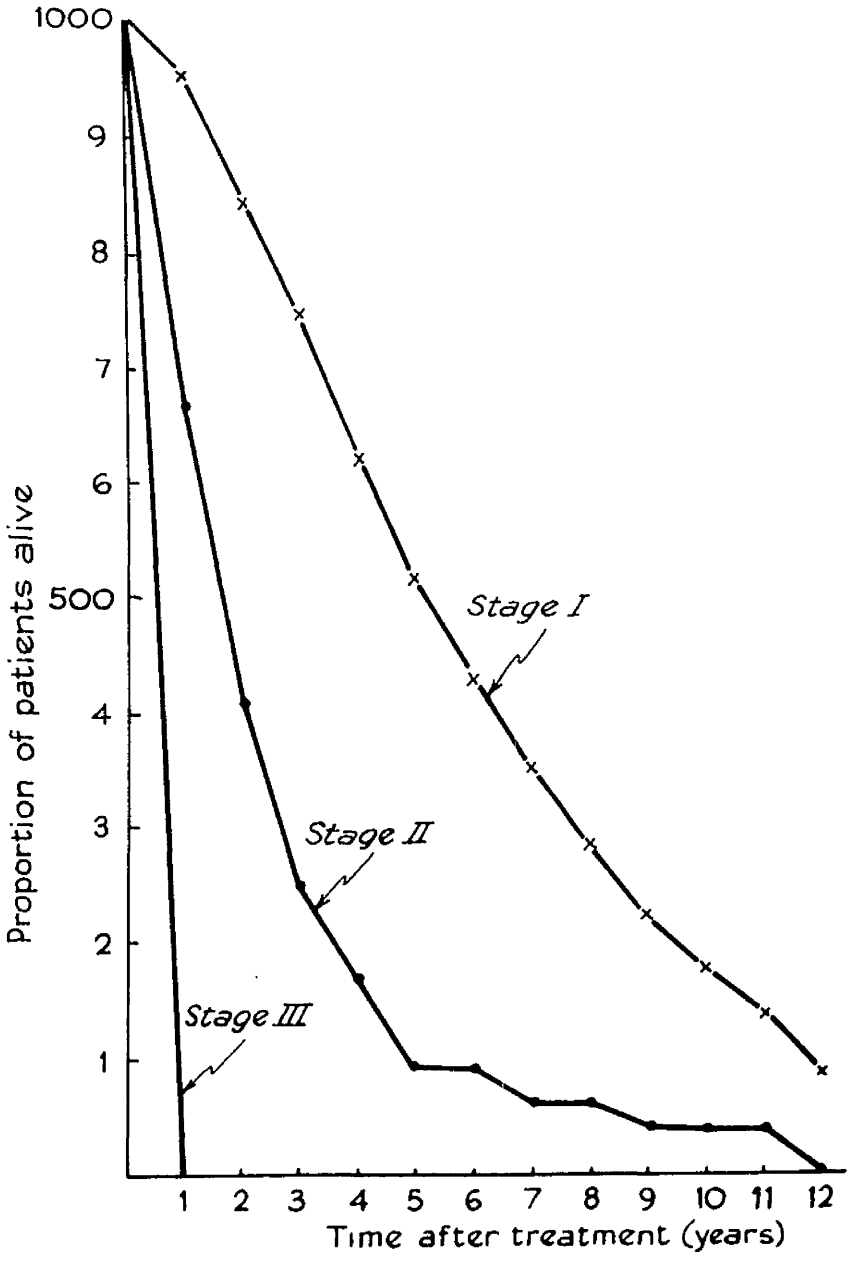


FIGURE 23 Showing the proportion of patients alive at varying periods after treatment (subdivided by clinical stage).

TABLE 34 SHOWING THE FATE, 5 YEAR SURVIVAL RATE AND INCIDENCE OF METASTASES IN PATIENTS SUBDIVIDED BY CLINICAL STAGE

Stage	Total	Dead Melanoma		Dead - Other Causes		Alive		Available 5 Year Follow Up	Alive at 5 Years		Local Recurrence		Nodal Secondaries		Intransit Secondaries		Disseminated	
		No.	%	No.	%	No.	%	No	No.	%	No.	%	No.	%	No.	%	No.	%
I	122	*46	37.7	28	23.0	44	36.1	95	57	60.0	24	19.7	30	24.5	6	4.9	44	36.1
II	37	32	89.0	2	5.5	2	5.5	34	4	11.8	-	-	37	100.0	-	-	32	89.0
III	4	4	100.0	-	-	-	-	4	-	-	-	-	-	-	-	-	4	100.0
ALL	163	82	50.4	30	18.4	46	28.2	133	61	45.9	24	14.7	67	41.0	6	3.7	80	49.0

*In four cases follow up information is incomplete.

hasten the extension of tumour cells from the primary sites.

11. SURVIVAL IN RELATION TO CLINICAL STAGING OF DISEASE AT THE FIRST VISIT

Of the 122 patients with stage I disease, 58 (47.5%) have remained free of disease for periods between 3 and 20 years. Figure 23 and Table 34. Thirty (24.5%) developed tumour metastases in the regional lymph nodes. The tumour recurred or a new primary malignant melanoma arose in or adjacent to the site of excision of the primary tumour in 24 patients (19.7%). Six patients (4.9%) developed subcutaneous secondary tumour deposits between the primary site and the regional lymph nodes, the so-called "in transit metastases". Forty-four patients (36.1%) went on to develop disseminated melanomatosis. This event was preceded by regional nodal metastasis in 30 patients. This latter figure is probably low since the terminal care of those patients was generally undertaken outwith the hospital and exact information as to the distribution of the tumour at death is not available in a number of cases. Twenty eight patients (23%) are stated to have died of disease unrelated to malignant melanoma with no clinical evidence of recurrent melanoma.

The 5 year survival figure for the 95 stage I patients available for 5 year study is 60%.

Analysis of the stage II cases reveals a less satisfactory situation. Thirty two of the 37 stage II patients

died of melanoma (69%). Only one of these patients survived for more than 5 years. Of the remaining 4 patients, 2 are alive with no evidence of recurrent disease 54 and 147 months after initial treatment and two have died of unrelated causes with no evidence of recurrent disease 48 and 96 months after treatment.

The 5 year survival figure for stage II cases is thus 11.8%.

All 4 stage III patients died of melanomatosis. The longest survival after diagnosis was 9 months.

The clinical stage of the disease is thus of the utmost significance in the assessment of prognosis. Patients with localised disease have a good prognosis for survival relative to patients with extended malignant melanoma and other forms of malignant disease.

This very basic fact has been noted by numerous previous authors, Sylven (1949), Bodenham et al. (1963), Preston et al. (1954) and Lane et al. (1958).

TABLE 35/

TABLE 35 SHOWS THE COMPARABLE SURVIVAL FIGURES REPORTED BY SOME PREVIOUS AUTHORS FOR PATIENTS WITH AND WITHOUT CLINICAL EVIDENCE OF NODAL METASTASIS

Authors	%ge 5 year survival of patients with clinically negative nodes.	%ge 5 year survival of patients with clinically positive nodes
Daland & Holmes (1939)	25.0	8.0
Ochsner & Harpole (1962)	86.0	47.0
Lund & Ihnen (1955)	44.7	3.1
Pack et al. (1952)	40.5	4.1
McNeer (1961)	40.5	14.1
Catlin (1954)	"almost" 100%	10.0
Hellwig (1963)	75.0	25.0
Gumport (1962)	50.0	13.0
This Series	60.0	11.8

METASTASIS IN MALIGNANT MELANOMA

The ability of this tumour to spread widely and seed in almost any organ is well known. This curious aggressive property is not surprising when it is realised that the stem cell of the tumour is already a highly successful symbiont, derived from the transient embryonic neural crest and located in adult life in the very specialised milieu of the dermo-epidermal junction. The magnitude of the clinical problem posed by this unfortunate attribute is clearly seen when the overall results of this series are/

are analysed. 108 patients out of the total of 192 with primary melanomas of the skin, mucous membranes and eyes developed metastases. This is an incidence of rather more than 1 in 2 (56.3%).

Several seperate but closely related clinical problems exist in the management of this facet of the disease.

1. The prevention of the occurrence of metastasis in patients whose disease process is clinically limited to the primary tumour when first seen.
2. The management of stage I patients who, despite attempts at eradication do develop recurrent or metastatic disease.
3. The management of patients who present initially with disease spread beyond the local lesion.

These are problems of the greatest importance and merit much attention. The large volume of literature on this subject reflects the awareness of clinicians and pathologists of the enormous significance of this aspect of cancer therapy. It is regrettable that, despite the mass of information available and the great effort expended, the results of treatment of malignant melanoma which has spread beyond the immediate area of the primary tumour are very poor and have shown little improvement over the past fifty years.

The opportunity has, therefore, been taken of analysing the patterns of metastasis and the prognostic significance of recurrences and metastases in relation to their type, time of development,/

development, antecedent therapy and methods of attempted control.

As noted above metastatic or recurrent disease developed in 108 out of 192 patients. The regional lymph nodes were involved in 64 cases (33.6% of all cases). Cutaneous recurrence and/or metastasis occurred in 35 cases (18.4% of all cases). This figure includes recurrences in and around the primary excision site, whether adjudged histologically to be new primary tumours or subepidermal secondary deposits and "in transit" subepidermal deposits in the superficial dermal lymphatics between the primary site and the regional lymph nodes, but NOT the subepidermal secondary deposits seen in terminal patients with disseminated disease. Widespread dissemination of the disease occurred in 81 cases (42.6% of all cases). From these figures it appears that in 64 of the 81 (79%) cases in which dissemination eventually developed the regional lymph nodes were involved prior to dissemination. This is the classically described metastatic pattern of malignant melanoma and is undoubtedly that most frequently encountered. There does, however, remain a small group in which dissemination occurs without prior clinical involvement of the regional nodes, presumably by haematogenous spread. This would appear to have occurred in 21% of the cases of this series which developed disseminated disease. This figure is undoubtedly high since the clinical information available on the terminal stages of disease in some of the patients is inadequate.

Despite the absence of clinical evidence of extended disease/

TABLE 36 ANALYSIS OF METASTATIC PATTERNS IN PATIENTS WITH CUTANEOUS STAGE I MALIGNANT MELANOMA

	No.	%ge of Stage I	Five Year Survival After first Treatment	Time from First treatment to development of secondary m	Range in months	Time from Development of Secondary to Death	Range	%ge surviving 5 Years after Development of Metastasis
Total No. of Stage I Melanomas	122	100	60	-	-	-	-	-
No. Developing Regional Nodal Metastasis	30	24.5	36.7	$\bar{m}$ = 25.9	3-120	$\bar{m}$ = 18.8	1-78	20.7
No. Developing Cutaneous Secondaries	24	19.7	75	$\bar{m}$ = 30	3-120	$\bar{m}$ = 28.6	7-84	47.5
No. Developing Disseminated Disease	43	36.1	25.3	$\bar{m}$ = 28	1-156	$\bar{m}$ = 5.65	1-52	NIL
No. Developing In transit Metastases	6	4.9	50	$\bar{m}$ = 34.5	6-84	$\bar{m}$ = 41	4-60	25

disease at the time of initial treatment 64 (52.5%) of 122 Stage I patients subsequently developed metastatic disease, Table 36.

1. Regional Nodal Metastasis

Tumour developed in the regional nodes of 30 patients (24.5% of all Stage I). The nodes were noted to be involved at an average of 25.9 months after the initial treatment. There is, however, wide variation in this time with a minimum intervening period of one month and a maximum of 10 years. The development of this form of metastasis is of grave significance and the average survival, after the development of nodal metastasis, of this group was 18.8 months (range 1 to 78 months). Eighty three point five per cent of these 24 patients died of melanometosis and only 6 of 29 on whom complete follow up information is available lived for 5 years after developing nodal metastasis. Four patients are alive at periods of 16, 78 and 102 months and 20 years after having excision of clinically and microscopically involved lymph nodes. One patient survived 7 years and died of cerebral degeneration and hypertension.

The development of regional nodal metastasis reduced the 5 year survival rate of this group to 20.7%, a figure similar to that of patients with clinically involved regional nodes at the time of first treatment i.e. Stage II (11.8%). The difference between these survival rates is not statistically significant (P = 0.5 - 0.3).

2. Local Cutaneous Metastases and Recurrences

Twenty four patients (19.7%) developed recurrent or locally metastatic subepidermal deposits in and around the site of the primary excision. This form of disease manifested itself on average 30 months after primary excision (range - 1-120 months).

The development of this type of metastasis does not seem to have as serious a significance as the development of nodal metastases or dissemination. The 5 year survival rate from first treatment for this group is 75%. Statistical comparison of this figure and the comperable one for patients developing nodal metastases (36.7%) shows a high degree of statistical significance in the difference between the 2 figures (P lies between 0.01 and 0.001). Thirteen (54.1%) patients of this group died of melanoma. Analysis of the survival of this latter group shows two distinct groups. Seven of the 13 died less than 15 months after developing cutaneous disease ($\bar{m}$ = 10.43 months, range 7 - 15 months). The remaining 6 survived longer before succumbing to the disease ($\bar{m}$ = 62.6 months, range 48 - 73 months).

Of the remaining 11 cases 4 are alive, free of disease at periods of 9, 9, 12 and 15 years after initial treatment. The remainder died of other causes, free of melanoma.

The figure for survival for 5 years after the development of cutaneous recurrences (47.5%) shows a significant difference from the/

the comparable figure for nodal metastasis (20.7%).

3. In transit Metastases

The number of such metastases is small. Three cases, not initially stage I, are included to allow analysis.

Nine cases developed subepidermal tumour deposits between the site of excision and the regional nodes. This represents 5.4% of all cutaneous and mucosal cases. The 5 year survival after first treatment in this group is 43%. It has been suggested that lymph stasis distal to a lymphadenectomy favours the development of this type of metastasis. In this series the appearance of in transit metastases was preceded by operation on the regional nodes in 6 out of 9 cases (66.7%). Nodal dissection was undertaken in 57 instances and in transit metastases developed in 6 cases - i.e. in 10.5%. Recurrent tumour developed in the seat of the nodal dissection in 14 of the 57 nodal resections - i.e. in 25%.

The number of cases available for study is small, but it seems that the appearance of this type of secondary is a rather serious prognostic sign. The mean period of survival after development of this type of secondary is only 11.5 months (range 3 - 28 months). Only 1 of 6 patients available for five year follow up survived this period. The important factor in the determination of the unhappy significance of this type of metastasis is undoubtedly the frequent coexistence of nodal involvement.

4. Disseminated/

4. Disseminated Melanomatosis

This is the terminal stage of most melanomas in which the disease may literally involve every organ and tissue in the body. Forty four (36.1%) of the stage I cases developed disseminated disease. The figures analysed include cases initially of stage II going on to develop dissemination. This gives a total of 80 cases for study. Analysis of the 44 initially stage I cases shows the survival rate for the 5 yearsfollowing initial treatment to be 25.3%. The mean interval between initial treatment and dissemination of the disease was 28 months (range 1 - 15 months). Thirty nine of the 80 (48.5%) patients had nodal involvement preceding dissemination. In this group the mean time between involvement of the regional nodes and dissemination was 13.1 months (range 1 - 80 months). 64% developed disseminated disease less than one year after nodal enlargement and 84% in less than two years. The development of disseminated disease is of the most sinister significance. The mean survival after clinically manifest dissemination is observed, being 2.8 months. If a few exceptional cases surviving for periods over 15 months are included the mean survival only rises to 5.65 months. The stark fact is that after developing disseminated melanomatosis 71% are dead within 6 months, 84.15% within 1 year and 95.4%within 15 months.

The Pattern of Metastatic Deposits in Cases coming to Post Mortem

The/

TABLE 37 SHOWING THE DISTRIBUTION OF METASTASES IN 16 CASES COMING TO POST MORTEM AND A COMPARISON WITH THE REPORTED INCIDENCE IN PREVIOUS SERIES

Site	Number with Metastasis in Site		%ge of Group at Risk	Comparative Figures		
	Male	Female		Henrix	Ponka et al.	Howes et al.
Brain	-	5	31.2%	27.8%	-	9.6%
Meninges	-	1	6.25%	29.4%	45.5%	-
Subcutaneous Deposits	3	6	56.2%	41.2%	59.0%	-
Thyroid	-	-	-	13.7%	-	-
Lung Parenchyma	3	4	46.7%	62.7%	81.8%	25.0%
Myocardium	1	3	26.7%	35.3%	45.5%	-
Pericardium	2	1	20.0%	7.8%		-
Stomach	-	2	13.3%	-	-	-
Liver	3	7	66.7%	56.7%	77.8%	15.8%
Kidneys	2	1	20.0%	23.5%	31.7%	-
Spleen	-	3	20.0%	25.5%	-	-
Small Bowel	2	1	20.0%	-	-	-
Testis	1	N/A	20.0%	10.3%	-	-
Ovaries	N/A	2	18.4%	13.6%	-	-
Pancreas	3	-	20.0%	17.6%	54.5%	-
Bone & Bone Marrow	-	4	26.6%	47%	45.5%	18.6%
Lymph Nodes	2	7	60.0%	68.5%	91.0%	-
Adrenals	3	5	50.0%	47%	31.7%	-
Posterior Abdominal Wall	1	1	13.6%	[illegible]	-	-
Uterus	N/A	1	9.2%	4.5%	-	-

The majority of patients dying of malignant melanoma do so at home. The number of post mortem examinations available for study is, therefore, small. Sixteen are in fact available, 13 from the decade under study and 2 from the year immediately prior to the study period and 1 from the period subsequent. In all but 2 cases the necropsies were performed in the Western Infirmary. The histological material has been obtained for study in the case of the two necropsies performed elsewhere.

In view of the small number of cases it has not proved possible to delineate any specific route of spread from the various sites or to note patterns of organ involvement. The liver, involved in 66.7% of cases, the various lymph node groups (60%), the subcutaneous tissues (56.2%), the adrenal glands (50%) and the lung parenchyma (46.7%) are most frequently involved. The adrenals are particularly noteworthy in view of their small volume and blood supply relative to the larger viscera. Onuigbo (1961, 1964) in this Department noted a very high incidence of adrenal metastases, 39.9% in a study of 12,000 bronchial carcinomas.

In the 2 cases in which the original tumour was situated in the eye and which came to autopsy, it is of interest to note that the metastases occurred in the liver alone in 1 and in the liver and pancreas in the other. This finding agrees with the analysis of 51 post mortems by Hendrix (1963). This is in contrast with cutaneous primaries where there are usually secondary deposits in many organs. The relatively high incidence of

metastases/

FIGURE 24(a) Showing metastatic malignant melanoma in a kidney

FIGURE 24(b) Showing a polypoid secondary malignant melanoma of the small intestine

FIGURE 24 (c) Showing metastatic malignant melanoma in an ovary

FIGURE 24(d) Showing an intussusception caused by a polypoid tumour like that seen in Figure 24(b)

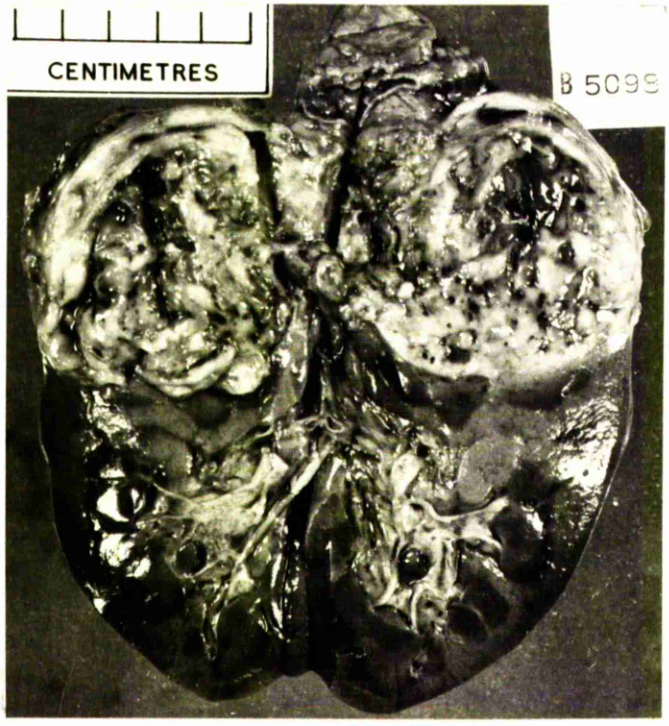


FIGURE 24(a)

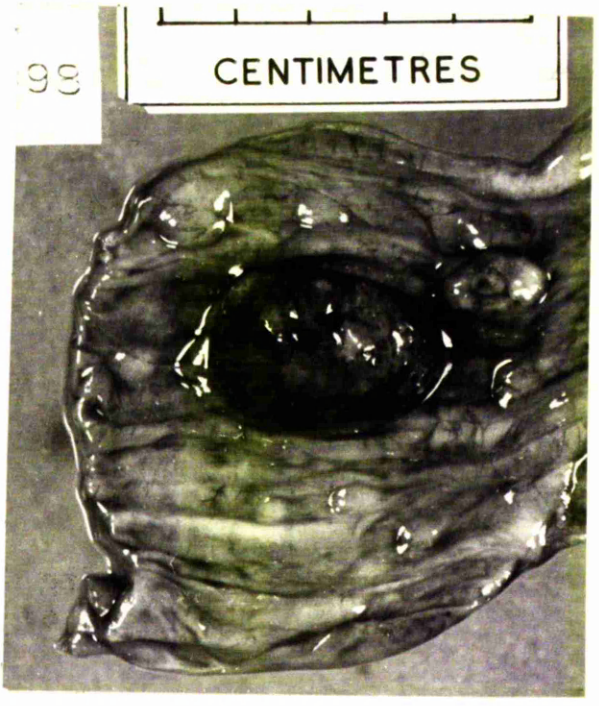


FIGURE 24(b)

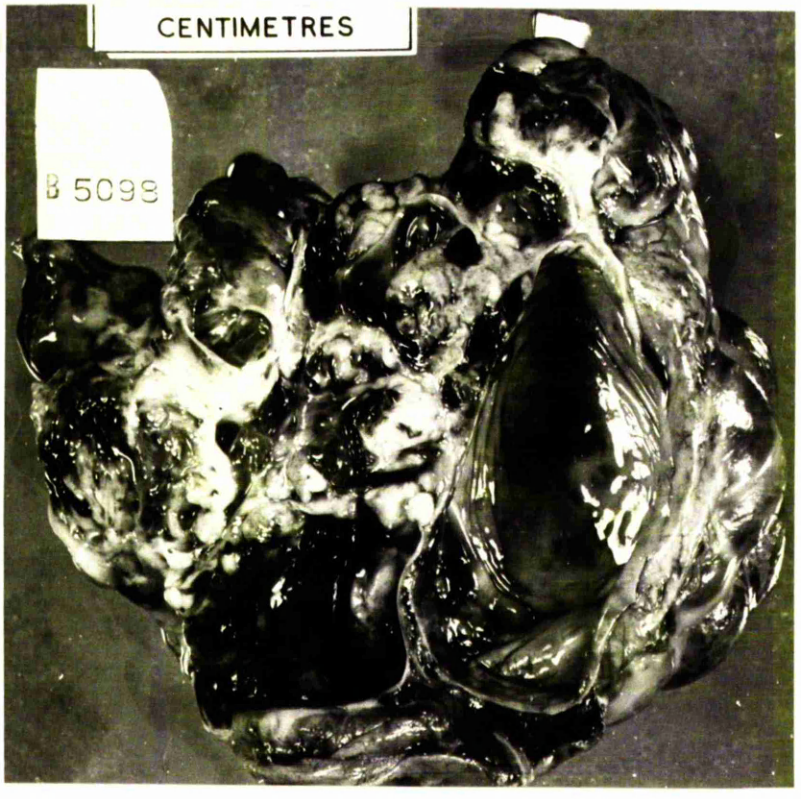


FIGURE 24 (c)

FIGURE 24 (d)

metastases to the heart and pericardium (33.3%) is worthy of note. It is now realised that secondary tumour in the heart is by no means as uncommon as was once believed (Moragues, 1939, Lefkovits, 1948). Goudie (1955), in this Department, found metastatic tumours in the heart and pericardium of 10% of all patients dying of malignant disease. The incidence in the present small series of necropsies is still surprisingly high. Moragues (1939) reports that in none of his 4 cases was cardiac involvement suspected clinically. This is true of the 5 cases reported from this material. For a cardiac metastasis to declare itself clinically seems rare (Goudie, 1955). The report by Denkewalter and Klassen (1957) of a case in which a deposit of malignant melanoma caused symptoms similar to mitral stenosis is, therefore of special interest.

The distribution of metastases encountered in this material is very similar to that reported by Hendrix (1963) and Ponka et al. (1958). There are, however, certain marked differences from the figures quoted by Howes and Birnkrant (1943). Since it is not clear in what manner the latter figures were arrived at they are not strictly comparable.

Figure 24 shows specimens from a recent post mortem examination of a woman who died of melanomatosis. The cause of death was obstruction due to two separate jejunal and ileal intussusceptions (Figure 24(d) at the leading edge of which were polypoid/

polypoid tumours similar to that illustrated in Figure 24(b). The secondary tumour in the ovary presented a considerable diagnostic problem by simulating the naked eye appearance of a cystadenocarcinoma of ovary. Histological examination left no doubt as to its true nature.

THE HISTOLOGICAL FEATURES OF MALIGNANT MELANOMA AND THEIR RELATION TO THE ASSESSMENT OF PROGNOSIS

The histology and cytology of malignant melanoma has been described by many previous authors and attempts have been made to relate the varied appearances to prognosis. With a few exceptions such attempts have failed. Such a correlation would have inestimable value in the management of this most difficult disease, but over the years has become something of a histologists' "philosophers' stone". Critical and close examination of the abundant literature on this matter has revealed certain positive observations and the existence of such reports plus the availability of a statistically valid group of cases suggested that a close examination of the histological material might be not unrewarding.

In the assessment of the fate of individual patients the same criteria are used as in the section correlating clinical factors and prognosis. Figures are available for all populations but are recorded only where statistically significant variations were noted. The population at risk varies from group to group because the histological material available in some cases was regarded as inadequate for the accurate assessment of specific features.

1. Depth of Dermal Invasion

Allen and Spitz (1953), Lund and Ihnen (1955), Krogh et al. (1960), Block and Shattuck (1961) and Rodenhan and Lloyd (1963) have noted that the more superficially situated malignant melanomas/

TABLE 38 SHOWING THE FATE, 5 YEAR SURVIVAL RATE AND INCIDENCE OF METASTASIS IN PATIENTS WHOSE TUMOUR LAY ABOVE AND BELOW THE EPIDERMAL APPENDAGES

Relation to the Epidermal Appendages	Total	Dead Melanoma		Dead Other Causes		Alive		Available 5 Year Follow Up	Alive at 5 Years		Local Recurrence		Nodal Secondaries		Intransit Secondaries		Disseminated	
		No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Above	67	24	35.8	14	20.9	29	43.3	51	27	53.0	9	13.4	17	25.4	2	3.0	24	35.8
Below	56	31	55.4	14	25.0	11	19.4	43	17	39.5	10	17.9	16	28.6	3	5.3	32	57.2

melanomas have a rather better prognosis than those penetrating more deeply into the dermis. Allen and Spitz (1953) describe this type of tumour in great detail and regard it as almost a separate entity. Bodenham and Lloyd (1963) used the depth of dermal invasion as a basis of histological staging and reported that the prognosis worsened with increasing depth of dermal invasion. Wright (1949), on the other hand, reported that the depth of local infiltration was of no prognostic value.

A slightly different, rather simpler approach to this problem was adopted in the analysis of the present material. Tumours were grouped according to whether or not the deepest point reached by the tumour lay above or below the lowest level of the epidermal appendages.

The tumour lay above the level of the epidermal appendages in 69 cases, below in 58 cases, while in 34 instances the histological material available did not allow accurate assessment of the depth of invasion of the tumour. Statistical analysis of the figures in Table 38 shows no significant difference in the 5 year survival of the 2 groups (P lies between 0.1 and 0.2) but there is a statistically significant difference between the proportions of patients in each group dead of melanoma at the end of the study period (P lies between 0.05 and 0.02) and those alive at the end of the study period and free of recurrent melanoma (P lies between 0.01 and 0.001). The development of disseminated melanomatosis was noted to occur significantly more frequently/

FIGURE 25(a) Showing a malignant melanoma with cells arranged in sheets. H. and E. (x 200).

FIGURE 25(b) Showing a malignant melanoma with cells arranged in sheets. H. and E. (x 500).

FIGURE 25(c) Showing a malignant melanoma with cells arranged in packets. H. and E. (x 500).

FIGURE 25(d) Showing a malignant melanoma with cells arranged in packets. H. and E. (x 350).

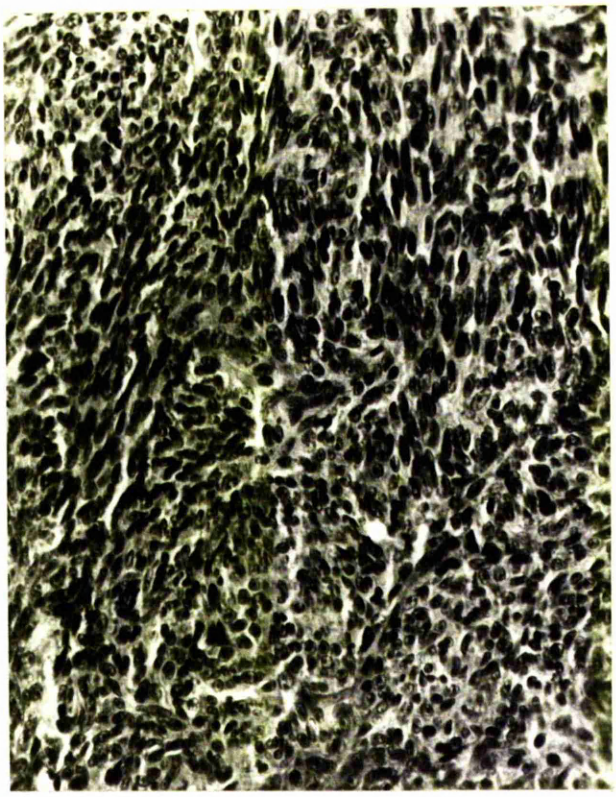


FIGURE 25(a)

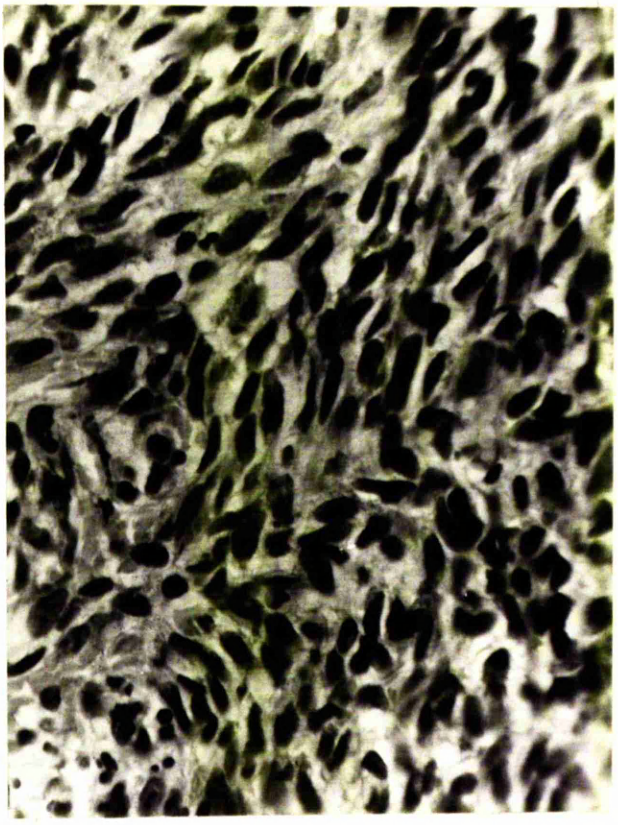


FIGURE 25(b)

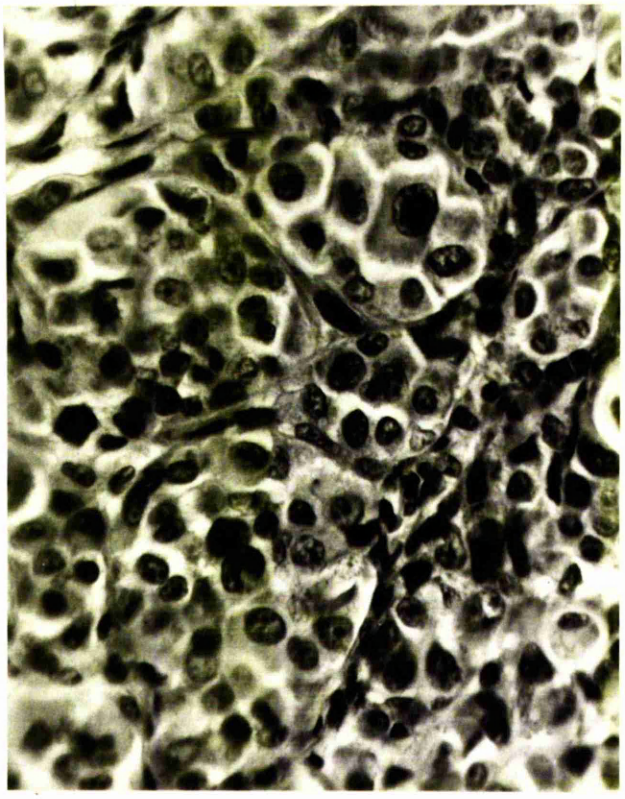


FIGURE 25(c)

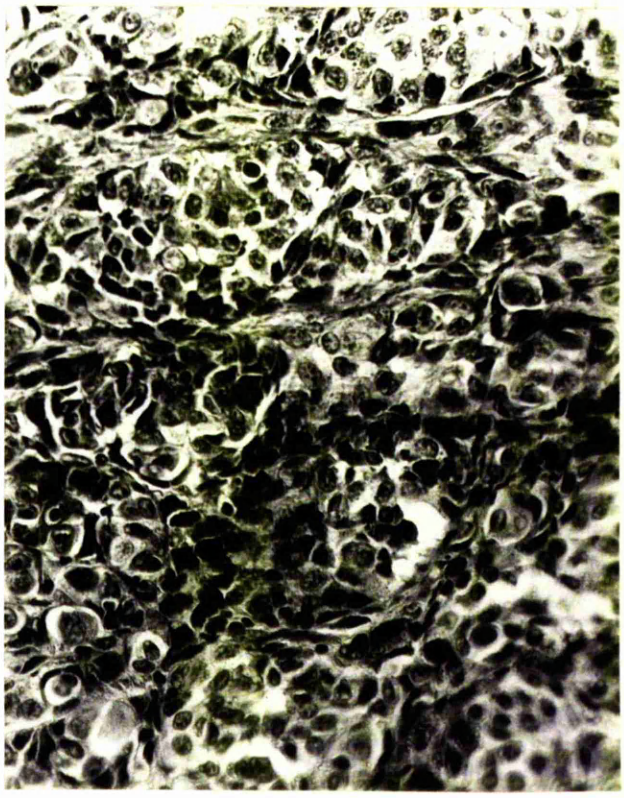


FIGURE 25 (d)

FIGURE 26(a) Showing a malignant melanoma with the cells arranged in trabeculae. H. and E. (x 500).

FIGURE 26(b) Showing a malignant melanoma with the cells arranged in pseudo-alveoli. H. and E. (x 350).

FIGURE 26(c) Showing a malignant melanoma with the cells arranged in pseudo-alveoli. H. and E. (x 500).

FIGURE 26(d) A malignant melanoma showing a "fenestrated" pattern. H. and E. (x 150).

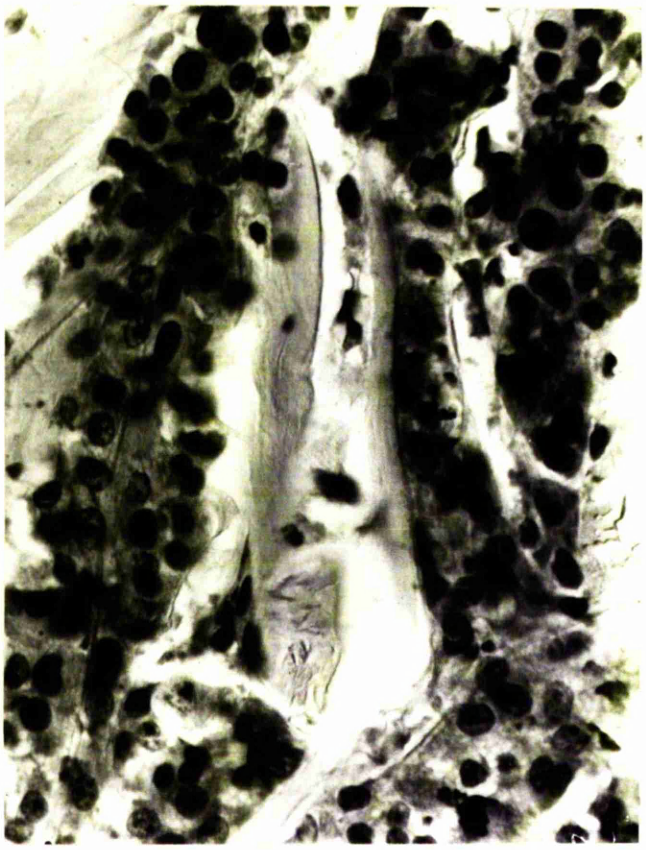


FIGURE 26(a)

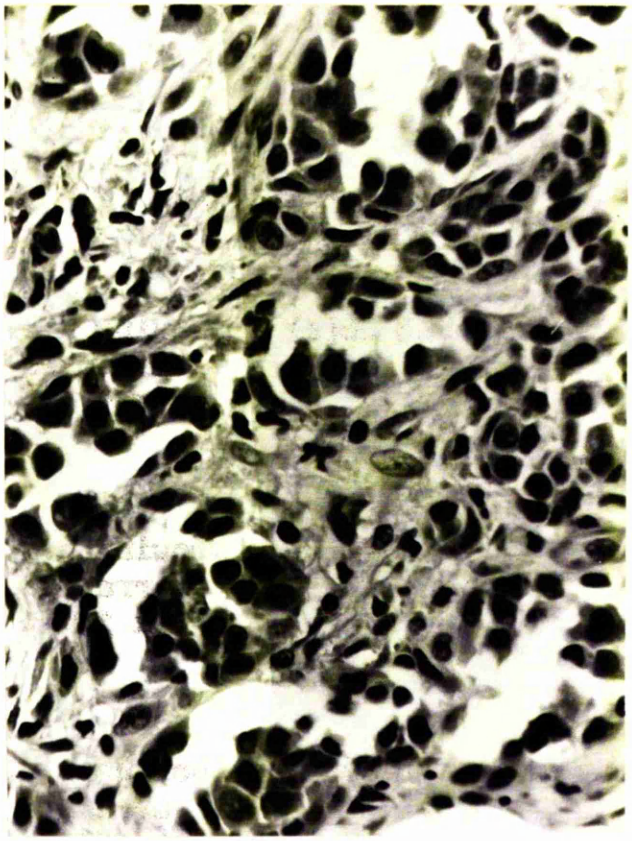


FIGURE 26(b)

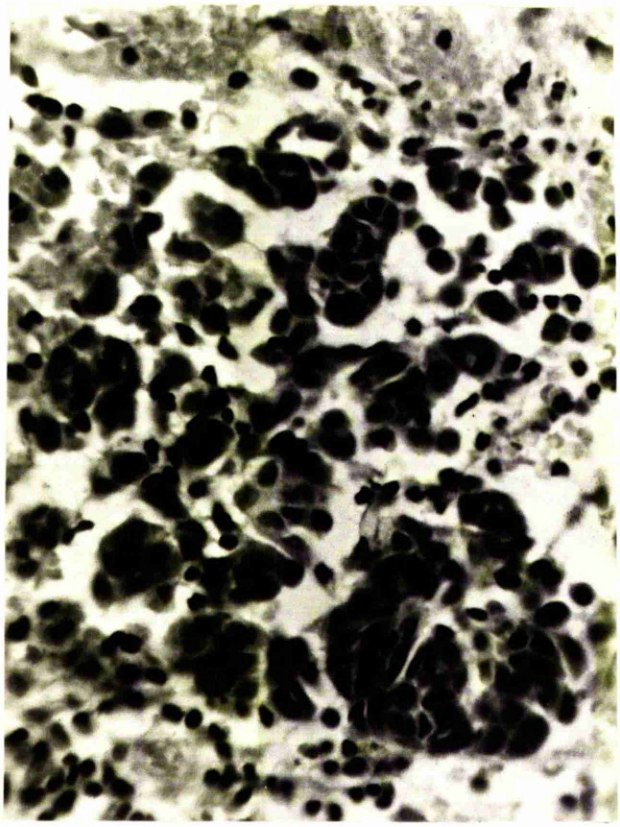


FIGURE 26(c)

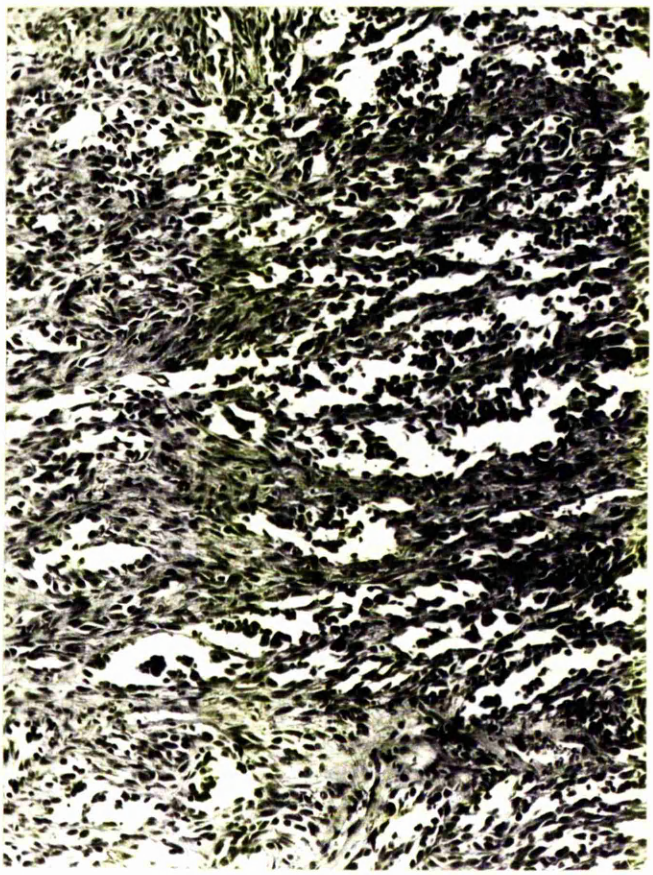


FIGURE 26(d)

frequently in patients with more deeply invasive tumours (P lies between 0.02 and 0.01). In short, patients with superficially placed tumours are less likely to die of malignant melanoma.

2. Cellular Patterns

The arrangement of tumour cells varies widely within individual tumours and from tumour to tumour. Haber (1961) described alveoli, fasiclesand medullary structures. Wright (1949) noted that in tumours showing a fibrosarcomatous appearance with whorls of cells the prognosis was good. Womack (1927) noted that the predominant pattern in his subungual tumours was interlacing masses of spindle cells. Allen and Spitz (1953) and Lane et al. (1958) found no correlation between cellular pattern and prognosis.

In the analysis of the present material it was found possible to divide primary tumours into three groups on the basis of cellular pattern. Eighty five tumours had the cells arranged predominantly in sheets. Forty tumours showed a marked subdivision of the tumour into circumscribed areas of cells which we have called cell packets. We have included in this group whorls, pseudo-alveoli and the short thick cords of tumour cells sometimes encountered. In a third group of tumours no pattern was predominant and this we have designated as the mixed group. Figures 25-26 show these patterns as interpreted in this study.

Statistical/

Statistical analysis of the fate, 5 year survival and incidence of metastasis in these groups of patients reveals only 2 statistically significant variations in the results. At the end of the study period 17 of the 40 patients whose tumours showed a distinct packeted pattern were alive (42.5%). The comparable figure for the tumours with cells disposed in sheets is 19 patients alive out of 85 (22.4%) and for tumours with a mixed pattern 6 patients out of 24 (25.0%). Comparison of the figures for the packeted tumours with the combined figures for tumours showing other patterns reveals a statistically significant difference (P lies between 0.02 and 0.01). Comparison of the incidence of regional nodal metastasis shows that in the patients with packeted tumours only 7 of the 40 patients developed such metastasis (17.5%). The comparable figure for tumours with other patterns is 39 out of 109 patients (36.0%). Statistical analysis of these figures reveals a significant difference (P equals 0.02). In view of this latter finding it is disappointing to note that disseminated melanomatosis occurred with equal frequency in tumours with all patterns. Melanomas showing a packeted pattern appear to account for many of the tumours which disseminate without prior nodal involvement.

The difference in the number of patients alive at the end of the study period is thus not attributable to any difference in the incidence of death from melanoma but to a considerably lower death rate from intercurrent disease in the group/

group of patients whose tumours exhibited marked packeting. It is realised that some of these patients may have died of melanoma and been classified wrongly, vide infra.

The mean age at onset of tumour in the patients with tumours exhibiting marked "packeting" is 50.9 years. The comparable figure for patients with tumours showing sheets of cells is 55.7 years and for patients with tumours exhibiting a mixed pattern is 59.25 years. Analysis of the difference between the mean age at onset of patients with packeted tumours and patients with other patterns, using the "t test" shows that the difference between these mean ages just fails to reach significance (P lies between 0.10 and 0.05). Despite this it seems reasonable to attribute the lower incidence of deaths from intercurrent disease in the former group to the slightly younger age of these patients. Another significant fact in this respect is the high proportion of female patients in this group. In the 40 patients with markedly packeted tumours 29 (72.5%) where female and 11 (27.5%) were male.

3. Cell Type

It is widely accepted that the cells constituting a malignant melanoma may be oval or round in shape, when they are described as epithelioid, or spindle shaped. All manner of variations and combinations of these cell types exist and in the past the descriptionsmelanotic carcinoma and melanotic sarcoma

were/

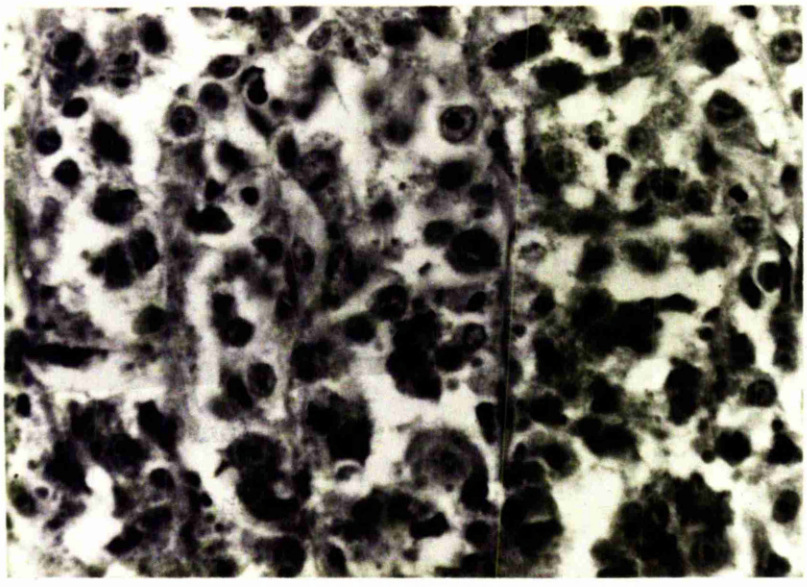


FIGURE 27(a) Showing an epithelioid malignant melanoma. H. and E. (x 500).

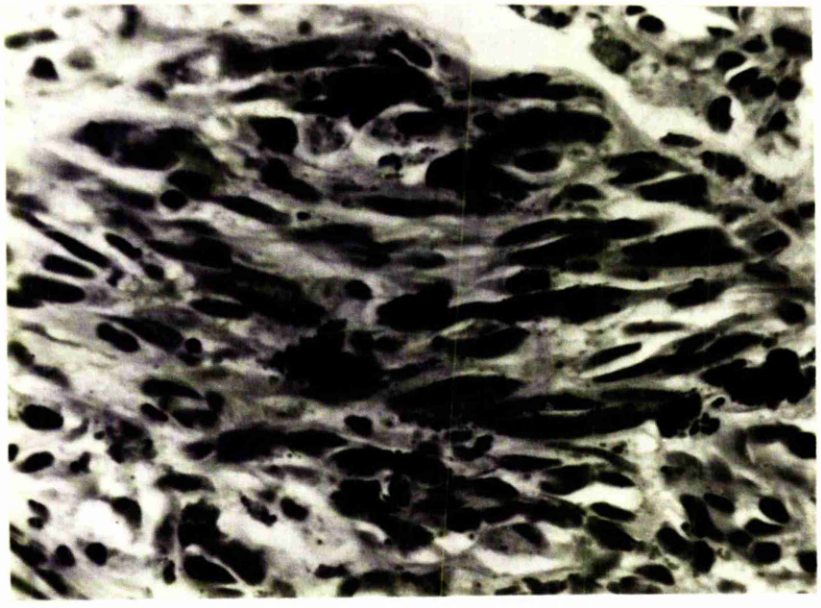


FIGURE 27(b) Showing a spindle celled malignant melanoma H. and E. (x 500).

were used on the basis of these appearances. Petersen et al. (1962) divided their cases into epithelioid, spindle and mixed cell type, but noted no prognostic value in this form of subdivision. Wright et al. (1953) further subdivided the group of spindle celled tumours on the basis of the nuclear pattern into Spindle A and Spindle B. They too found no difference in the fate of patients with tumours consisting of different cellular types.

Tompkins (1953) and Lund & Ihnen (1955) noted no correlation between the degree of pleomorphism and prognosis. Other authors have noted some correlation between the degree of anaplasticity and prognosis e.g. Wright (1949), Hall et al (1952) and Allen and Spitz (1953).

In the analysis of the material of this series 76 of the primary tumours showed a predominantly epithelioid cellular type, 14 showed a predominance of spindle cells and 38 tumours were of mixed cellular type, there being no predominant cell.

No statistically significant difference in fate, 5 year survival or incidence of metastasis was noted between the cellular types. The spindle-celled tumours do seem to have a rather worse prognosis than the epithelioid tumours, but the number of spindle celled cases available for study is very small. Figure 27 shows these cellular types of tumours.

It was noted that many tumours contain a greater or lesser number of cells similar in morphology and staining characteristics/

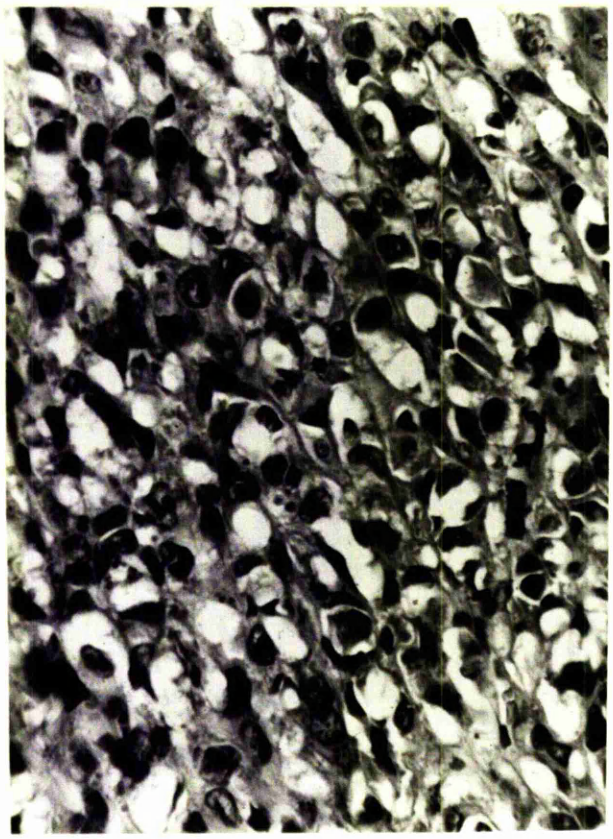


FIGURE 28 Showing a malignant melanoma with cells resembling melanocytes. H. and E. (x 420).

characteristics to the large clear cells seen in active junctional change. In most tumours the number of such cells is small. There were, however, 15 cases in which a considerable number of cells were of this clear-cell type. The number of cases available for study is small, but the results of treatment suggest that the outlook for patients with this type of tumour may be marginally better than that of patients with tumours of other cellular type. In particular 6 of these 15 patients were alive at the end of the study period (40.0%) and 8 of the 14 such patients available for 5 year study were alive at 5 years (57.2%). Since these cells may well represent a well differentiated form of this tumour it would be very desirable to see the results of analysis of a significant group of these patients. Figure 26 shows an example of this type of tumour.

It has been noted that certain tumours arising on the mucous membranes have a recognisably separate cytology. In these tumours the tumour cells tend to be slightly larger than the more conventional epithelioid cells. This is due mainly to an increased content of cytoplasm. The cytoplasm usually shows a pale eosinophilia and occasionally is amphophilic. The nucleus is usually eccentric lying in the narrower pole of these "pear shaped" cells. The cell morphology is very striking and quite unmistakable. The most frequent cellular form is that of a rather squat pear. Figures 7 and 9. Minor variations from this pattern have been noted. The most frequent variation is the appearance of a more angular form

which/

which has the appearance of a truncated pyramid (Figure 10). The pigment content of these cells shows the same variation as noted in the more frequently encountered melanoma cells. It is not suggested that this type of cell is exclusive to mucosal malignant melanoma. (We have seen cells of this type in an anaplastic thyroid carcinoma). It is, however, suggested that the presence of this type of cell in a tumour containing non-ferrous pigment should lead to a careful examination of mucosal sites for a primary malignant melanoma. Figures 7 - 13 show examples of this type of cell arising in various sites.

4. Mitotic Rate

Lane et al. (1958) noted mitotic figures in almost all cases, but found no correlation with prognosis. Allen and Spitz (1953) graded the tumours in their series by the frequency of mitoses in the tumour. They found that in many cases the mitotic rate was very low and that in 72.4% of the patients who survived either no mitoses were seen or examination of the whole slide revealed only one or two. In the patients dying of melanoma only 44.2% showed no mitoses or a low mitotic rate. Cook (1963) reported that mitoses were usually not numerous.

In the analysis of the material comprising this study the cases were divided into those with less than one mitosis per high power field and those with one or more mitoses per high power/

TABLE 39 SHOWING THE FATE, 5 YEAR SURVIVAL AND INCIDENCE OF METASTASES IN PATIENTS WHOSE TUMOURS HAD LESS THAN ONE MITOSIS PER HIGH POWER FIELD AND ONE OR MORE MORE MITOSIS PER HIGH POWER FIELD

Mitotic Rate	Total	Dead Melanoma		Dead Other Causes		Alive		Available 5 Year Follow Up	Alive at 5 Years		Local Recurrence		Nodal Secondary		Intransit Secondary		Disseminated	
		No.	%	No.	%	No.	%	No	No.	%	No.	%	No.	%	No.	%	No.	%
Less than 1/HPF	79	34	43.0	17	21.5	28	35.4	61	31	50.8	16	24.2	20	25.3	3	3.8	34	43.0
More than 1/HPF	68	40	58.8	15	22.0	13	19.1	62	24	38.7	11	15.4	28	40.0	4	5.9	40	59.0

power field. This assessment was obtained by examination of the whole primary tumour. In 79 cases (53.7%) less than one mitosis per high power field was noted and in 68 cases (46.3%) one or more mitoses per high power field were noted.

Comparison of the 5 year survival rate for patients in these groups shows no significant difference (P lies between 0.2 and 0.1). The proportion of patients with tumours of relatively low mitotic rate who developed disseminated melanomatosis and died of melanoma appears lower than that noted in the high mitotic rate group. Statistical analysis of these figures shows that the difference between them just fails to reach statistical significance (P slightly more than 0.05). There is, however, a statistically significant difference between the number of the low mitotic rate group alive at the end of the study period and those of the high mitotic rate group alive at this time (P lies between 0.05 and 0.02). 35.4% of the low mitotic rate group (28 of 79 patients) were alive at the end of the study period as against 19.1% (13 of 68 patients) of the high mitotic rate group. Table 39.

5. Ulceration

Tompkins (1953), in an analysis of 46 cases of malignant melanoma reported that 60% of patients with ulcerated tumours were dead within 3 years whereas only 5% of patients with non-ulcerated tumours were dead within this period. He regarded ulceration as a highly unfavourable prognostic sign. Allen and

Spitz/

TABLE 40 SHOWING THE FATE, 5 YEAR SURVIVAL AND INCIDENCE OF METASTASES IN PATIENTS WITH ULCERATED TUMOURS

Total	Dead Melanoma		Dead Other Causes		Alive		Available at 5 Year Follow Up	Alive at 5 Year		Local Recurrence		Nodal Secondaries		In transit Secondaries		Disseminated	
	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
76	44	57.8	16	21.1	16	21.1	59	20	33.8	10	13.2	27	35.6	3	3.9	43	56.5

Spitz (1953) noted that 69% of their fatal cases had an ulcerated tumour, while only 50% of the nonfatal tumours were ulcerated. Lane et al. (1958) reported that 36% of their 90 cases of malignant melanoma showed ulceration or bleeding. Only 31% of these patients were alive at the end of their study period. Per contra 45% of patients showing no evidence of bleeding or ulceration were alive at the end of the study period. Hellwig (1963) noted that 50% of his malignant melanomas were ulcerated.

Ulceration was noted on microscopic examination in 76 of the 164 cutaneous and mucosal malignant melanomas in this study. This is an incidence of 46.4%.

Comparison of the 5 year survival rate of this group (33.8%) with that of patients with no evidence of ulceration shows a high degree of statistical significance (P is considerably less than 0.001). Ulceration is confirmed as a highly unfavourable prognostic factor. Table 40.

6. Microscopic evidence of Lymphatic Invasion or Vascular Invasion

Lane et al. (1958) stated that obvious invasion of the dermal lymphatics or blood vessels was rare. Attie and Khafif (1964) believe that the finding of obvious vascular invasion indicates a poor prognosis. Petersen et al. (1962) believe that the prognosis is worsened by finding evidence of lymphatic invasion.

Microscopic evidence of invasion of the cutaneous lymphatics/

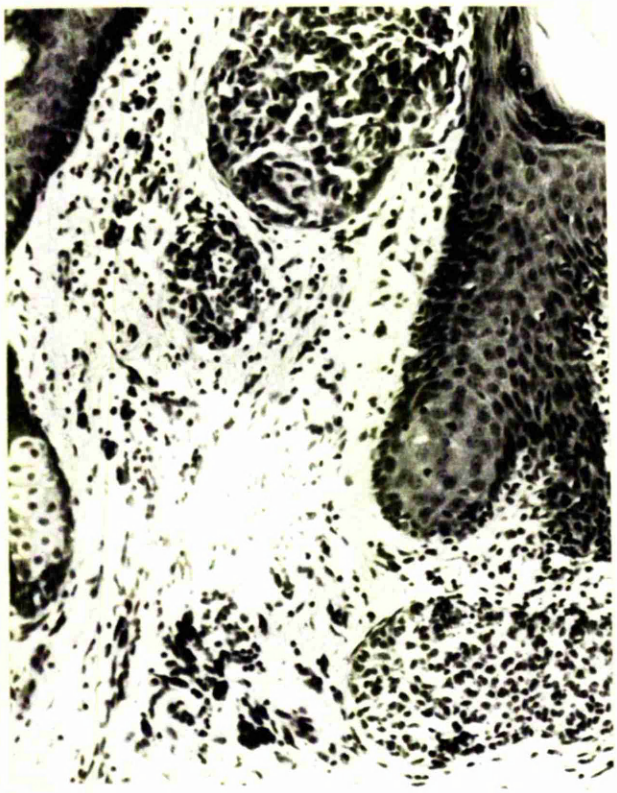


FIGURE 29(a)

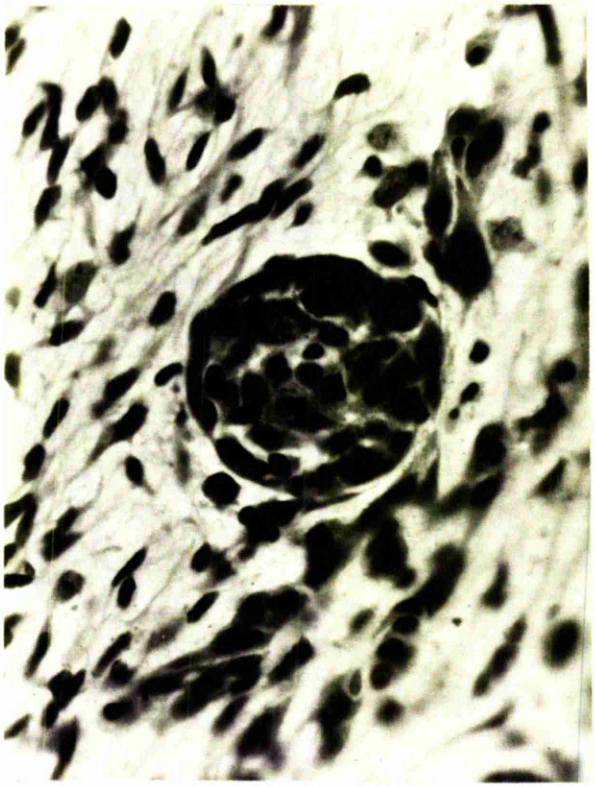


FIGURE 29(b)

FIGURE 29(a) Showing malignant melanoma in dermal lymphatics H. and E. (x 155).

FIGURE 29(b) A high power detail of a minute dermal lymphatic containing malignant melanoma H. and E. (x 500).

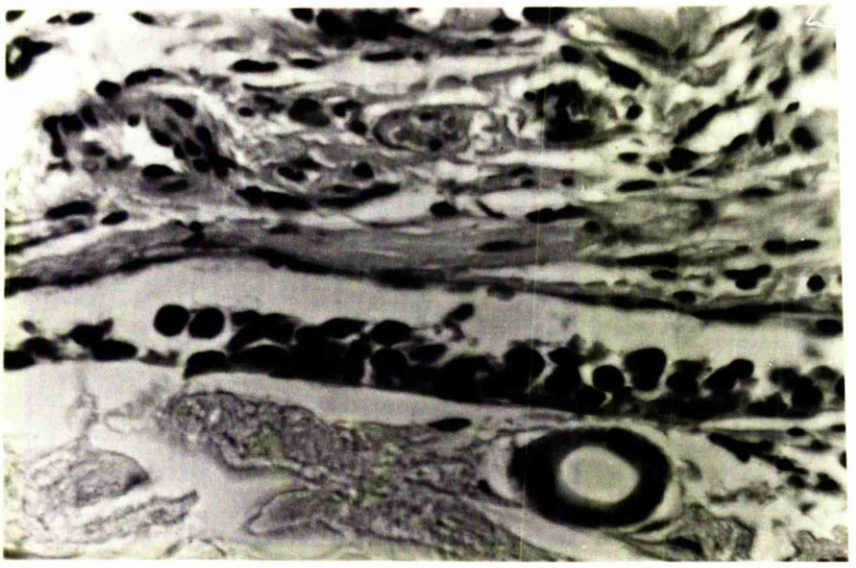


FIGURE 30(a) Showing invasion of a capillary by malignant melanoma. H. and E. (x 500).

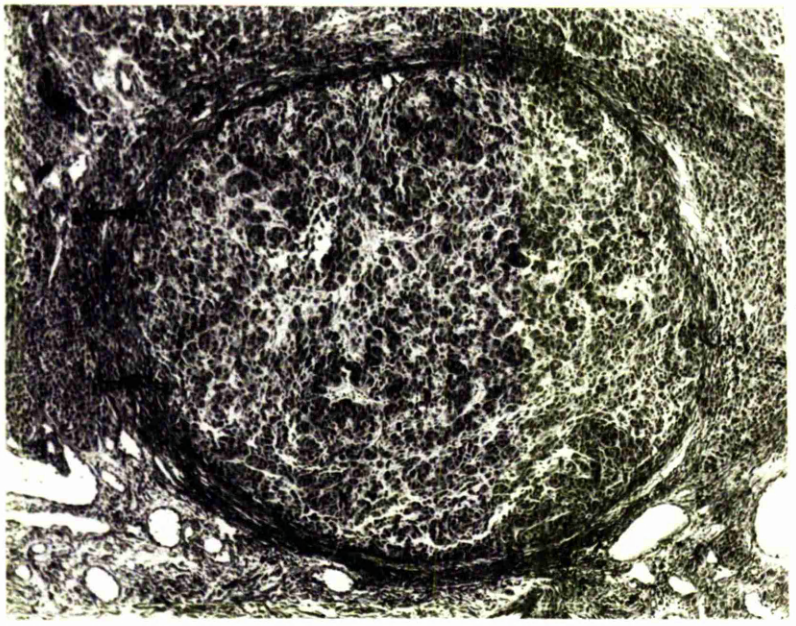


FIGURE 30(b) Showing invasion of a muscular artery by malignant melanoma. H. and E. (x45).

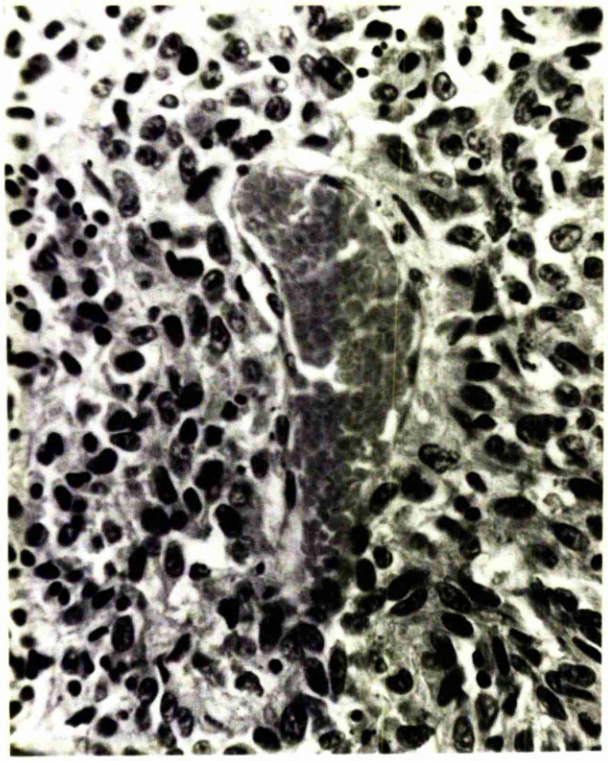


FIGURE 31 Showing tumour investing a blood vessel. H. and E. (x)

TABLE 41 SHOWING THE FATE, 5 YEAR SURVIVAL AND INCIDENCE OF METASTASES IN PATIENTS WITH MICROSCOPIC EVIDENCE OF LYMPHATIC OR VASCULAR INVASION

Group	Total	Dead Melanoma		Dead Other Causes		Alive		Available 5 Year Follow Up	Alive at 5 Year		Local Recurrence		Nodal Secondary		In transit Secondary		Disseminated	
		No.	%	No.	%	No.	%	No	No.	%	No.	%	No.	%	No.	%	No.	%
Lymphatic Invasion	50	31	62.0	11	22.0	8	16.0	44	9	20.5	5	10.0	15	30.0	3	6.0	31	62.0
Vascular Invasion	5	3	60.0	1	20.0	1	20.0	4	1	25.0	1	20.0	-	-	-	-	3	60.0

lymphatics was noted in 51 of the 148 primary tumours from which adequate histological material was available (34.4%) (Figure 29). Vascular invasion was noted in only 5 instances (3.4%) (Figure 30). One of the cases showing lymphatic invasion has been lost to follow up. Table 41 shows the fate of the remaining 50 patients showing evidence of lymphatic invasion and of the 5 patients showing vascular invasion.

Comparison of the results of treatment in the group of patients with evidence of lymphatic invasion against those of the remaining patients in the study group who showed no evidence of lymphatic involvement shows that a significantly larger number of the former group of patients are dead of melanoma at 5 years (79.5%) and that a significantly larger proportion of these patients develop disseminated melanomatosis (62%). P is less than 0.001 in the former case and between 0.05 and 0.02 in the latter.

The number of tumours showing vascular invasion is too small to allow of any statistical analysis. The effect of vascular invasion would appear to be roughly comparable to that of lymphatic invasion. The existence of these appearances in a tumour indicate that the patient's prognosis is worse than average.

Some tumours show marked perivascular and perilymphatic "cuffing" by tumour cells (Figure 31). Others show lymphangiectasis and/or telangiectasis. The numbers involved are too small to allow of any analysis.

7. Microscopic/

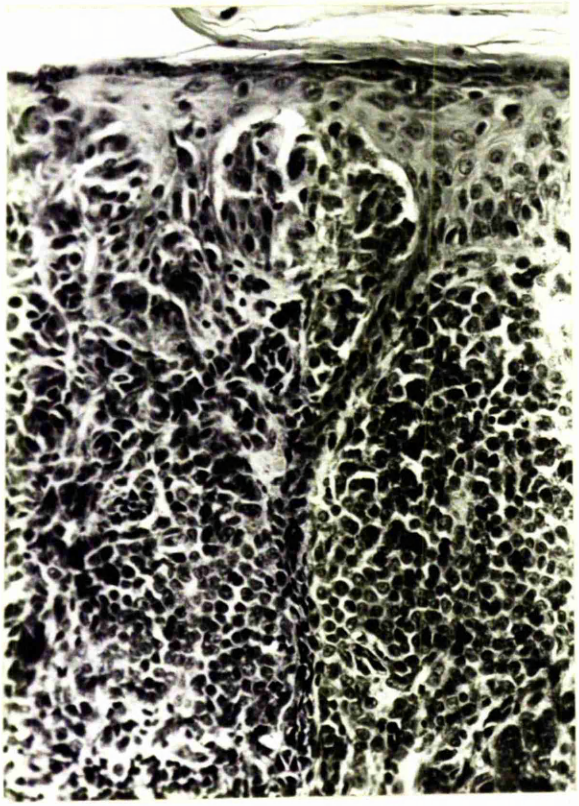


Figure 32

Showing a malignant melanoma arising adjacent to a (compound) naevus H. and E. (x 190).

7. Microscopic Evidence of a Previous Naevus

It was noted in the analysis of the clinical features of malignant melanoma that 46.0% of the patients gave a history of a pre-existing pigmented lesion at the site of the melanoma. It was felt that it would be of interest to see in what proportion of cases there was residual evidence of a naevus, on microscopy. Hellwig (1969) in a review of 392 patients with malignant melanoma found microscopic evidence of naevus cells in only 20% despite a clinical history of a previous pigmented lesion in 80%. He suggested that the melanoma might well destroy the sessile dermal naevus cells in many instances. While this may well be the case in some instances it seems likely that the previous pigmented lesion is, in many cases, a junctional naevus or lentigenous area in which there are no dermal naevus cells. If this is the case it is not surprising that a disparity exists between the clinical history of a naevus and microscopic evidence of such a structure.

The available histological material was regarded as suitable for assessment of this situation in 135 cases. Naevus cells were seen adjacent to the tumour in 38 instances. This is an incidence of 28.2%. Figure 32 shows an example of residual naevus cells adjacent to a primary malignant melanoma.

The fate, 5 year survival and incidence of metastasis is similar in this group of patients to those noted in the study group/

group as a whole. It is concluded that the biological characteristics of this group of tumours is not recognisably separate. The presence of residual naevus cells is of no value in assessing prognosis.

8. Lateral Junctional Change

Lane et al. (1958) noted that malignant melanomas could be subdivided by the presence or absence of junctional activity lateral to the tumour edge. Such junctional activity lateral to the tumour edge they called "lateral junctional change". These authors believe that this change represents "superficial field cancerisation" (sic) and noted that it was more commonly present adjacent to smaller tumours. They postuleted that it might represent an early form of growth from which tumour cells would subsequently grow into the dermis producing the isolated tumour appearance more commonly seen in large tumours. They reported a 5 year survival rate of 87% in 15 cases showing lateral junctional change and a 5 year survival rate of 38% in 16 cases not showing this appearance. This striking difference in survival is no doubt also related to the fact that the tumours showing lateral junctional change were all smaller than 2.0cm. diameter whereas the tumours of the other group were all larger than this.

It was found possible to divide the primary tumours seen/

seen in this study into those two groups. Since it has already been shown that the size of the primary tumour has a definite prognostic significance it was felt that the two groups should be compared regardless of size.

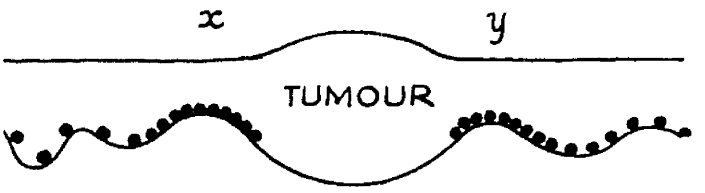
The histological material was regarded as adequate to allow assessment of this change in 128 cases. Lateral junctional change was seen in 69 cases i.e. 53.9% of this group. There was no junctional activity beyond the tumour edge in the remaining 59 cases (46.1%).

The fate, 5 year survival and incidence of metastases were identical in the two groups. It is concluded that the presence or absence of junctional activity lateral to the tumour edge is of no prognostic value.

9. Field Change as Assessed by the Incidence of Melanocytes

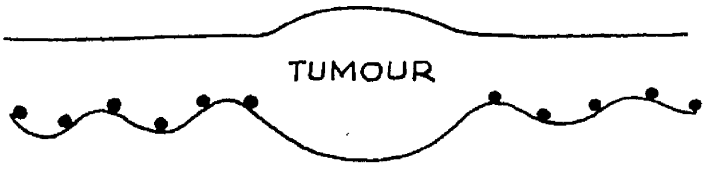
Examination of the epidermis adjacent to the primary tumours reveals three basic patterns of melanocyte distribution. Firstly the incidence of melanocytes may be exactly that of the normal epidermis of the area of skin affected. For the purposes of this analysis the upper limit of normal melanocyte incidence is regarded as 15% of the basal cells. This figure is based on an analysis of the incidence of melanocytes in normal skin described elsewhere in this paper. The primary tumour in this situation is regarded as an isolated focus of malignancy arising in an apparently normal epidermis. For the purposes of this study this is referred to as Pattern B. Secondly the incidence of melanocytes/

PATTERN A



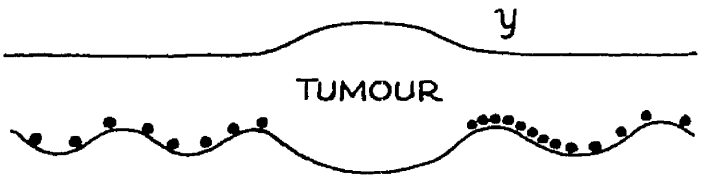
The incidence of basal melanocytes increases as the tumour is approached. Junctional activity may be present at or between x and y.

PATTERN B



Incidence of melanocytes is similar to that normal for the site of the tumour. Junctional activity present over tumour only.

PATTERN C



A combination of A and B. Junctional activity may be present at y as well as over tumour.

FIGURE 33 Showing patterns of melanocytes adjacent to malignant melanomas.

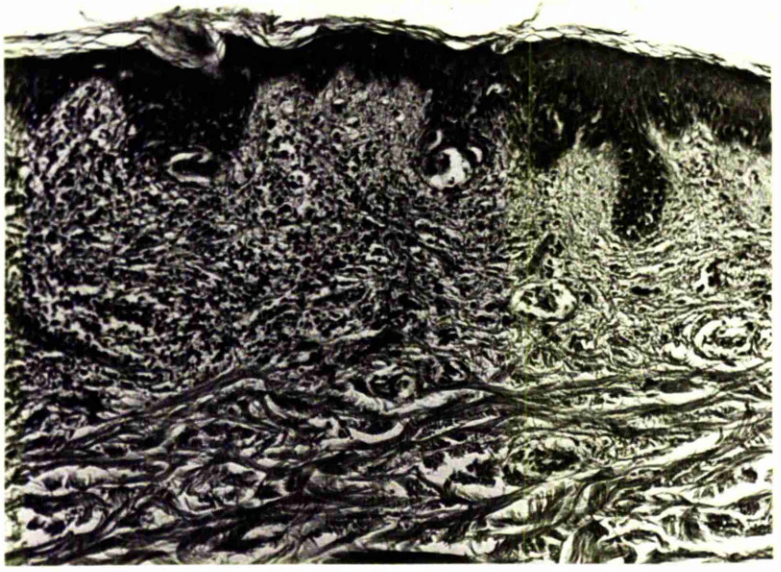


FIGURE 34 Showing a round cell reaction to an active area of epidermis and the absence of a reaction to the adjacent quiescent epidermis.

NOTE abrupt cessation of cellular reaction

H. and E. (x 95).

melanocytes may be increased on both sides of the tumour, Pattern A. The opportunity has arisen to examine wide areas of skin around primary malignant melanomas. The incidence of melanocytes is seen to increase progressively from that normal for the area in which the tumour is situated up to a maximum immediately adjacent to or over the tumour. In the immediate vicinity of the tumour junctional activity may be seen or the appearances described as lentigo may be present. A third pattern exists in which the epidermis on one side of the tumour has a normal incidence of melanocytes and is apparently normal while that on the other side shows an increased incidence of basal melanocytes and sometimes foci of junctional activity. This is designated Pattern C. These patterns of field change are illustrated in Figure 33.

It was initially considered that the areas of symmetrical epidermal change seen around some tumours might be due to some locally active chemical agent released by the tumour. The existence of Pattern C is against such a concept. A more credible interpretation of the situation is that these areas of altered epidermis represent areas of field change. Evidence in support of the activity of these areas of altered epidermis is available in the not infrequent presence of a considerable lymphocyte and plasma cell infiltrate beneath them. This infiltrate has been seen to stop abruptly and dramatically where the normal and altered epidermis abut. (Figure 34).

The only histological material suitable for this

type/

TABLE 42(a) SHOWING THE FATE, 5 YEAR SURVIVAL AND INCIDENCE OF METASTASES IN PATIENTS WITH TUMOURS SHOWING PATTERNS A, B AND C

Group	Total	Dead Melanoma		Dead Other Causes		Alive at end Study		Available at 5 Years	Alive at 5 Years		Local Recurrence		Nodal Secondary		Intransit Secondary		Dissem-inated	
	No.	No.	%	No.	%	No.	%	No	No.	%	No.	%	No.	%	No.	%	No.	%
A	24	7	29.2	6	25.0	11	45.8	17	11	64.6	3	12.5	5	20.8	2	8.3	6	25.0
B	30	17	56.6	6	20.0	7	23.3	26	10	38.5	7	23.3	10	33.3	1	3.3	16	53.3
C	30	11	36.7	10	33.3	9	30.0	22	10	45.4	5	16.7	7	23.3	-	-	11	36.7

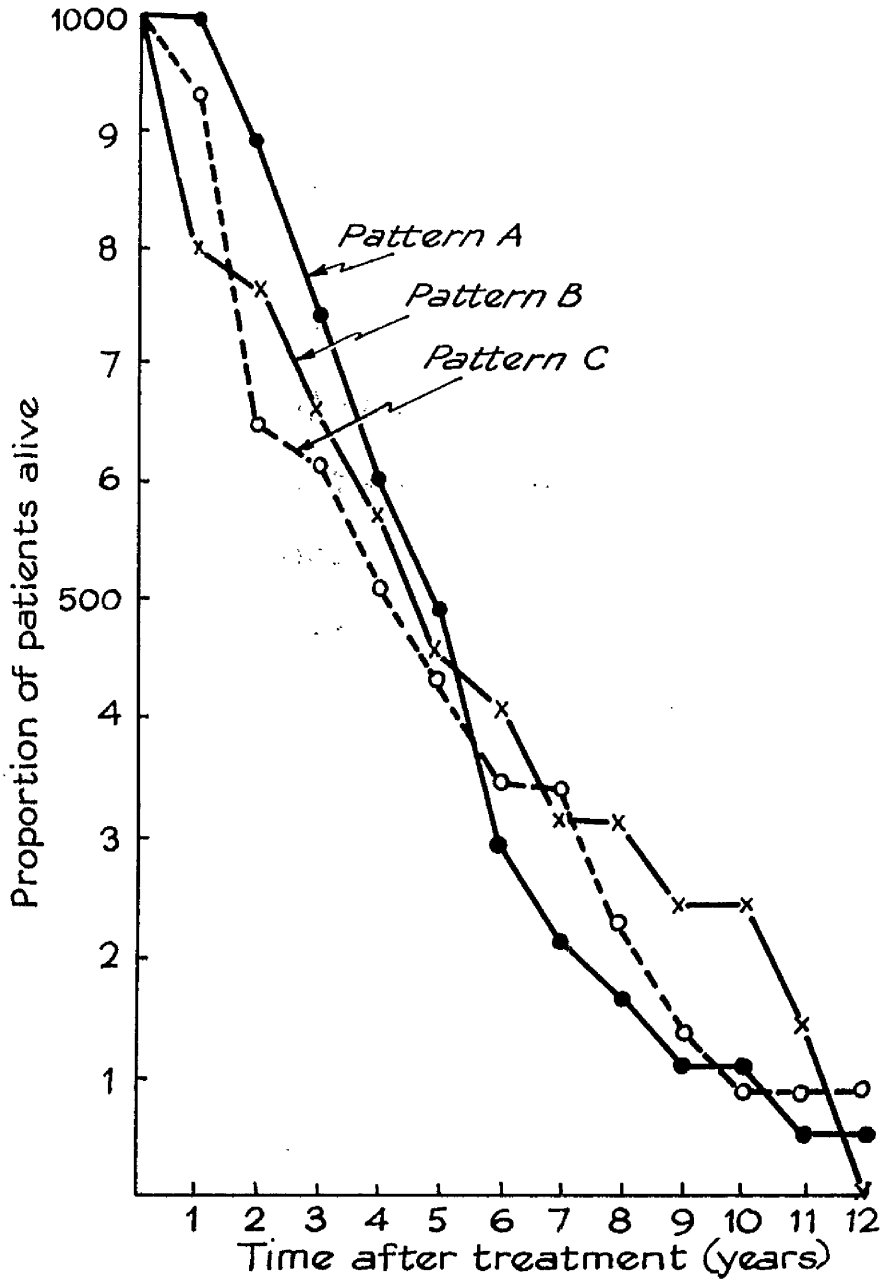


FIGURE 35 Showing the proportion of patients with tumour showing melanocyte pattern, A, B and C alive at varying periods after treatment.

type of assessment is that in which a wide margin of the adjacent epidermis is included in the tumour excision specimen. This was available in 84 instances in the present study. Excision and re-excision specimens were not included in view of the difficulties of orientating the tissues.

There was no increase in the incidence of basal melanocytes on either side of the tumour (Pattern B) in 30 instances. This is an incidence of 35.7% of the tumours examined in this way. The incidence of basal melanocytes was raised symmetrically (Pattern A) in 24 instances. This is an incidence of 28.6%. There was an increase of basal melanocytes on one side of the tumour (Pattern C) in 30 instances. This is an incidence of 35.7% of the study group.

Statistical comparison of the groups exhibiting Patterns A and B shows that a significantly larger proportion of patients with pattern B develop disseminated melanomatosis and die of melanoma. (P lies between 0.05 and 0.02). Figure 35 and Table 42 (a). Comparison of the 5 year survival rates and incidence of metastases show no statistically significant differences in the results. It had been considered on an *a priori* basis that the tumours exhibiting marked alteration of the epidermis adjacent to the tumour might be the source of some local recurrences since current criteria of adequate and complete local excision depend on the degree of clearance of the most lateral foci of junctional change. The results of this study do not show any evidence that the

presence/

presence or absence of a raised incidence of basal melanocytes in the epidermis lateral to a malignant melanoma has any influence on the frequency of local recurrence.

Comparison of the fate, 5 year survival and incidence of metastasis in patients with tumours showing Pattern C with those showing Patterns A and B show no statistically significant differences.

In summary the presence of a raised incidence of melanocytes in the stratum basale of the epidermis around a malignant melanoma would appear to indicate a better than average prognosis for patients with tumours showing this feature.

10. Cellular Reaction

A certain proportion of malignant melanomas show an aggregation of round cells and plasma cells at and in the periphery of the tumour. This is well known and is mentioned specifically by Meischer (1933), Becker (1948), Allen and Spitz (1953), Lever (1954) and Lund and Kraus (1961). A similar infiltrate has been noted in other tumours such as breast carcinoma (Berg, 1959 and Moore and Foote, 1949), seminoma testis (Dixon and Moore 1952), squamous carcinoma and thyroid carcinoma (Cappell, 1964). Cappell regards the presence of these cells as "indirect evidence of an immunological reaction in tumours, presumably of delayed type".

A/

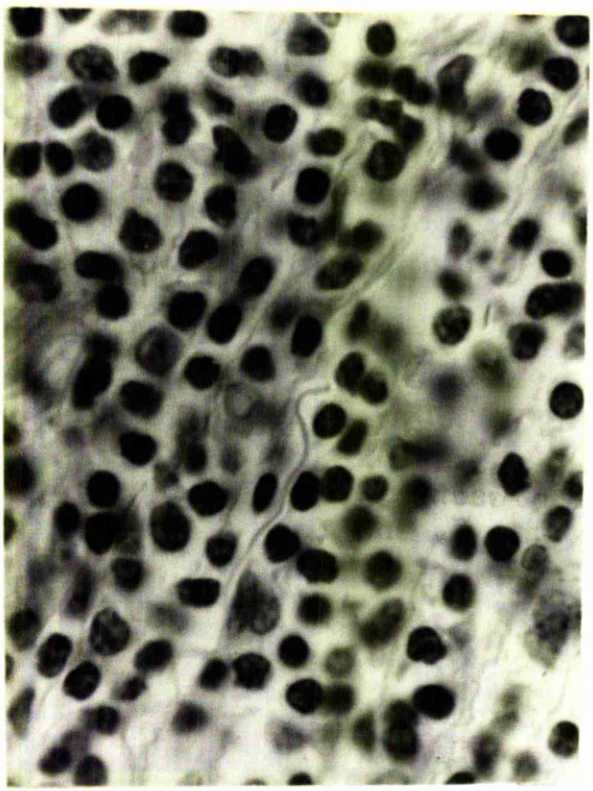


FIGURE 36(a)

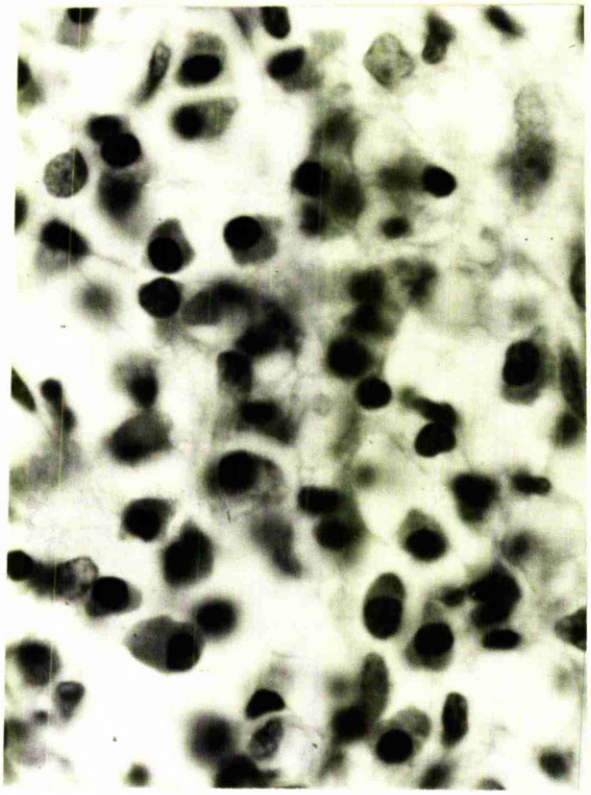


FIGURE 36(b)

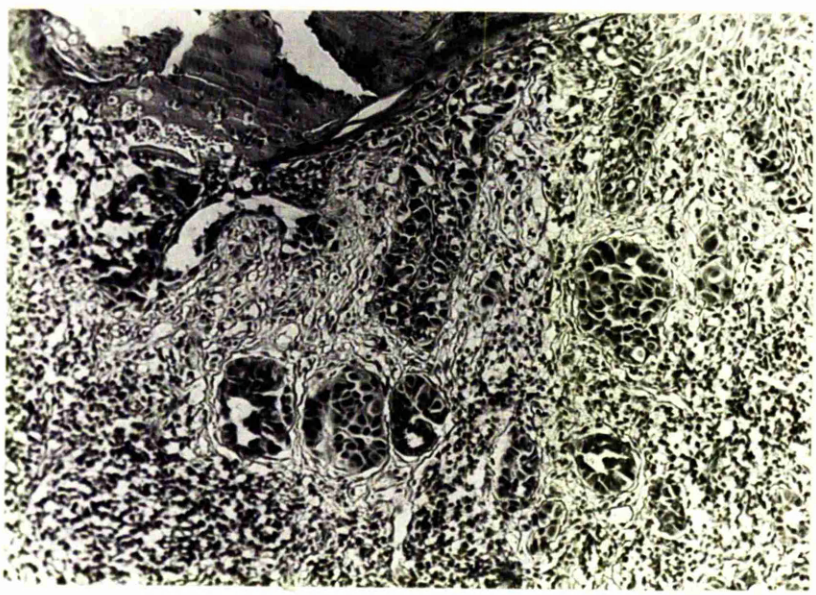


FIGURE 36 (c)

FIGURE 36(a) Showing a lymphocyte reaction to a malignant melanoma. H. and E. (x 1,000).

FIGURE 36(b) Showing a plasma cell reaction to a malignant melanoma. H. and E. (x 1,000).

FIGURE 36(c) Showing a lymphocyte reaction to an area of "active" epidermis adjacent to a malignant melanoma and to dermal lymphatics containing malignant melanoma. H. and E. (x 95).

TABLE 42(b) SHOWING THE FATE, 5 YEAR SURVIVAL AND INCIDENCE OF METASTASES IN PATIENTS WITH DIFFERENT TYPES OF CELLULAR AGGREGATE AROUND THEIR TUMOUR AND THOSE SHOWING NO CELLULAR AGGREGATE

Group	Total	Dead Melanoma		Dead Other Causes		Alive at end Study		Available at 5 Years	Alive at 5 Years		Local Recurrence		Nodal Secondary		Intransit Secondary		Disseminated	
	No.	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
No Cellular Reaction	38	19	50.0	8	21.1	11	28.9	31	16	51.6	10	28.9	9	23.7	-	-	18	47.3
Cellular Reaction	100	48	48.0	22	22.0	30	30.0	79	36	45.6	14	14.0	31	31.0	1	1.0	45	45.0
Lymphocytes	51	20	39.2	11	21.6	20	39.2	41	23	61.6	10	19.6	16	31.4	-	-	19	37.3
Plasma Cells	49	28	57.1	11	22.5	10	20.4	38	13	34.2	4	8.2	15	30.6	1	2.0	26	53.0
Eosinophils	12	5	47.7	4	33.3	3	25.0	11	6	54.6	1	8.3	4	33.3	-	-	6	50.0

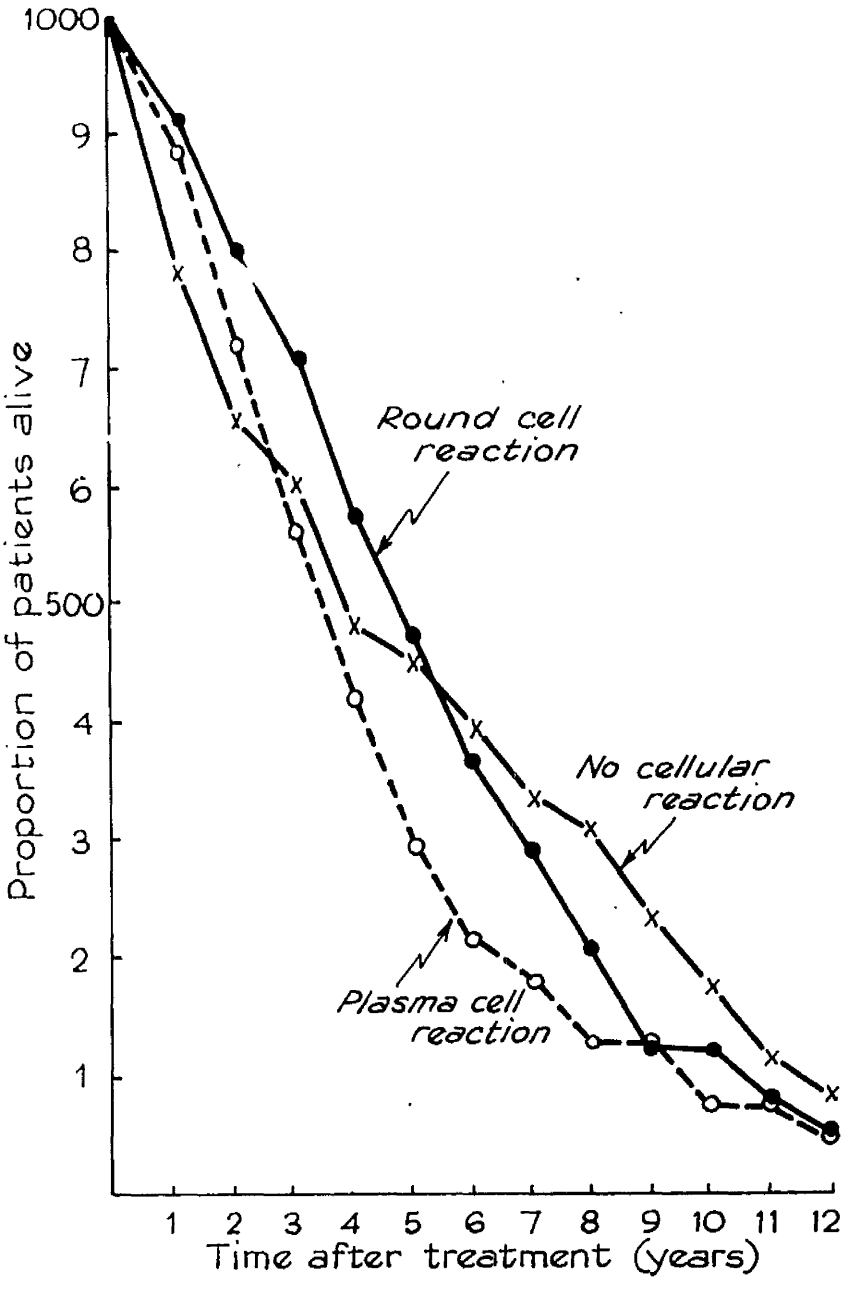


FIGURE 37 Showing the proportion of patients alive at varying periods after treatment (subdivided by presence or absence of cellular reaction to the tumour).

A careful examination of the incidence and nature of these cellular aggregations was made in this study. Sufficient histological material was present in 138 cases to allow assessment of this point. No evidence of a cellular aggregation was noted in 38 tumours (27.6%). A definite aggregation of cells was noted in the remaining 100 tumours (72.4%). It was found possible to further subdivide the latter group on the basis of the nature of the cells composing the infiltrate. The predominant cell noted at the periphery of 51 tumours was a small cell with a deeply basophilic compact nucleus and minimal cytoplasm. These were regarded as lymphocytes. Figures 36a and 36b. Even in these tumours an occasional plasma cell was visible, but no aggregation of these latter cells was noted. In the remaining 49 cases a considerable proportion of the cells were plasma cells. Figure 36c. Eosinophilic polymorphonuclear leucocytes were present in considerable numbers in 12 instances.

Statistical comparison of the survival of patients with tumours attended by a cellular aggregation and those with no evidence of cellular reaction reveals no statistically significant differences in fate and five year survival. Figure 37 and Table 42b show the fate of patients with and without evidence of a cellular reaction. Local recurrences are significantly more common in the former group. (P lies between 0.01 and 0.001).

A statistically significant difference is noted between the five year survival rate of patients with a lymphocyte response,/

response, 61.6% and those with a mixed plasma cell and lymphocyte aggregation, 34.3% (P = 0.05). A similar significant difference was noted between the proportion of patients in these two groups alive at the end of the study (P lies between 0.05 and 0.02).

In summary, patients whose tumours are attended by a peripheral lymphocyte aggregation have a rather better prognosis than those who demonstrate a mixed plasma cell/lymphocyte response or no cellular response at all.

Becker (1948), Allen and Spitz (1953) and Lever (1954) all record that the cellular reaction becomes less marked in lesions of long duration and deep penetration. Allen and Spitz talk of the defensive barrier being broken through. This fact, the diminishing cellular response, is difficult to prove. We have, however, examined several cases in which there were repeated local recurrences and in these the cellular response appeared to diminish with successive recurrences.

In the present state of our knowledge of autoimmune mechanisms the separate behaviour of tumours attended by recognisably different cellular reactions is difficult to explain. It is at present held that plasma cells manufacture antibodies. Lymphocytes are believed to be related to the delayed hypersensitivity type of reaction. The cellular reaction must, therefore, represent a degree of host response to an antigenically distinct tumour.

The diminution of the cellular response with passing time is puzzling. This is particularly so since we have seen several/

several tumours where, despite an absence of cellular reaction subjacent to the tumour itself, there was a brisk reaction to the junctional and lentigenous change in the adjacent epidermis. The immunological competence of the individual would not appear to have been totally overwhelmed.

11. Pigmentation

The melanin content of these tumours varies widely from tumour to tumour and primary to secondary (Schoolman, 1950). Hewer (1935) noted that the pigment is usually most marked at the periphery of the tumour. The pigment content, despite indicating a high degree of differentiation is generally regarded as being of no prognostic value. (Wright, 1948, Mason and Friedmann, 1955, Wright et al., 1953, Ackerman and del Regato, 1947, Petersen et al., (1962) and Allen and Spitz, 1953). The last named authors attempted a quantitative analysis of the pigment content, grading the tumours 0 - 4.

In a total of 139 cutaneous malignant melanomas examined in this series 75 (54.0%) were amelanotic or lightly pigmented, 33 (23.8%) contained moderate quantities of pigment and 31 (22.2%) were heavily pigmented.

Statistical analysis and comparison of the fate of the patients in these groups shows no statistically significant differences between them. The amount of pigment present in a malignant/

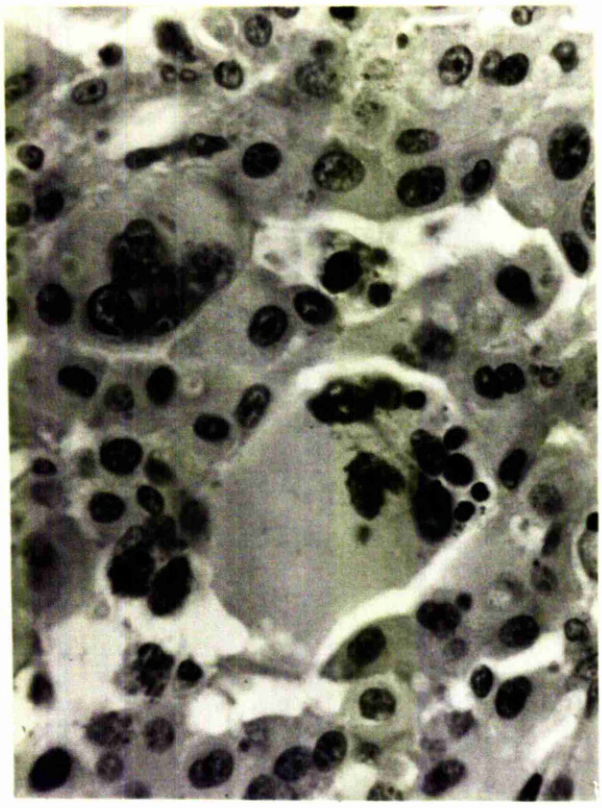


FIGURE 38(a)

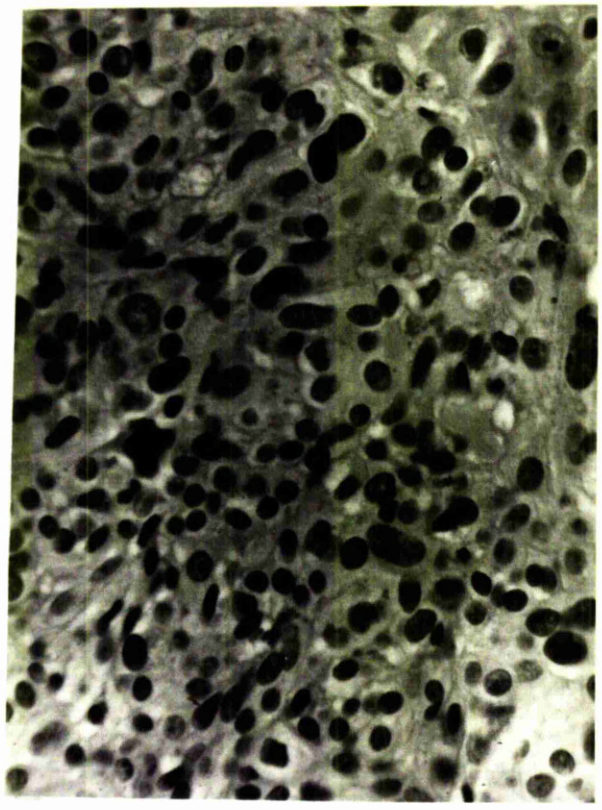


FIGURE (b)

FIGURE 38(a) Showing multinucleate giant cells. H. and E. (x 430).

FIGURE 38(b) Showing mononuclear giant cells. H. and E. (x430).

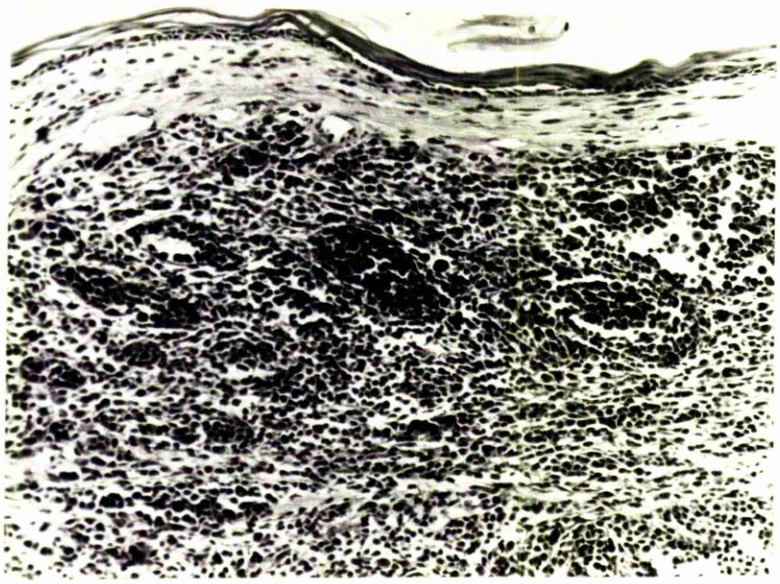


FIGURE 39 Showing a tumour-free zone beneath the epidermis in a primary malignant melanoma. Junctional activity was noted in another area of the tumour. H. and E. (x 95).

malignant melanoma is thus seen to be of no prognostic value.

12. Giant Cells

Haber (1961) reported many multinucleate cells in the tumours of his series. This has not been our experience. Multinucleate and/or mononuclear giant cells (Figure 38) were seen in only 17 of the 147 primary tumours examined i.e. 10.2%. Giant cells were seen in one other case, but were regarded as part of a foreign body reaction. Giant cells were noted in 6 of the 12 juvenile melanomas examined (50%) but were less common in compound naevi (15.0%), simple naevi (31.6%) and none were seen in the 7 blue naevi examined.

The number of tumours showing this feature is small, but examination of the fate, 5 year survival and incidence of metastases in the group shows a pattern similar to the whole study group. The presence of giant cells is not considered to be of value in the assessment of the prognosis.

13. The presence of a Tumour-Free Zone between Tumour and Epidermis

Spitz (1948) in her classic description of the juvenile melanoma described a tumour-free area between the under-surface of the epidermis and the most superficial tumour cells. This was noted in 8 of the 147 primary melanomas, (5.45%). Figure 39 shows this appearance. Five of these patients died of melanoma and

3/

FIGURE 40 Showing a fibrous tissue "capsule" adjacent to (a) a dermal deposit of secondary melanoma and (b) the deep aspect of a primary malignant melanoma.

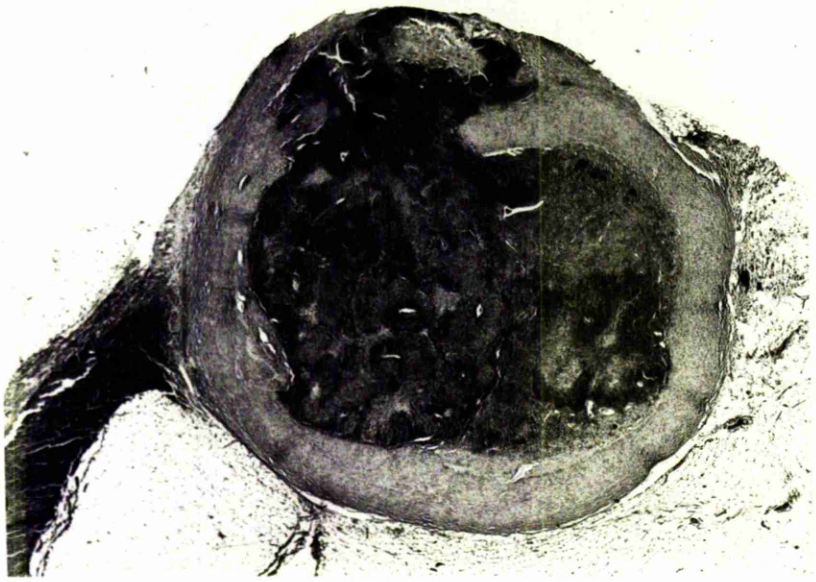


FIGURE 40(a) H. and E. (x14)

FIGURE 40(b) H. and E. (x45)

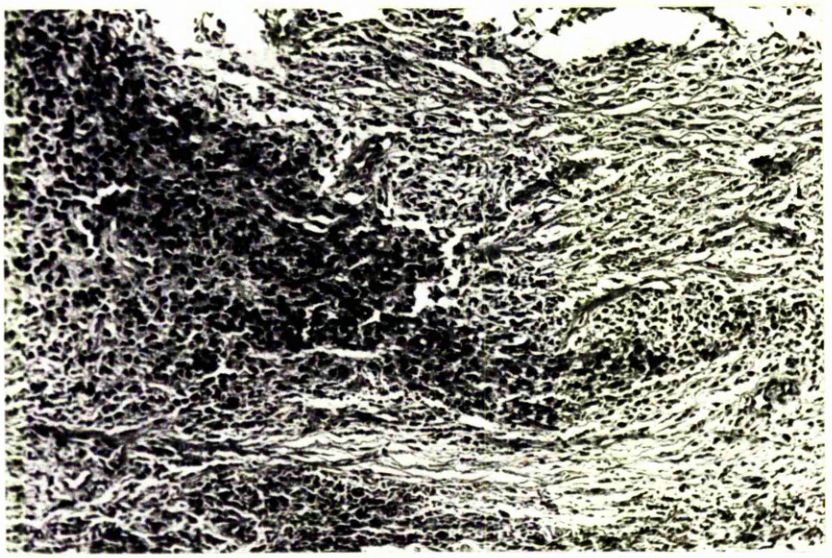


FIGURE 41 Showing tumour cells growing through a connective tissue capsule. H. and E. (x95).

3 are alive at this time. The 5 year survival rate was 42.8%. The appearance of a "clear" subepidermal zone was not indicative of a lower malignancy in these tumours.

14. The Distribution of Connective tissue Within and Around the Tumour

Wright et al. (1953), using the technique described by Callender (1931) in his studies on melanoma of the eye, examined the disposition and nature of connective tissues within these tumours. They conclude that while certain distinct patterns exist they are of no value in the assessment of prognosis. In view of this negative report the examination of connective tissue patterns was confined in this study to a search for evidence of attempts at fibrous encapsulation of the tumour.

It may seem rather naive to look for the erection of perimeter walls around a rapidly growing tumour, but we have seen this in 17 instances. Figures 11 and 40. It is of interest to note that this occurs in relation to both primary and subepidermal secondary tumours. In one interesting case, Figure 11, the fibrous capsule encloses a focus of apparently ei ete tumour cells. That this mechanical barrier is not "leakproof" is shown by Figure 41 in which viable tumour cells have transgressed the fibrous area.

The group is too small for any form of analysis, but the fate, five year survival rate and incidence of metastases seem essentially similar to those of the group as a whole.

TABLE 43

A comparison of the histological appearances of benign and malignant pigmented tumours.

Tumour	Malignant Melanoma		Juvenile Melanoma		Compound Naevus		Intradermal Naevus		Lentigo		Blue Naevus	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. ■	164	100	12	100	154	100	40	100	7	100	8	100
Ulceration	76	46.3	-	-	1	0.6	2	5.0	-	-	-	-
Field change	54/84	64.3	3	25.0	31	20.1	-	-	7	100	1+	12.5
Subepidermal clear zone	8/147	5.5	5	41.6	60	38.9	40	100	7	100	7	87.5
Epidermal invasion	131/134	97.7	1	8.33	5	3.2	-	-	4	57.0	-	-
Giant cells	15	9.1	6	50.0	24	15.6	9	22.5	-	-	-	-
Mitotic rate $<$ 1/H.P.F.	79/147	53.7	12	100	154	100	40	100	7	100	8	100
Mitotic rate $>$ 1/H.P.F.	68/147	46.3	-	-	-	-	-	-	-	-	-	-
Cellular reaction	100/138	72.4	6	50.0	30	19.5	4	10.0	2	28.6	2	25.0
Cell Pattern (i) mixed	24/149	16.2	4	33.3	61	39.6	13	32.5	-	-	2	25.0
(ii) sheets	85/149	57.0	1	8.33	90	58.5	10	25.0	-	-	1	12.5
(iii) packets	40/149	26.8	8	66.7	102	66.2	24	60.0	-	-	3	37.5
(iv) single cells	-	-	-	-	9	5.8	5	12.5	-	-	6	75.0
Mean incidence Melacocytes (tumour)		22.6		28.5		22.6		15.3		23.1		16.9
Mean incidence melacocytes Over-adjacent epidermis		14.7/19.7		13.6		13.2		14.0		19.7		15.5
Pigment (i) Nil - light	75/139	54.0	9	66.7	129	83.7	36	90.0	6	85.6	-	-
(ii) moderate	33/139	23.8	2	16.7	20	13.0	3	7.5	-	-	1	12.5
(iii) heavy	31/139	22.2	1	8.33	5	3.2	1	2.5	1	14.4	7	87.5
Cell type (i) necrosis	-	-	2	16.7	151	98.0	40	100	-	-	1	12.5
(ii) epithelioid	76/143	53.1	10	83.3	4	2.6	30	75.0	-	-	4	50.0
(iii) spindle	14/143	9.8	5	41.7	1	0.6	3	7.5	-	-	4	50.0
(iv) clear cell	15/143	10.5	-	-	29	18.8	2	5.0	7	100	-	-
(v) mixed	38/143	26.6	8	66.7	29	18.8	5	12.5	-	-	1	12.5
Above epidermal appendages	69/127	54.2	10	83.3	146	94.7	40	100	7	100	2	25.0
Below epidermal appendages	58/127	45.8	2	41.7	8	5.3	-	-	-	-	6	75.0

■ The number of cases in which the available histological material was suitable for the assessment of a particular feature varies. Where the total available is less than that stated in the gross total it is indicated as a denominator in the appropriate section of the table.

\+ Blue naevus associated with compound naevus.

A COMPARISON OF THE HISTOLOGICAL FEATURES OF MALIGNANT MELANOMAS, JUVENILE MELANOMAS, COMPOUND NAEVI, INTRADERMAL NAEVI, LENTIGOS AND BLUE NAEVI.

TABLE 43 synopsises these observations (see facing page)

1. Ulceration

Ulceration was noted in 76 of the 164 cutaneous malignant melanomas examined, 46.3%. This high incidence contrasts with that noted in simple tumours. Two of the 40 intradermal naevi were ulcerated, 5.0% and 1 of the compound naevi was ulcerated, 0.6% No ulceration was noted in the 12 juvenile melanomas, 8 blue naevi and 7 areas of lentigo examined.

2. Field Change

Field change as evidenced by junctional change and/or a raised incidence of melanocytes lateral to the tumour was noted in 54 of 84 malignant melanomas so examined, 64.3%. This type of change in the epidermis was present in all areas of lentigo examined, in 31 of the 154 compound naevi, 20.1%, and in 3 of the 12 juvenile melanomas, 25%. Field change was noted adjacent to 1 of the blue naevi, but as this blue naevus was associated with a compound naevus the change was probably a function of the latter rather than the former condition. None of the 40 intradermal naevi examined showed evidence of this type of change in the epidermis.

3. Subepidermal/

3. Suberidermal Clear Zone

A tumour free area existed between the epidermis and the main tumour mass in all 40 intradermal naevi, in 7 of the 8 blue naevi, 87.5%, in 5 of the 12 juvenile melanomas, 41.6%, in 60 of the 154 compound naevi, 38.9% and in 8 of 147 malignant melanomas 5.5%. It is seen to be an uncommon finding in primary malignant melanoma.

4. Epidermal Invasion

As this is one of the diagnostic features of malignant melanoma it was no surprise to find it present in 131 of 134 malignant melanomas, 97.7%. It is also noted relatively frequently in lentigo, 4 or 7 cases of this kind showing the change in this series, 57.0%. In the remaining simple tumours an appearance of this kind was rare. It was present in 5 of the compound naevi, 3.2%, 1 of the 12 juvenile melanomas, 8.3% and was not noted in any of the intradermal naevi.

5. Giant Cells.

Mononuclear or multinuclear giant cells were noted in 6 of the 12 juvenile melanomas, 50%. They were of relatively frequent occurrence in intradermal and compound naevi (22.5% and 15.6% respectively). In malignant melanomas giant cells were noted in 15 of the 164 cases, 9.1%. No giant cells were seen in the blue naevi and lentigos reviewed in this series.

It/

It is worth noting, however, that the melanocytes which are present at the epidermodermal junction in lentigo may themselves be larger than normal

6. Mitotic Rate

Mitoses were very rarely seen in compound naevi, intradermal naevi, juvenile melanomas, lentigos and blue naevi. The maximum mitotic rate recorded in these tumours was 1 mitosis in 10 high power fields. In malignant melanomas the mitotic rate was higher than 1 mitosis per high power field in 68 of 147 cases, 46.3%. The mitoses in the malignant melanomas were frequently aberrent. No mitoses of this type were seen in the simple tumours.

7. Cellular Reaction

It has been noted that a cellular reaction was present in relation to 100 of 138 malignant melanomas, 72.4%. Cellular reactions were less frequently seen around simple tumours. Six of the 12 juvenile melanomas (50%) and 2 of the 7 areas of lentigo (28.6%) showed this type of reaction. Two of the 8 blue naevi (25%), 30 of the 159 compound naevi (19.5%) and 4 of the 40 intradermal naevi showed an aggregation of lymphocytes and plasma cells at their periphery. It is of interest to note that such reactions were more frequently associated with the "active" tumours.

8. Cell/

8. Cell Patterns

Twenty-four of 149 malignant melanomas, 16.2%, showed a mixed pattern with cells in sheets, packets, whorls, pseudo-alveoli and scattered singly. This type of pattern was seen in 4 of the 12 juvenile melanomas 33.3%, 61 of the 154 compound naevi, 39.6%, 13 of the 40 intradermal naevi, 32.5%, and 2 of the 8 blue naevi, 25.0%.

The cells were arranged in sheets in 85 of the 149 malignant melanomas, 57.0%, 90 of the 154 compound naevi, 58.5%, 10 of the 40 intradermal naevi, 25.0% and 1 of the 8 blue naevi, 12.5%. A distinct subdivision of the cells by fibrous tissue strands into packets, whorls or pseudo-alveoli was seen in 40 of the 149 malignant melanomas, 26.8%. 8 of the 12 juvenile melanomas, 66.7%, 102 of the 154 compound naevi, 66.2%, 24 of the 40 intradermal naevi, 60.0% and 3 of the 8 blue naevi, 37.5%. Packetting is thus seen to occur more frequently in simple tumours, but is not confined to them.

A distribution of tumour cells singly through the dermal tissues was seen in 6 of the 8 blue naevi, 75.0%, 5 of the 40 intradermal naevi, 12.5% and 9 of the 154 compound naevi, 5.8%. No example of this type of distribution has been seen in a malignant melanoma.

9. The Incidence of Basal Melanocytes Over and Adjacent to Tumours

This subject is considered in detail in the section/

section on melanocyte distribution (vide infra.).

10. Pigmentation

With the exception of blue naevi the pigment content of these tumours is usually not heavy. Pigmentation was assessed as absent or light in 75 of the 139 malignant melanomas, 54.0%, 9 of the 12 juvenile melanomas 66.7%, 129 of the 154 compound naevi, 83.7%, 36 of the 40 intradermal naevi, 90% and 6 of the 7 areas of lentigo, 85.6%.

A moderate quantity of pigment was seen in 33 of 139 malignant melanomas, 23.8%, 2 of the 12 juvenile melanomas, 16.7%, 20 of the 154 compound naevi, 13.0%, 3 of the 40 intradermal naevi, 7.5% and 1 of the 8 blue naevi, 12.5%.

Heavy pigmentation was seen in 31 of 139 malignant melanomas, 22.2%, 1 of the juvenile melanomas, 8.3%, 5 of the 154 compound naevi, 3.2%, 1 of the 40 intradermal naevi, 2.5%, 1 of the 7 areas of lentigo, 14.4% and 7 of the 8 blue naevi 87.5%.

In the malignant melanomas, compound naevi, intradermal naevi and juvenile melanomas the pigment was mainly in the superficial portions of the tumours. It lay in the stratum basale, the cells of the areas of junctional activity, in the superficial tumour cells in the melanocytes of junctional changes and in macrophages in the dermis. In lentigo the pigment/

pigment is mainly in the epidermal cells of the stratum basale and the melanocytes, but some is often visible in phagocytes (melanophores) in the dermis and the separation of such cells from tumour cells is frequently difficult. The pigment in blue naevi lies deeply and is often of a darker colour than that seen in the naevi and malignant melanomas. This hue, the depth of these tumours and the intervening vascular channels between tumour and epidermis are responsible for the distinctive colouration of these tumours on clinical examination. Much of the pigment in blue naevi is contained in phagocytic cells interspersed between the true tumour cells. It is of interest to note that many of the melanophores are dendritic in form.

11. Cell Type

The cytology of malignant melanoma has been discussed in a preceding section (vide supra.). Cells resembling naevus cells, apart from those residual from an antecedent naevus, do occur in malignant melanomas. In 2 of the 12 juvenile melanomas, 16.7%, a proportion of the tumour cells were naevus cells, circular, oval or polygonal cells with small deeply basophilic nuclei and a minimum of cytoplasm. Classical naevus cells were the predominant cell in 151 of the 154 compound naevi, 98.0%, all of the 40 intradermal naevi and 1 of the 8 blue naevi, 12.5%. In the latter case the overall histology, depth of the tumour in the dermis, melanin distribution and

absence/

absence of a raised level of basal melanocytes favoured the diagnosis of blue naevus despite the cell type.

Epithelioid cells similar to those seen in 76 of 143 malignant melanomas, 53.1%, were seen in 10 of the 12 juvenile melanomas, 83.3%, 4 of the 154 compound naevi, 2.6% and 4 of the 8 blue naevi, 50.0%. Close examination of the naevus cells in the intradermal naevi revealed an occasional cell of this type in 30 of the 40 such naevi examined, 75.0%. These cells usually lay in the superficial portion of the tumour.

As in malignant melanomas, where only 14 of the 143 tumours, 9.8% showed a predominantly spindle cell pattern, spindle cells were rare in naevi. One of the 154 compound naevi was spindle celled, 0.6%, and only 3 of the 40 intradermal naevi, 7.5%, contained spindle shaped cells. Such cells were rather more common in juvenile melanomas and blue naevi. Five of the 12 juvenile melanomas contained significant numbers of spindle cells, 41.7% as did 4 of the 8 blue naevi, 50.0%. The relatively frequent occurrence of spindle cells in blue naevi may be considered as evidence in support of their origin from Schwann cells.

Clear cells, morphologically similar to melanocytes, were noted in 15 of the 143 malignant melanomas, 10.5%, 29 of the 154 compound naevi, 18.8%, and 2 of the 40 intradermal naevi, 5.0%. Cells of this type were not seen in juvenile/

juvenile melanoma or blue naevi.

It has been noted frequently that the morphology of the cells of a naevus may be quite variable from area to area within a tumour. In general the more superficial cells are larger, have more cytoplasm, a less basophilic nucleus and may closely resemble melanocytes. Such mitoses as are seen usually lie in these superficially placed cells. This variation in appearance is interpreted as a maturity gradient and appears to have no prognostic significance.

12. Depth of Tumour Penetration

Sixty nine of 127 malignant melanomas lay above the level of the epidermal appendages, 54.2%. With the exception of the blue naevi a considerably higher proportion of simple tumours were superficially placed. Ten of the 12 juvenile melanomas, 83.3%, 146 of the 153 compound naevi, 94.7%, all intradermal naevi and 2 of the 6 blue naevi, 2%, lay above the epidermal appendages. Conversely 2 of the 12 juvenile melanomas, 16.7%, 8 of the 154 compound naevi, 5.3% and no intradermal naevi extended deeper than the line of the epidermal appendages. The comparable figure for malignant melanomas is 58 out of 127 tumours, 45.8%. It is well recognised that blue naevi tend to lie deeply in the dermis and it is, therefore, not surprising that 6 of 8 such tumours, 75%, reviewed in this series lay deep to the epidermal appendages.

Para/

From these observations it is apparent that while the histology of the simple pigmented tumours is generally distinct from that of their malignant counterparts, many common features and similarities exist. These similarities are the basis of many of the difficulties encountered in the microscopic diagnosis of this group of tumours.

Follow-Up Studies on simple Pigmented Tumours

The results of follow up studies on these tumours are described in the succeeding paragraph. It can, however, be shortly stated that none of the patients who had a diagnosis of simple pigmented tumour made on the basis of histological examination of biopsy material have, as far as is known, had a recurrence of the tumour or developed a malignant melanoma.

Nine of the patients who had juvenile melanomas excised have been followed up for periods between 2 and 11 years. All are alive and well with no evidence of recurrent disease. Four of the "blue naevus patients" have been traced. All are alive and well at periods between 4 and 12 years after treatment. Ninety six of the 154 "compound naevus patients" have been traced. Ninety five are alive and well with no evidence of recurrent disease at periods between 5 and 12 years after treatment. One patient is known to have died of a bronchial carcinoma two years after treatment of a compound naevus. Only 3 of the 7 patients with areas of lentigo have been traced. These patients/

patients were alive and well with no evidence of recurrent disease 2, 3 and 10 years after treatment. No follow up information is available for patients with simple intradermal naevi.

TABLE 44 SHOWING THE AGE AT ONSET OF 27 PATIENTS WITH OCULAR MELANOMA

Age Range	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
No.	-	1	1	4	5	7	5	3	1
%	-	3.7	3.7	14.8	18.5	25.9	18.5	11.2	3.7

OCULAR MELANOMA

The primary tumour arose within the ocular globe in 27 instances. The cases are included primarily to allow a comparison of the fate of patients with ocular melanoma with that of those with cutaneous primaries. The clinical and histological features have been examined and are recorded. The number of cases available is too small to allow any division into subgroups in respect of the survival of patients with specific clinical or histological features.

CLINICAL FEATURES

Sixteen of these patients were male, the remaining 11 female. Their ages ranged from 20 to 83 with a mean of 53.35 years. Table 44 shows the distribution of these cases divided by age at onset. The tumour is seen to occur most frequently in the 5th to 7th decades. This is in agreement with the findings of Wright (1949) and indeed with most previous authors.

Not surprisingly the left and right eye were equally frequently affected (L: 13. R: 14). The choroid was the primary site in 25, the iris in 1 and a combined origin from the ciliary body and adjacent choroid was noted in the remaining case.

The most frequent symptom was that of diminishing vision. Sixteen patients (59.3%) had this complaint. Secondary glaucoma (5 cases i.e. 18.6%) and iritis (3 cases i.e. 11.2%) were the/

TABLE 46 SHOWING THE DURATION OF PRESENTING SYMPTOMS IN OCULAR MELANOMA

Duration	Less than 3/12	3-6/12	6-12/12	1-2 Years	More than 2 Years
No. of Cases	12	2	1	2	5
% of Whole Group	44.5	7.4	3.7	7.4	18.5

the next most common presenting features. Other complaints were of a visibily increasing growth on the eye and a "fullness" in the eye. One tumour was noted incidentally by an ophthalmologist while treating a patient for cataract. A history of previous trauma was recorded by one patient and another had had exudative retinitis for several years. Table 45 summaries these findings.

TABLE 45 SHOWING THE FREQUENCY OF OCCURRENCE OF CERTAIN SYMPTOMS IN MALIGNANT MELANOMA OF THE EYE

Clinical Feature	Number	%
Diminishing vision	16	59.3
Secondary glaucoma	5	18.6
Iritis	3	11.2
Eye felt full	1	3.7
Visible growth	1	3.7
Noted by attending doctor	1	3.7
History of trauma	1	3.7
Exudative Retinitis	1	3.7

The symptoms produced by tumours in this site are directly attributable to the mechanical effects of their growth, e.g. detachment of retina, blockage of anterior angle. The duration of such symptoms does not, therefore, accurately indicate the time during which a tumour has been present, merely the time at which it became large enough to produce such symptoms. Table 46 shows/

shows the duration of these symptoms. From this table it is clear that the symptoms in 12 instances (44.5%) had been present for a very short time, a matter of days in some cases. At the other extreme in 5 instances (18.5%) the symptoms had been present for more than 2 years, as long as 4 years in 1 case.

HISTOLOGICAL FEATURES

1. Cell Type

The predominant cell was spindle shaped in 8 cases (29.6%), epithelioid in 7 cases (25.9%) and a mixture of both was noted in12 (44.5%). Considerable numbers of cells with clear cytoplasm like melanocytes were noted in 2 instances (7.4%).

The type of cell forming these tumours has been carefully examined and used as the basis for a method of assessing prognosis by Callender (1931). This author divided the cells into spindle A and B, fascicular and epithelioid and believed that the spindle forms were less malignant. This has been confirmed by several subsequent authors such as Hogan and Zimmermann (1962). These authors believe it is possible to simplify the classification into spindle celled tumours and epithelioid or mixed tumours and report, respectively, a 33% and 82% 10 year mortality for these groups. Reese (1947) thought that tumours containing distinctly branched cells had a specially bad prognosis, but Hogan and Zimmermann (1962) believe this to be due to the association of epithelioid/

epithelioid cells in this type of tumour. Flocks et al. (1955) noted that small tumours had a frequent association with spindle cells and postulated that the spindle cell tumour might represent a midpoint between naevus and melanoma.

2. Mitotic Rate

Mitoses were seen very infrequently. At most one or two were visible on examination of the whole tumour area.

3. Cellular Response

In contrast to the findings in cutaneous malignant melanoma a significant cellular reaction at the periphery of the tumour was noted in only 3 cases (11.1%). In two instances the cellular response consisted of lymphocytes alone, in the other a mixture of lymphocytes and plasma cells was noted.

4. Pigment Content

This varied widely. No pigment or very light pigmentation was noted in 12 cases (44.4%). The pigment content was adjudged heavy or very heavy in 12 instances (44.4%). Wright (1949) stated that heavily pigmented tumours exhibited a higher degree of malignancy.

5. Connective Tissue Pattern

No evidence of attempted encapsulation was noted. The connective tissue content of these tumours was generally low. Four tumours showed some evidence of subdivision into packets.

It has been shown by Wilder and Paul (1951) that tumours with a high content of reticulin are of a relatively low malignancy. This is thought to be evidence of a host response. Another interpretation of these facts is that these tumours are inherently of slow growth allowing the growth of the stroma to keep pace with tumour growth.

6. Evidence of Extraocular Spread

This was seen in 9 cases (33.3%). Of these 9 cases, 4 are alive and apparently free of disease at periods varying from 4 to 9 years after treatment, 2 died of unrelated causes 3 and 7 years after treatment and 3 died of melanomatosis 8 months, 2 years and 5 years after treatment respectively. Extraocular spread, despite the results noted in this small series is generally held to be an unfavourable sign in the evaluation of prognosis.

Type of Treatment

All patients had enucleation of the affected eye. This was followed by exenteration of the orbital contents in 3 of the patients who had evidence of extraocular spread. Enucleation was preceded by diagnostic iridectomy in one case.

One/

TABLE 47 SHOWING THE RATE AND 5 YEAR SURVIVAL RATE OF 27 PATIENTS WITH OCULAR MELANOMAS

Total Cases	Dead Melanoma		Dead Other Causes		Alive		Lost to Follow up		Available 5 Year		Alive 5 Years	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
27	9	33.3	2	7.4	13	48.3	3	11.1	19	70.4	12	63.2

TABLE 48 SHOWING THE SITE OF METASTASES IN POST MORTEM EXAMINATION OF PATIENTS WITH OCULAR MALIGNANT MELANOMA

Site	Local	Nodal	Disseminated	Liver	Brain	Pancreas	Lung	Skin
No. of Cases	2	1	8	6	1	1	1	1

One patient developed a pigmented area on the retina of his remaining eye after 28 months. This was treated initially by light coagulation to no effect. In view of this therapeutic failure he was given a course of radiotherapy.

Results of Treatment of Ocular Melanoma

It has proved impossible to obtain accurate follow up information concerning 3 of the patients. Of the remaining 24, 13 (54.2%) are alive and well at times varying from 2 to 11 years after treatment, 9 (37.5%) certainly died of melanomatosis and 2 (8.3%) are thought to have died of other unrelated disease with no clinical evidence of malignant melanoma at the time of death. The mean time between treatment and death in the 9 patients dying of melanoma was 34.2 months.

Nineteen cases were available for 5 year study. Twelve of these 19 patients were alive and free of disease 5 years after treatment. This represents a five year survival of 63.2% which is considerably better than than noted in the case of cutaneous primaries. (Table 47).

Metastasis in Malignant Melanoma of the Eye.

This was noted in 11 of the 27 patients (40.7%). The mean time from initial treatment to development of metastases was 23.9 months. The organs affected are shown in Table 48.

The high incidence of secondary melanoma in the liver is well known (Hogan and Zimmermann, 1962).

The/

The experience gained in this small series of cases provides a remarkably close parallel to that of Wright (1949) and Wilder and Paul (1951) and indeed is similar to the published results of most other authors reporting series of this kind.

THE MELANOCYTE, ITS DISTRIBUTION IN NORMAL SKIN AND IN THE VICINITY OF TUMOURS OF AND IN THE SKIN

It was noted in the examination of the histological material of this survey that there appeared to be an increased incidence of melanocytes in the stratum basale of the epidermis overlying and adjacent to tumours of melanocytic origin. Since the absolute number of melanocytes present in a tissue depends entirely on the mitotic activity of the antecedent melanocytes at that site, it wasconsidered that the estimation of the incidence of these cells would more accurately reflect the proliferative activity of the tissue than would any attempt at quantitative examination of pigmentation. It is important to realise that the degree of pigmentation represents functional rather than proliferative activity of melanocytes.

The assessment of the proliferative activity of melanocytes is of value in determining the extent of "field change" around a tumour. It may also be possible using this technique to estimate the degree of activity of an area of field change. In order to be of value to a routine histologist such a technique must be simple and not involve a lengthy delay for complicated tissue processing. In the examination of numerous vertical skin sections it has been found relatively simple to recognise the melanocytes. These lie intercalated between the cells of the stratum basale (Figure 6) or immediately beneath this layer of cells. Snell and Bischitz (1963) have also noted and commented upon the

presence/

presence of melanocytes in the latter position. At high power magnification (x320) and using tissues fixed and stained in the routine manner dendrites are not readily visible. Careful search, however, usually shows some evidence of these processes.

It is quite possible to count the number of melanocytes in a thin vertical skin section and to relate that number to the total number of cells in the stratum basale. This operation is greatly facilitated by the use of two hand operated counting devices. The total number of cells is recorded on one, the number of melanocytes on the other. In all instances at least 1,000 cells were counted and wherever possible a larger number. The tissues examined were stained by haemotoxylin and counterstained by eosin. Where pigmentation was heavy the tissue was bleached prior to examination. The incidence of melanocytes so obtained is mostly neatly expressed as a percentage of all basal cells and this is referred to as the "percentage incidence of basal melanocytes", (B.M.%).

The epidermal cells of the stratum basale can occasionally simulate melanocytes by having lightly staining cytoplasm. (Figure 6). The nuclear morphology of these cells is usually sufficiently typical to allow differentiation. Another source of occasional difficulty was the presence of a lymphocyte apparently located in or immediately below the stratum basale. In this context it is interesting to note that Andrew and Andrew (1949) regarded basal clear cells as lymphocytes in transition to epidermal cells/

cells. Since Wasserman (1963) reported that lymphocytes can transport melanin it is possible that these cells might well present some difficulty of interpretation. In fact no lymphocytes containing melanin were noted in this study and the occasional cell of this kind encountered adjacent to the epidermis was readily recognised.

In order to check the accuracy of recognition of the cells included in these counts as melanocytes two techniques were employed.

1. The melanocyte incidence was assessed on a slide stained for melanin and compared with that noted on a comparable slide from the same tissue stained by haematoxylin and eosin. A good measure of agreement was obtained in each case.
2. Some months after the original counts were performed random slides were selected and the counts repeated. A close measure of agreement was noted between the first and second counts.

THE INCIDENCE OF MELANOCYTES IN NORMAL SKIN

Prior to any examination of the incidence of melanocytes adjacent to tumours it was deemed necessary to establish the incidence of melanocytes in normal skin from patients of varying ages.

One hundred and thirty nine specimens of skin were obtained post mortem from 27 patients dying of various diseases in which/

which no disturbance of pigmentation was evident. Appendix 2 shows the incidence of melanocytes in these skin specimens.

The overall mean incidence of melanocytes regardless of site, sex and age is noted to be 9.1% with a range of values from 4 - 26%. The wide range of values from individual to individual and between areas within the same individual confirms the experience of Szabo (1954) and Staricco and Pinkus (1957).

THE EFFECT OF SEX ON MELANOCYTE INCIDENCE

TABLE 49 SHOWING THE EFFECT OF SEX ON THE INCIDENCE OF BASAL MELANOCYTES

Sex	No. of Specimens Available	Mean B.M.%	Range (%)
Male	54	8.01	4 - 23
Female	84	9.80	4 - 26

Melanocytes were found to occur with greater frequency in the epidermis of the skin of females than in that of males. Application of the "t" test to these figures reveals a statistically significant difference between the means (P lies between 0.05 and 0.02). Snell and Bischitz (1963) and Staricco and Pinkus (1957), using epidermis separation techniques and examining areas, noted no difference in melanocyte incidence between the sexes. If there is a higher incidence of melanocytes in the female this might/

might partially explain the higher incidence of melenomas in females.

THE EFFECT OF AGE ON MELANOCYTE INCIDENCE

TABLE 50 SHOWING THE INCIDENCE OF MELANOCYTES IN PATIENTS YOUNGER AND OLDER THAN 50 YEARS OF AGE

Age Group	No. of Specimens	Mean B.M.%	Range (%)
Under 50	16	11.32	6 - 26
50 and Over	109	8.60	4 - 23

Melanocytes were of less frequent occurrence in the older patients. The difference between the means is statistically significant (P lies between 0.05 and 0.02). This finding is in agreement with the work of Snell and Maschitz (1963) who reported a decrease in the incidence of melanocytes per square millimetre with increasing age. On a priori grounds it seems reasonable that in the process of senile skin atrophy these cells would not be selectively spared.

THE EFFECT OF SITE ON MELANOCYTE INCIDENCE

TABLE 51/

TABLE 51 SHOWING THE INCIDENCE OF MELANOCYTES IN VARIOUS AREAS OF THE BODY

Site	No. of Specimens	Mean B.M.%	Range (%)
Scalp	16	9.5	4 - 15
Thigh	22	8.2	4 - 16
Chest	21	9.6	4 - 26
Abdomen	28	8.0	4 - 14
Forearm	20	11.7	5 - 23
Upper Arm	10	12.0	5 - 22
Foot	21	7.4	4 - 15
Vulva	1	5.0	-
Prepuce	1	12.0	-

The data was analysed by the conversion of the percentage melanocyte incidences to angles using the usual arc-sin transformation. An analysis of variance was carried out after making suitable adjustments for missing values (Appendix 2). From these calculations it is apparent that the main variation in site incidence is between the upper limb and the remainder of the body. Other lesser variations were noted between areas in the female cases, but none approached the magnitude of the difference between the upper limb and other areas.

Regional variations in melanocyte incidence have been noted previously. Billingham (1948) noted a high incidence of melanocytes in the ear. Szabo (1954) noted a higher melanocyte population in the ear, cheek, forehead and neck and a lower population in the upper arm, forearm and thigh. Staricco and Pinkus (1957) noted a wide regional variation in incidence. Examination of the figures from this latter paper shows that the highest incidence noted

noted was in the genital area with a mean melanocyte count of 1668/sq. m.m. The back, head and neck and upper limb showed the next highest incidence with 1340, 1340 and 1302 melanocytes per sq. m.m. respectively. The lowest incidence of melanocytes was noted in the chest and abdomen with 860 and 754 melanocytes per sq. m.m. respectively.

The occurrence of high values such as 22 and 23% in the material of this study is surprising and somewhat disconcerting. These represented a true diffuse increase in the incidence of melanocytes in which the ratio of basal cells to clear cells is reduced from around 10:1 to 4:1. Focal aggregations of cells such as are present in lentigo were not seen. Comparative studies have shown that there are marked species variations in the disposition of melanocytes, Hamilton (1940), Rawles (1953), Dalton (1953), Berg and Gordon (1953), Ghadially et al. (1960) and Straile (1964). It is possible that islands of high melanocyte concentration may exist in human skin. Such foci would not be clinically apparent in the absence of increased melanogenesis.

The figures for melanocyte incidence presented in this thesis are derived exclusively from vertical skin sections. Snell and Bischitz (1963) stated that accurate melanocyte counting was not possible using vertical skin sections. Having compiled the data on the normal incidence of melanocytes present in the foregoing sections it was thought useful to see if it were possible to compare the results obtained by this simple technique and those obtained /

TABLE 52 SHOWING THE INCIDENCE OF MELANOCYTES IN VARIOUS AREAS OF THE BODY IN THE ADULT EPIDERMIS AS DETERMINED IN THIS STUDY AND COMPARING THESE FIGURES TO THE RESULTS OF PREVIOUS AUTHORS. RESULTS EXPRESSED IN MELANOCYTES PER SQUARE MILLIMETRE

	PRESENT SERIES				COMPARATIVE FIGURES		
Case No.	Site of Specimen	Age in Years	Sex	Incidence of Melanocytes/ M.M.^{2}	Staricco & Pinkus	Szabo	Snell & Bischitz
6.64	Forearm	78	F	2360	950-2500	820-2320	-
5.64	Chest	55	F	1610	550-1050	-	-
5.64	Abdomen	55	F	2330	400-1273	-	740-2200
4.64	Foot	75	M	896	1441	-	-
4.64	Forearm	75	M	1490	950-2500	820-1210	-
6.64	Scalp	78	F	1575	700-1870	1280-2300	-
6.64	Upper Arm	78	F	1460	950	820-1540	-
5.64	Foot	55	F	1130	1441	-	-

obtained by separating the epidermis from the dermis and counting area incidences. It is possible to measure accurately the exact length of a segment of dermoepidermal junction using a projecting microscope and a graticule. By counting the total number of cells in the stratum basale of such a segment of known length the number of cells per millimetre of epidermis can be derived. The comparable figure per square millimetre is simply obtained by squaring the total number of cells per millimetre. Since the percentage incidence of melanocytes is known and has been derived from a number of random samples it is mathematically acceptable to apply the linear percentage incidence to the estimation of area incidence of melanocytes. An alternative to this is to take the square root of the area incidence per square millimetre of melanocytes reported by previous authors and compare this with the linear incidence per millimetre observed in this material.

Table 52 shows the results of several calculations of the kind described above and compares them with comparable results from Szabo (1953), Staricco and Pinkus (1957) and Snell and Bischitz (1963). Szabo's study is based on 34 cases, Staricco's on 63 and Snell's on 30.

In all three previous series the examination followed separation of the epidermis and staining with D.O.P.A.

Examination of Table 52 shows that the figures from this series, derived as they are from vertical skin sections, are of the same order as and quite comparable with the earlier results. The/

TABLE 53 SHOWING THE INCIDENCE OF MELANOCYTES OVER AND ADJACENT TO VARIOUS TUMOURS DERIVED FROM THE MELANOCYTE

Type of Tumour	No.	Mean Incidence of Melanocytes over Tumour (%)	Junctional Activity Over Tumour	Mean Incidence of Melanocytes Over Tumour (%)	Junctional Activity Adjacent to Tumour
Primary Malignant Melanoma	59	22.6	Yes	17.2	Some
Lentigo Maligna	8	23.1	No	19.7	No
Compound Naevus	133	22.6	Yes	13.2	No
Simple Intradermal Naevus	30	15.3	No	14.0	No
Juvenile Melanoma	12	28.5	Yes	13.6	No
Dermal Secondary Malignant Melanoma	12	12.9	No	11.7	No
TOTAL	252				

The main significance of this is that, from the standpoint of a routine histologist, the figures reported for the normal incidence of melanocytes in routine vertical skin sections seem likely to be correct. From a practical point of view a melanocyte incidence in excess of 15% may generally be regarded as abnormal. It must, however, be remembered that there is wide variation from area to area within the individual and between individuals and that occasional areas of high incidence do appear to occur in a random manner.

THE INCIDENCE OF MELANOCYTES IN RELATION TO SKIN TUMOURS.

Having established the incidence of melanocytes in normal skin the distribution of those cells in relation to various cutaneous tumours was examined. The tumours were divided into those of melanocytic origin and those not derived from the melanocyte.

A. MELANOCYTE DERIVED TUMOURS

1. Simple Intradermal Naevi

By definition there is no evidence of junctional activity over or adjacent to these tumours. The incidence of melanocytes in the epidermis over the tumour and adjacent to it is either normal or minimally raised. The mean incidence of melanocytes over the tumours is 15.3% with a range of 9 - 26%. The mean incidence

of/

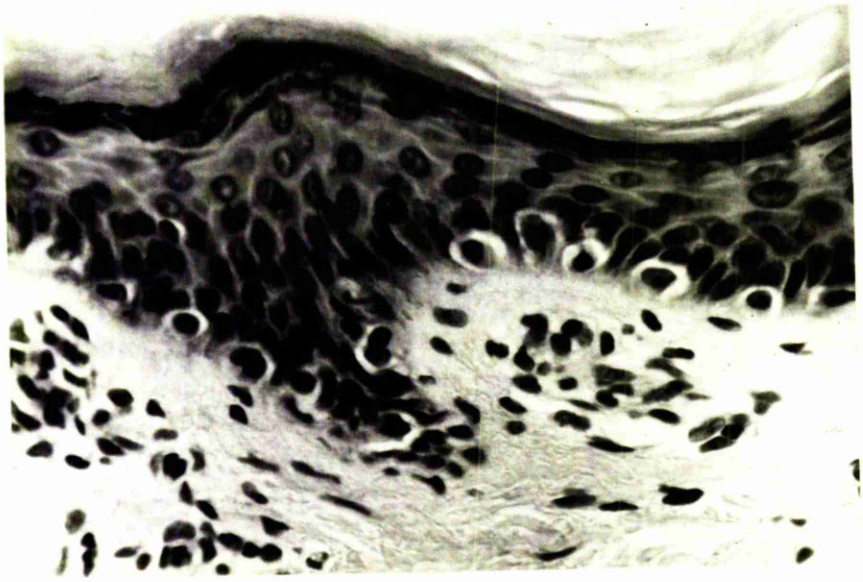


FIGURE 42 Showing the histology of an area of lentigo maligna. H. and E. (x450).

of melanocytes in the epidermis adjacent to the tumour is 14.0% with a range of 6-30%.

2. Compound Naevi

Junctional change is present over the tumour in all these tumours and is a diagnostic feature. In no case was junctional activity seen beyond the limit of the main tumour. The mean incidence of basal melanocytes over the tumour (excluding the foci of junctional activity) was 22.6% with a range of 6-50%. In the majority of cases the incidence of melanocytes was markedly above the normal value. Per contra the mean incidence of basal melanocytes in the adjacent epidermis was 13.2% with a range of 4-40%. A high incidence of basal melanocytes in this situation was seen in a minority of cases (21.5%). Patterns of melanocyte distribution similar to those designated A, B and C in the case of malignant melanoma (vide supra) were noted. Pattern A (symmetrical field change) was noted in 20 cases, 21.5%. Pattern B (no field change) was noted in 53 cases, 57.7%. Pattern C(asymmetrical field change) was noted in 19 instances, 20.8%.

3. Lentigo

In the histological diagnosis of this condition it has been considered that such a diagnosis is only appropriate if the increase in melanocytes is a linear one i.e. parallel to the epidermo-dermal interface. (Figure 42). If more than one layer of/

of such cells is present, whether focally or over an area it has been considered that such an appearance represents junctional change and the diagnosis of junctional naevus has been recorded.

The mean incidence of melanocytes in the epidermis of such lesions is 23.1% with a range from 10-40%. The low figure of 10% included in the range is explicable in the following manner. Two patterns of lentigenous change have been noted. In the first, which is that classically described, there is a diffuse increase in the population of basal melanocytes. This may be of such a magnitude that stretches of the stratum basale may consist exclusively of melanocytes. In the second type there are scattered foci in which groups of 5 - 10 melanocytes lie side by side separated from othersimilar groups of cells by apparently normal tissue.

The mean incidence of melanocytes in the epidermis adjacent to areas of lentigo is 19.7% with a range from 8 - 30%. The most frequent appearance is of a gradual decrease in the number of melanocytes until the basal cell/melanocyte ratio is that normal for the area of skin involved. It is, however, worth reiterating that a "pepper pot" punctate distribution does occur not infrequently.

4. Juvenile Melanoma

The mean incidence of melanocytes in the epidermis overlying these tumours is 28.5% with a range of 11 - 51%.

Junctional/

Junctional activity is associated with this high incidence of melanocytes in 11 of the 12 cases examined. It is of interest to note that these tumours and malignant melanomas had the highest incidence of melanocytes noted in this study. This no doubt reflects the intense proliferative activity of these tumours which makes their benign behaviour the more enigmatic. The high melanocyte incidence may also be related to the youth of the patients. Melanocytes are of more frequent occurrence in the skin of young people. One of the juvenile melanomas occurred in an adult, a woman aged 31. It is of interest to note that the proportion of melanocytes in the stratum basale over the tumour in this case was 27.0%. This is a high figure, but not by comparison with other juvenile melanomas. Spits (1948) in her original description of the juvenile melanoma noted that the epidermal changes, so abundant over these tumours were not seen lateral to them. This fact is confirmed by the results of the present study. The mean incidence of melanocytes in the epidermis adjacent to the e tumours is 13.6% with a range from 9 - 31%. There wasno evidence of junctional activity lateral to any of these tumours.

The significant points from these observations are:

1. Simple intradermal naevi, compound naevi, junctional naevi, lentigo and juvenile melanomas are all associated with a raised incidence of melanocytes in the stratum basale of the epidermis over the tumour and in some instances in that adjacent to the tumour.

2. The degree of increase of the incidence of melanocytes appears

to/

to be related to the degree of activity of the tumour.

3. In some cases the increase is almost physiological in others probably a form of premalignent change or carcinoma in situ.

It seems possible that this relatively high incidence of melanocytes associated in some cases with junctional activity, is the true reason why a disproportionately large number of malignent melanomas appear to arise in relation to pigmented tumours.

5. Malignant Melanoma.

1. Primary Malignant Melanoma

All primary malignent melanomas, in which there was no ulceration, showed junctional activity over the tumour. The mean incidence of melanocytes in the epidermis over the tumour was 22.6% with a range of 5 - 56%. Junctional change was present lateral to the tumour in 54 of 80 cases, 67.5%. In these cases the mean incidence of bosal melanocytes adjacent to the tumour was 19.7% with a range of 4 - 45%. In the remaining 32.5% of cases where no lateral junctional change was present the mean incidence of basal melanocytes in the epidermis adjacent to the tumour was 14.7% with a range of 1 - 31%.

The existence of three patterns of field change in relation to primary malignant melanoma has already been noted and their significance in relation to prognosis discu sed.

2. Dermal/

2. Dermal Secondary Malignant Melanoma

Adequate material for study of this type of tumour was available in 8 instances. The mean incidence of melanocytes in the epidermis over the tumour is noted to be 12.87% with a range from 5 - 17%. The comparable figure for the epidermis adjacent to the tumour is 11.66% with a range from 6 - 19%. There was no evidence of junctional activity over or adjacent to the tumour.

There is, therefore, no significant increase in the melanocytes of the epidermis in relation to these tumours. In this respect secondary malignant melanoma behaves similarly to secondary neoplasms of non-melanocytic origin which are located subepidermally. This finding has another significance. It supports the contention that epidermal changes adjacent to a primary malignant melanoma are part of a field change and not secondary to the influence of the tumour.

Petersen et al. (1962) suggested that a dermal secondary malignant melanoma might occasionally evoke junctional change in the overlying epidermis. This is contrary to the experience of Allen and Spitz (1953). We have certainly noted no evidence of such a phenomenon in the material of this series. Botha and Lennox (1954) reported what they regarded as the repigmentation of an amelanotic dermal secondary malignant melanoma on contact with the overlying epidermis. They did not note any evidence of junctional activity.

TABLE 54 SHOWING THE INCIDENCE OF MELANOCYTES IN RELATION TO VARIOUS COMMON SKIN TUMOURS

Condition	No. of Cases	Mean Incidence of Melanocytes Over Tumour (%)	Range %	Mean Incidence of Melanocytes adjacent Tumour (%)	Range %
Rodent Ulcer	4	10.6	7 - 13	12.9	8 - 19
Squamous Carcinoma	3	6.5	3 - 10	9.8	8 - 11
Basal Cell Papilloma	12	10.2	5 - 16	9.1	7 - 16
Secondary Carcinoma	20	9.75	7 - 18	8.87	-
Squamous Papilloma	1	7.2	-	7.5	-
Basal Tumour	1	7.1	-	9.8	-
Peutz Jegher Syndrome	1	8.4	-	-	-

B. TUMOURS NOT DERIVED FROM THE MELANOCYTE

1. The Jadassohn-Tièche Naevus (Blue Naevus)

Eight blue naevi were available for examination. In one of these the tumour was associated with a compound naevus. The incidence of basal melanocytes (associated with junctional change) overlying this was 28.0%. In the remaining 7 tumours the mean incidence of basal melanocytes over the tumour was 15.6% with a range from 10 - 24%. The mean incidence of basal melanocytes in the adjacent epidermis was 15.8% with a range from 7 - 23%. It is apparent that there is no increase in the incidence of basal melanocytes in the epidermis overlying these tumours in comparison with the adjacent epidermis. This is considered to be evidence against a melanocytic origin of these tumours.

2. Dermal Secondary Tumours other than Malignant Melanoma

Twenty secondary deposits of tumour in the dermis were examined. These comprised eleven carcinomas derived from a breast primary, 6 adenocarcinomas from an alimentary primary, 1 adenocarcinoma from the uterus, one squamous carcinoma from bronchus and 1 deposit of leukaemia. The tumour deposits lay at varying levels in the dermis, some in close proximity to the epidermis.

The mean incidence of melanocytes in the epidermis overlying these tumours was 9.75% with a range from 7 - 18%. The mean/

mean incidence of melanocytes in the epidermis adjacent to these tumours was 8.8%. It is apparent that there is no increase in the incidence of epidermal melanocytes in proximity to tumours of non-melanocytic origin.

It is considered that this is a valid point to be considered in the diagnosis of difficult dermo-epidermal or dermal tumours in whichthe possibility of malignant melanoma is being considered. The absence of an increase in the incidence of melanocytes adjacent to and above the tumour could be construed as evidence against the melanomatous nature of the tumour.

3. Primary Skin Tumours

Four rodent ulcers and 3 squamous carcinomas were examined. (Table 54). The mean incidence of basal melanocytes at the deep edge of the growing tumour was 9.0% with a range from 3 - 13%. The mean incidence of melanocytes in the epidermis adjacent to the tumours was 10.5% with a range from 8 - 19%. It is again to be noted that there is no increase in the incidence of basal melanocytes over that normal for the site of the tumour.

This can be interpreted as evidence against the origin of melanocytes from basal epidermal cells. If they were so derived it would be reasonable to expect some increase in these cells in relation to the gross increase of the cells of the stratum germinativum seen in these tumours. Instead this increase of epidermal cells seems to serve merely to separate the existing melanocytes/

melanocytes further than is normal and in some instances produce a remarkably low incidence of clear cells.

4. Basal Celled Papillomas

Since these are frequently confused with malignant melanomas clinically it was considered that histological examination of a group of such tumours would be of interest. Twelve were examined. The mean incidence of basal melanocytes in the deep surface of the expanded epidermis produced by these tumours was 10.17% with a range from 5 - 16%. The mean incidence of melanocytes in the epidermis adjacent to the tumours was 9.1% with a range from 7 - 16%. No increase in melanocytes was noted in the epidermis over the tumour.

5. Dermatofibroma (Sclerosing Angioma)

Three of these tumours were examined. The mean incidence of melanocytes in the epidermis over the tumour was 8.2% with a range from 7 - 9%. The mean incidence of melanocytes in the epidermis adjacent to the tumour was noted to be 7.6% with a range from 6 - 10%.

6. Other Skin Tumours

A squamous papilloma and a simple basal celled tumour of uncertain type were examined. No increase in the incidence of/

of basal melanocytes was noted in either case.

7. Peutz Jegher Syndrome

The mean incidence of basal melanocytes in a portion of pigmented skin from a petient with this condition was noted to be 8.4%. The lesion is thus similar to a freckle with increased pigmentation of the cells of the stratum basale, but no increased incidence of melanocytes.

THE MORPHOLOGY OF THE MELANOCYTE AND SOME OBSERVATIONS ON ITS PHYSIOLOGY

No attempt at examination of the morphology of the melanocyte was made in this study. Excellent descriptions of this facet of the subject have been produced by various authors including Billingham (1948) and Shukla et al. (1954). The latter authors in addition to the descriptive aspects of their study make the interesting suggestion that the melanocyte network may occupy a space or potential space at the epidermo-dermal junction. Morphologically distinct sub-groups of melanocytes have been described by Grand et al. (1935), Szabo (1954), Shukla et al. (1954) and Staricco and Pinkus (1957). A morphological similarity to glial cells was noted by Billingham (1948) and Staricco and Pinkus (1957).

The location of these cells in the epidermo-dermal region is generally agreed. Szabo (1954) and Shukla et al. (1954) reported/

reported that there was an increased density of melanocytes on the epidermal ridges. Staricco and Pinkus (1957) while not entirely disagreeing with this view believe that the appearance is exaggerated by the optical effect of looking at a sloping surface in the plan view. The experience gained from the examination of the material comprising this study (vertical skin sections without exception) is that there is a tendency for the melanocytes to be more common on the epidermal ridges.

Relatively little is known of the control of melanogenesis and melanocyte proliferation. Some recent work on the effect of hormones on melanocytes is, therefore, very welcome. Snell (1962) reported that in guinea pigs, following administration of Beta M.S.H. melanocytes became more frequent, larger and the dendrites more complex. An increase in pigmentation, both intracellular and free, was also noted. This author believes that oestrogen and progesterone stimulate melanogenesis. The concept of hormonal control of the melanocyte is by no means recent. Snell (1962) quotes Smith (1916) and Allen (1916) as the earliest workers in this field.

The variable morphology of melanocytes is generally attributed to one or both of two causes:

1. Variations in maturity (Staricco, 1960).
2. Melanogenetic activity.

It is not possible to relate the overall melanocyte incidence to the common sites of occurrence of primary malignant melanoma. It is possible that one or other of the morphologically seperate/

separate types of melanocyte is more prone to malignent transformation. Such a suggestion is purely speculative, but information on the distribution within the body of both types of melanocyte might well prove to be of considerable interest.

A METHOD FOR THE ASSESSMENT OF PROGNOSIS IN MALIGNANT MELANOMA

The aim of this study was, by examination and analysis of the histological material from a group of patients with malignant melanomas to correlate the histological appearances of malignant melanoma with subsequent clinical course. No single histological attribute has been noted which would allow unequivocal assessment of prognosis. In view of the numerous previous reports on this subject, it is probably rather ingenuous to consider that such a single histological feature might exist. The value of accurate assessment of prognosis is self evident and it seems that, although there is no one major factor on which an opinion on this subject can be based, there are numerous smaller factors which taken together allow an informed and intelligent opinion to be ventured in an individual case. Experienced clinicians can frequently offer a very accurate prognosis in individual cases of malignant disease. Such accuracy is doubtless the result of long clinical experience and an ability to recognise combinations of clinical and pathological features which have an especially favourable or unfavourable significance. Since this type of familiarity with a disease is less readily obtained by the individual in the management of less common forms of malignancy it would be of great value if such information, obtained from a large number of cases, were available in a readily useable form. With this end in view an attempt has been made to delineate the clinical

and/

TABLE 55

PROGNOSTIC SCORE SHEET

Clinical			Pathological	
Feature		Score	Feature	Score
SEX	Female	1	Relation to Epidermal Appendages above	1
	Male	6	below	4
SITE			Mitotic Rate	
	Head and Neck	1	Less than 1 per High Power Field	1
	Lower Limb	3	1 per High Power Field of More	3
	Trunk	6	Ulceration	
	Upper Limb	2	No	1
	Anogenital	6	Yes	4
	Occult	8	Invasion of Lymphatics or Vessels	
	Subungual	4	No	1
	Mucosal	8	Yes	4
SIZE			Field Change**	
	Less than 2.0 cm. Diam	1	A	1
	2.0cm. or Larger Diam	4	B	5
			C	2
DURATION OF SYMPTOMS			Cellular Reaction	
	Less than 2 years	1	Lymphocyte	1
	2 Years of More	2	None	2
	Exposed Site	1	Lymphocyte/Plasma Cell	3
	Non-Exposed Site	5		
NODAL INVOLVEMENT				
	No	1		
	Yes	10		
DISSEMINATED DISEASE		15		
INCISION BIOPSY		2		

** Based on incidence of melanocytes *vide supra*.

and pathological features which seemed significant in the patients of this series.

An attempt was made to assess the quantitative effect of each of these attributes. In this respect the quantitative analysis is necessarily a very approximate one. The method adopted was to consider each attribute in turn and compare the overall incidence of death from melanoma in patients with and without the feature under consideration. The group of patients with the lowest incidence of death from melanoma was considered to represent unity and for each 5% by which the incidence of death from melanoma in the less favoured group exceeded the incidence of death in the lower death rate group a further point was added to the score. An example will clarify this system. In the analysis of the fate of patients divided by sex it was noted that, at the end of the study period, 69.3% of the males were known to have died of melanoma. The comparable figure for female patients was 40.0%. In the scoring system 1 point is awarded to a female patient and 6 (i.e. 6x5%, the difference in incidence of death between males and females) to a male patient. This technique was applied to all attributes in which a significant difference in prognosis was noted between sub-groups in this series. Table 55 shows the results of applying this technique to the material of this study. All patients in whom full and accurate clinical and pathological information was available were assessed using these values and the sum of the individual values calculated. This latter value is known as the "Initial

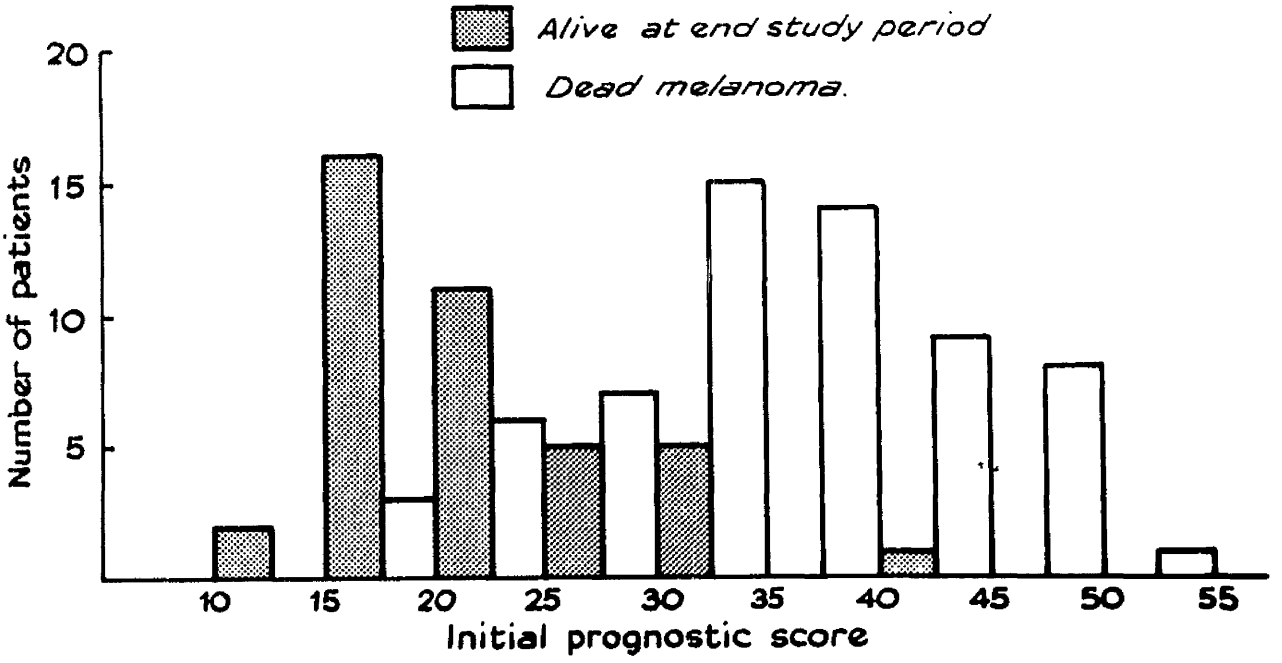


FIGURE 43 A nomogram showing the initial prognostic scores of patients with cutaneous malignant melanomas.

TABLE 56 SHOWING THE "INITIAL PROGNOSTIC SCORES" OF PATIENTS WITH CUTANEOUS MALIGNANT MELANOMA

Score Range	Total	Dead Melanoma		Alive end Study		Dead other Causes		Corrected Dead Melanoma	
		No.	%	No.	%	No.	%	No.	%
10 - 14	2	-	-	2	100.0	-	-	-	-
15 - 19	27	3	11.3	16	59.3	8	29.6	7	25.9
20 - 24	22	6	27.3	11	50.0	5	22.7	8	36.4
25 - 29	22	7	31.9	5	22.7	10	45.4	12	54.5
30 - 34	23	15	65.2	5	21.8	3	13.0	16	69.5
35 - 39	15	14	93.4	-	-	1	6.7	15	100.0
40 - 44	11	9	81.8	1	9.1	1	9.1	9	81.8
45 - 49	8	8	100.0	-	-	-	-	8	100.0
50 - 54	1	1	100.0	-	-	-	-	1	100.0
TOTAL	131	63	48.1	40	30.6	28	21.3	76	58.0

"Initial Prognostic Score".

Figure 43 and Table 56 show the results of application of the Initial Prognostic Score Technique to 131 patients from this series. It is stressed that these values are based on the information available at the time of initial biopsy. No allowance is made in this assessment for subsequent clinical developments. These figures are thus based on an assessment made at a fixed moment in time when assessment of prognosis is highly important in the light of difficult decisions on further treatment.

It is apparent that while there is a bimodal distribution of patients in Figure 43, the separation of good and bad prognosis patients is not complete. It would be surprising if the situation were different in dealing with such an unpredictable tumour. Examination of Table 56 does reveal certain interesting figures. Of 51 patients with an initial prognostic score of less than 25, 29 (57.0%) were alive at the end of the study and 9 (17.7%) were known to have died of melanoma. Forty five patients had an initial prognostic score between 25 and 34. Ten (22.2%) of these were alive at the end of the study period and 22 (49.0%) were known to have died of melanoma. Thirty five patients had a prognostic score of 35 or more and only one of these patients (2.9%) was alive at the end of the study period. Thirty two (91.5%) were known to have died of melanoma.

The final column in Table 56 requires some explanation. It is headed "Corrected Dead Melanoma". The assessment of the cause of/

of death in an individual patient is dependent, in most cases, on the clinical assessment of the physician attending that patient at the time of death. Purely clinical assessment is necessarily an inexact procedure and the separation of, for instance, a purely infective chest condition and an area of infection secondary to a metastatic deposit in the lung, in the absence of radiographic of autopsy evidence must necessarily be fallible. It is possible that some of the patients reported as dying of unrelated disease may in fact have died of melanomatosis.

In an attempt to assess more accurately the death rate from melanoma the group of patients believed to have died of other diseases was re-examined. It was found possible to divide these patients into two subgroups on the basis of time of death in relation to initial treatment for melanoma, stated cause of death and clinical information on the mode of death. Of 32 patients alleged to have died of intercurrent disease there was a strong probability that death was NOT due to melanoma in 19 (59.3%). In the remaining 13 cases (40.7%) it was not possible to exclude melanoma as the cause of death. Table 57 summarises these findings.

TABLE 57/

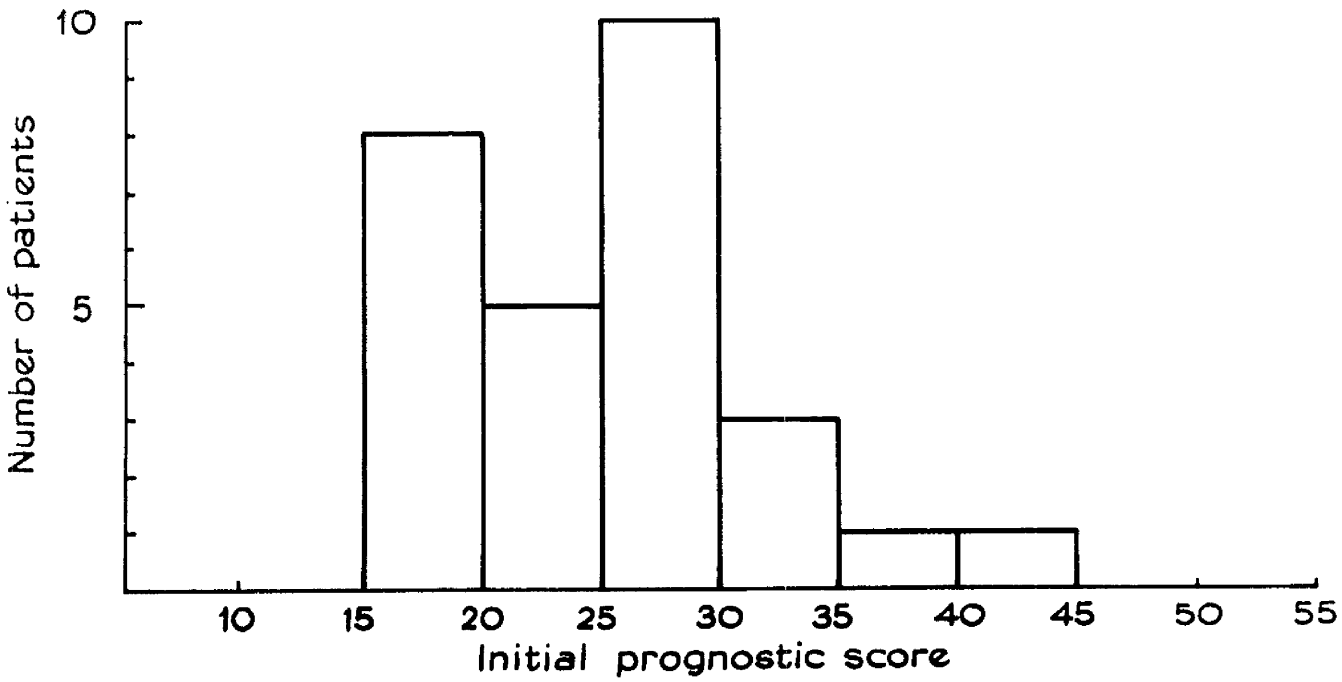


FIGURE 44 Showing the "initial prognostic scores" of patients alleged to have died of causes other than malignant melanoma.

TABLE 57 AN ANALYSIS OF PATIENTS ALLEGED TO HAVE DIED OF CAUSES OTHER THAN MALIGNANT MELANOMA

	No.	%
Total number of patients alleged to have died from causes other than melanoma	32	100.0
Patients in whom melanoma was unlikely as a cause of death	19	59.3
Patients in whom melanoma could not be excluded as a cause of death	13	40.7

From these figures it seems that, at worst, half of the patients alleged to have died of causes other than melanoma may have died of melanomatosis. Figure 44 provides possible confirmation of this. It is seen that the Prognostic Scores of the group of patients alleged to have died of intercurrent disease, are divided around 25. Thirteen patients had a score less than 25, 15 a score greater than 25.

The column in Table 56 headed "Corrected Dead Melanoma" is seen to consist of known deaths from melanoma plus 50.0% of deaths alleged to be due to causes other than melanoma. It represents the highest probable mortality from melanoma.

It is clear from Table 56 and Figure 43 that there is a direct relationship between the Initial Prognostic Score and the proportion of patients dying of melanoma (observed and corrected groups). Per contra there is an inverse relationship between the proportion of patients alive at the end of the study period and the Initial Prognostic Score.

Such/

TABLE 58 SHOWING THE FATE OF PATIENTS WITH PROGNOSTIC SCORES BASED ON HISTOLOGICAL APPEARANCES

Score Range	Total	Dead Melanoma		Alive end Study		Dead other Causes		Corrected Dead Melanoma	
		No.	%	No.	%	No.	%	No.	%
5 - 7	6	-	-	3	50.0	3	50.0	1	16.7
8 - 10	32	6	18.8	17	53.1	9	28.2	10	31.3
11 - 13	27	14	51.8	8	29.6	5	18.5	16	59.4
14 - 16	32	16	50.0	9	28.1	7	21.9	19	59.4
17 - 19	22	18	81.8	2	9.1	2	9.1	19	86.3
20 - 22	11	8	72.7	1	9.1	2	18.2	9	81.7
23 - 25	1	1	100.0	-	-	-	-	1	100.0
TOTAL	131	63	48.0	40	30.6	28	21.4	75	57.3

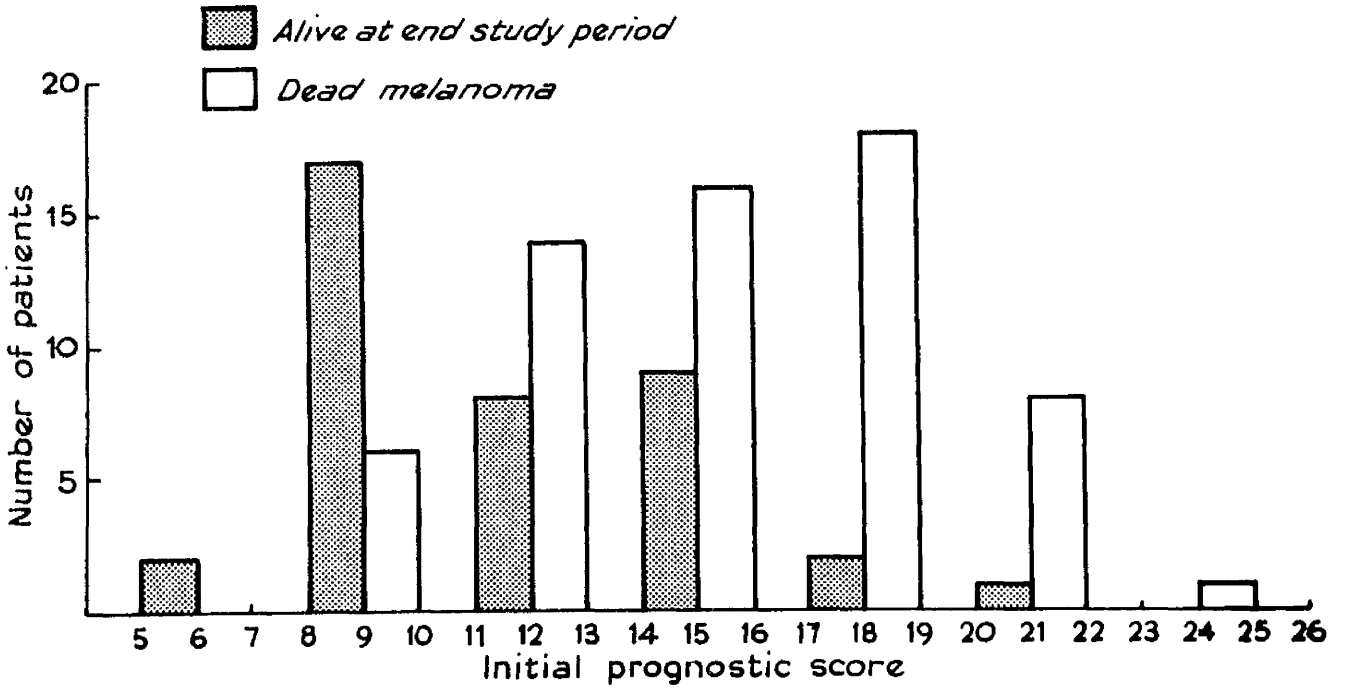


FIGURE 45 Showing the histology based prognostic scores of patients with cutaneous malignant melanoma.

Such a scheme could obviously be based on the other calculated results e.g. 5 year survival rate or death rate or proportions of patients alive at the end of the study period. This has been done, but no better separation of survivors and patients dying of melanoma has been noted by comparison with the technique described above.

THE ASSESSMENT OF PROGNOSIS BASED ON HISTOLOGICAL APPEARANCES

On occasion it may be necessary for a histologist to venture an opinion of prognosis based solely on histological material. This is always an undesirable practice and such a prognosis will inevitably be less reliable than one based on all available information, clinical and pathological. In an effort to see what correlation existed between histological appearances and prognosis the segment of the Initial Prognostic Score derived from histological appearances has been examined. Table 58 and Figure 45 show that there is a similar variation in survival and death rate with scoring to that noted with the "full" score. The overlap of good and bad prognosis cases is, however, more marked.

Certain observations can be made from the figures in Table 58. Thirty eight patients had a score of less than 10. Twenty of these patients (52.6%) were alive at the end of the study period and 6 (15.8%) were known to have died of melanoma. Fifty nine had a score between 10 and 16. Seventeen (28.8%) of

these/

these patients were alive at the end of the study period and 30 (50.8%) were known to have died of melanoma. Thirty four patients had a score in excess of 16. Only three of these patients (8.8%) were alive at the end of the study period and 27 (79.5%) were known to have died of melanoma.

A prognosis can, therefore, be offered on the basis of histology alone. Such a prognosis is less accurate than that based on a clinicopathological assessment at the time of initial definitive treatment and very much less accurate than that based on contin ous patient surveillance.

AN ANALYSIS OF THE PATIENTS IN THE AMBIGUOUS AREA OF THE SCORE CHART

It was initially considered possible that alteration of the loadings of individual attributes might produce a more complete separation of the two populations. Several alternative combinations of loadings have been tried with no striking improvement in population separation. The clinical and histological data of patients with ambiguous middle range scores has been examined. This group of patients is separable into survivors with high and, therefore, unfavourable scores and patients dying from melanoma despite a favourable low score. No common factor was noted in the former group and their score could not be reduced using the criteria accepted for the patients as a whole. All the favourable score patients who died of melanoma developed clinically evident nodal metastasis or dissemination. Of 9 such cases who had a prognostic score/

TABLE 59 SHOWING THE FATE AND PROGNOSTIC SCORES BASED ON CONTINUOUS SURVEILLANCE OF PATIENTS WITH CUTANEOUS MALIGNANT MELANOMA

Range Score	Total	Dead Melanoma		Alive and Study		Dead other Causes		Corrected Dead Melanoma	
		No.	%	No.	%	No.	%	No.	%
10 - 14	2	-	-	2	100.0	-	-	-	-
15 - 19	24	-	-	16	66.7	8	33.3	4	16.7
20 - 24	16	-	-	11	68.8	5	31.2	2	12.5
25 - 29	15	-	-	5	33.3	10	66.7	5	33.3
30 - 34	25	17	68.0	5	20.0	3	12.0	18	72.0
35 - 39	27	26	96.3	-	-	1	3.7	26	96.2
40 - 44	17	15	88.3	1	5.9	1	5.9	15	88.2
45 - 49	4	4	100.0	-	-	-	-	4	100.0
50 - 54	1	1	100.0	-	-	-	-	1	100.0
TOTAL	131	63	48.2	40	30.5	28	21.3	75	57.3

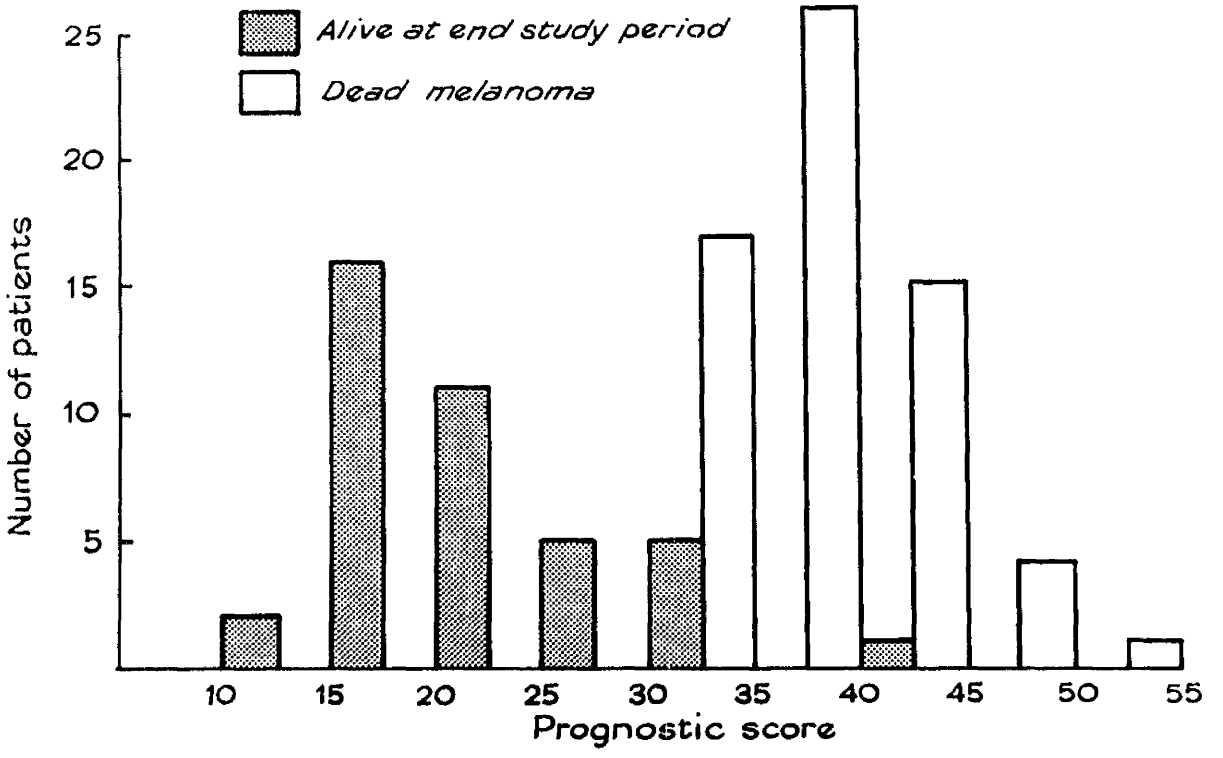


FIGURE 46 Showing the prognostic scores (based on continuous patient surveillance) of patients with cutaneous malignant melanoma.

score of less than 25 extended disease was evident in 5 in a relatively short time after treatment (less than two years). It seems likely that several of these patients had occult lymphatic metastases. This can be advanced as further evidence in favour of elective nodal dissection of clinically innocent lymph nodes.

THE ASSESSMENT OF PROGNOSIS BASED ON CONTINUOUS PATIENT SURVEILLANCE

The apparent prognosis for an individual patient will vary from time to time. In the previous section it was noted that much of the ambiguous middle portion of Figure 43 was attributable to patients who, despite favourable clinical or pathological features at the time of initial assessment, subsequently developed extended disease. A change from purely local to extended disease has a most sinister significance which has been discussed at some length in another part of this thesis. If at the time of development of extended disease the prognostic score is altered by adding 10 points for nodal involvement and 15 for disseminated disease the results illustrated in Table 59 and Figure 46 are obtained.

This type of dynamic scoring is certainly more appositeto the prospective continuous assessment of prognosis in patients under constant outpatient surveillance. From Figure 46 it is apparent that there is a direct relationship between the Prognostic Score and the proportion of patients dying of melanoma and an inverse relationship between score and proportion of patients alive at the end of the study period. Using probit

transformation/

transformation it is possible to construct a regression line for the proportion of patients alive or dead of melanoma against prognostic scoring. It has not been considered worthwhile to do this in view of :

1. The relatively small number of patients available for the assessment of parameters.
2. The wide scatter of individual values around such a line.

From Table 59 it is apparent that patients with a Prognostic Score which never reached 30 had a relatively favourable prognosis. Thirty four of 57 patients in this category were alive at the end of the study period (59.6%). None of this group are known definitely to have died of melanoma, but using the "worst possible" criteria 11 of the 57 may have died of melanoma (19.3%).

Patients whose prognostic score was thirty or more present a markedly worse result. Of 74 patients in this category only 6 were alive at the end of the study period (8.1%). Sixty three are definitely known to have died of melanoma (86.5%). In this group doubt as to the cause of death existed in only 5 cases. Application of these multiple criteria to the population from which they were derived demonstrates a clear relationship between score size and prognosis. The validity of this technique will be further tested in three ways.

1. By applying it prospectively to new cases of malignent melanoma seen in this region.
2. By independent use of the technique in other areas.
3. By/

3. By application of the technique to retrospective case material from other centres.

At present the technique would appear to have some value in the assessment of prognosis in melanoma. With the advent of analysis by computer the parameters used and the weighting to be placed on each parameter may be made more accurate and the technique extended to cover other forms of malignant disease.

CONCLUSIONS

In the 160 years since it was recognised as a disease entity this condition has been the subject of large numbers of studies, lectures and articles. The interest shown in the problem of malignant melanoma bears no relationship to the numerical frequency of the disease. The ubiquity of simple pigmented tumours and the evil reputation of their malignant counterparts probably accounts for the disproportionate interest shown in this subject. While we have seen malignant melanomas which pursued a "forest fire" type of course, leading to death from disseminated disease in a remarkably short time, we believe that care must be taken to recognise these tragic cases as exceptional. In the vast majority of cases the natural history of the untreated disease is between 3 and 5 years.

Malignant melanoma occurred more commonly in women in this series. It has been suggested (Haenszel, 1963) that this preponderance of tumours in women is more apparent than real and is due to the increased willingness of women to seek medical advice for any cutaneous blemish. Lancaster and Nelson (1957) noted that while melanoma was of more frequent occurrence in women, the death rate from melanoma was higher in men. A similar trend is apparent on examining the Annual Report of the Registrar-General for Scotland, 107, 1961. Between 1952 and 1961 210 males and 214 females died of malignant melanoma. The apparent preponderance of females noted in this study is not, therefore, mirrored in the death rate from melanoma. This disparity can be

interpreted as a further evidence of the lower malignancy of this disease in women or of the advantages inherent in early attendance for treatment.

Melanomas were noted in patients of all ages with the exception of those younger than 20. Allowing for the decreasing population at risk, the incidence of malignant melanoma certainly increases with increasing age. The mean age of patients with cutaneous melanoma was 55.1 years and that for patients with ocular melanoma was 53.25 years. It was noted in a previous section that these mean ages are very similar to the figures quoted by Gleave (1929), 56.3 years and 58.4 years. Any increase in incidence of the condition has been spread through the decades. The figures for mean age at onset derived from this study are in the same range as the mean age at death of patients dying of melanoma in 1961 (Registrar-General for Scotland, 1961) - mean age at death 57.1 years.

The experience of this study with respect to site of origin of the primary tumour is closely similar to that reported previously. More than 50.0% of all primary tumours were on the head and neck or lower limb areas. Malignant melanoma does arise in almost every area of the body and can cause the patient to seek advice from clinicians practising a wide range of specialities. This fact is well demonstrated in Table 20 showing the out-patient clinics attended. There is an undoubted sex difference in the frequency with which sites are affected. In males the order of frequency is head and neck, trunk, lower limbs

and upper limbs. In women the order is lower limbs, head and neck, upper limbs and trunk. The occurrence of a high proportion of malignant melanomas in women under 50 years of age on the calf-shin area is especially noteworthy. It is possible to divide the primary tumours into those arising on areas normally covered by clothing and those arising on exposed areas (Eastcott, 1963). This has been done and it appears that malignant melanomas arise with equal frequency on both types of area in men but are more common on exposed areas in women (Table 19). As in previous studies of this kind, cases were encountered in which no primary tumour was demonstrable. These are puzzling cases; in some instances the primary tumour may lie in an obscure site while in others it may remain small and possibly amelanotic rendering clinical recognition impossible. Sumner (1953) reported a primary malignant melanoma which underwent spontaneous "regression" leaving an area of vitiligo. This has been reported by other authors and it is suggested that the search for a primary tumour should include an examination for such an area of cutaneous depigmentation.

Malignant melanoma occurs in all races. It is, however, less common in those with pigmented skins. It is of interest to note the high incidence of this tumour in pale skinned people living in tropical and subtropical areas. An examination of the occupation and social class of the patients in this material showed no evidence of any trade bias or of a higher incidence of the tumour in outdoor workers.

Since this study was a retrospective one, it was not possible to assess skin and hair colouring or exposure to sunlight attributable to hobbies and sports. Lancaster and Nelson (1957) found that malignant melanoma in Australia was more common among red - fair haired people with fair skins who redden rather than brown on exposure to sunlight. They also believe that a history of habitual surfing or sunbathing is more commonly elicited from patients with malignant melanomas than from controls. Outdoor activities such as fishing which involve a lesser degree of nakedness do not appear to be related to an increased incidence of malignant melanoma. An examination of the blood groups of patients with malignant melanoma reveals no significant difference from the distribution of the ABO and Rhesus blood groups in the general population of the West of Scotland.

There is a wide variation in the history given by patients with malignant melanoma and in the objective findings in the clinical examination of patients with malignant melanoma. Certain guiding generalisations can be made. The most frequent history was a change of character in a pigmented tumour or cutaneous blemish or of the advent de novo of a pigmented tumour in adult life. The most frequent changes of character were increase in size, bleeding, ulceration, darkening, lightening, development of a halo and the appearance of satellite nodules. These symptoms and signs were present singly or in variable combinations in most cutaneous malignant melanomas. Presentation with lymphadenopathy is by no means uncommon. Tumours

in unusual sites, e.g. vagina and nose produced symptoms appropriate to their anatomical location. In the majority of cases these symptoms had been present for less than two years before treatment. Rather more than half of the patients gave a history of a more or less longstanding pigmented tumour or discoloured area of skin adjacent to the site of origin of the primary tumour. The incidence of such antecedent lesions was higher in women. This is probably a manifestation of "cosmetic awareness" (Haenszel, 1963).

Three quarters of the primary tumours in this series were in the size range 0.5 - 2.0 cm. With the exception of very large tumours, i.e. those larger than 4.0 cm., it was possible to demonstrate a direct relationship between tumour size and duration of symptoms. Clinically recognisable pigment was present in 75% of tumours. The remainder presented a considerable problem in diagnosis. Three out of four patients had no evidence of tumour spread beyond the local lesion when first seen. Of the remainder, all but four had clinically obvious involvement of the regional lymph nodes. The remaining patients presented with disseminated melanomatosis. It has been noted previously that this distribution of the various stages of melanometosis in this series is very similar to that noted by Wright et al. (1953) in the previous series from this area. This type of staging by clinical assessment appears to have a considerable value in the forecasting of prognosis and decision on therapy provided the limitations of the clinical assessment of nodal involvement are appreciated.

The clinical diagnosis of malignant melanoma is at times an extremely difficult one requiring experience and a constant awareness of this possibility. The difficulty is especially noted in amelanotic tumours. In this material a provisional clinical diagnosis of malignant melanoma was confirmed histologically in 49.5% of cases. Conversely the provisional clinical diagnosis was correct in only 43.3% of the cases diagnosed histologically. This level of diagnostic accuracy compares poorly with the situation in the diagnosis of other skin tumours. The low incidence of correct diagnosis has been previously noted by Becker (1948), Swerdlow (1952), McMullan and Hubner (1956) and Bowen and Walton (1961). It is apparent that, at present, only careful histological examination of multiple representative sections from skin tumours offers a reasonable level of diagnostic accuracy. The institution of therapy on a clinical diagnosis alone does not seem a rational procedure. Frozen section examination by an experienced histologist may at times be acceptable. The conditions most commonly confused clinically with malignant melanoma in this series were basal cell papillomas, naevi, angiomata, pigmented rodent ulcers and, in the case of subungual melanomas, subungual haematomas.

From the volume of material available for this study, compared to that reported by Wright et al. (1953) for a previous decade, the impression was gained that the incidence of malignant melanoma was increasing. This impression was confirmed by examination of the figure reported by the Registrar-General for Scotland in his Annual

Report for 1961. The death rate from malignant melanoma in 1952 was 0.47 per 100,000 population. In 1961 the comparable figure was 1.18 per 100,000 population. This rate of increase is higher than that noted for other forms of cancer. A similar increase in deaths attributable to malignant melanoma has been noted in Australia (Lancaster, 1956 and 1965), in Denmark (Clemmensen et al., 1960) and in the South-west of England (Peterson et al., 1962). It is, of course, possible that part of this apparent increase in incidence may be due to an increased availability of histological facilities and an increased accuracy of diagnosis. It is apparent that, while the efficacy of treatment of malignant melanoma has improved over the past two or three decades, there is no room for complacency in the treatment of this disease. The techniques available are inadequate for the treatment of all but the most localised disease.

Two major problems exist in the treatment of clinically localised malignant melanoma (Stage I). Firstly, how wide should a local excision be? In this study almost one in three of the patients who had a single limited local excision which did not require grafting developed locally recurrent disease. By contrast, fewer than one in ten of the patients who had a re-excision of the scar area or a primary excision wide enough to necessitate skin grafting developed this type of metastasis. Lazarov-Ikonopisov (1964) claimed that the P^{32} uptake technique allowed estimation of lateral field change. This technique might well allow a more rational approach to the

problem of planning local excision. It is pertinent to note that extra-wide excision of the primary tumour area did not reduce the incidence of subsequent nodal metastasis and that local recurrences per se did not have the serious prognostic significance of nodal metastasis.

The second major problem in the management of Stage I malignant melanoma arises in the clinical assessment of whether or not a group of lymph nodes is free of tumour. The stark facts of this problem are:

(1) in this series regional nodal involvement became apparent after initial treatment in 30 of the 122 Stage I patients (24.5%);

(2) the five year survival rate of this latter group of patients was 20.7%, marginally better than that for patients adjudged Stage II at their first visit (11.8%), but catastrophically worse than the five year survival figure for the whole Stage I group (60.0%);

(3) the average survival of patients developing nodal metastasis was 18.8 months after the appearance of metastasis;

(4) of 11 Stage I patients who underwent dissection of clinically uninvolved lymph nodes 10 were alive and free of disease 5 years after treatment, 91.0%. Tumour was noted on histological examination of the lymph nodes in two of these patients.

The main argument against elective nodal dissection is that its general use submits three out of four patients to an unnecessary major surgical procedure. It is also suggested that scarring subsequent to

lymphadenectomy will cause lymph stasis distal to the operation site and this in turn may favour the development of in transit metastases. In the absence of a reliable method for the assessment of nodal invasion we believe that the value of removing minute deposits of viable tumour by elective nodal dissection outweighs the surgical risk involved in this technique. It seems that in transit metastases per se do not present a very great surgical problem. We believe that the considerable worsening of prognosis associated with this type of metastasis is in reality due to the frequent coexistence of proximal nodal invasion.

The results of treatment of Stage II malignant melanoma are depressing. The five year survival rate of this group of patients, 11.8%, indicates how unsatisfactory the present methods of treatment of this stage of the disease are. Cytotoxic drugs may well provide assistance in the treatment of this stage of the disease but the results published to date are few in number and not encouraging. It seems that radioactive amino acids may have a useful role in this context. They may produce a highly selective destruction of widely separated active deposits of tumour. They may also allow the localisation of clinically unsuspected nodal deposits of tumour by Geiger counter detection. This would allow a rational approach to the planning of nodal dissection.

The mean survival after the development of disseminated melanomatosis was 2 - 8 months in this series. Radiotherapy and

cytotoxic drugs provide valuable relief of pain in terminal malignant disease but offer no prospect of cure. We have seen no examples of spontaneous regression of this condition nor has any attempt been made to utilise "immune sera" in the treatment of the patients of this series. Peck (1950), Bellisario and Milton (1961) and Burdick and Hawk (1964) describe attempts to stimulate the reticulo-endothelial system by the innoculation of various viruses. We have no experience of this interesting technique. The technique of pituitary ablation by Radon or Yttrium pituitary implant practised in the Western Infirmary by Forrest et al. (1960) has proved of no apparent value in the management of disseminated melanomatosis and has been discontinued. The true value of the administration of radioactive amino acids, oncolytic viruses, virus vaccines and the use of lasers remains to be established. Treatment of disseminated melanomatosis remains largely palliative and offers no real hope of cure.

More than half of the patients in this series developed some form of metastasis. The prognostic significance of the various forms of metastasis varies widely.

Disseminated melanomatosis developed in 80 patients, 44 of whom were initially regarded as Stage I. The mean period between initial treatment and dissemination was 28 months. Dissemination was preceded by nodal involvement in just under half of these cases. Dissemination has the gravest significance, 71% of those patients dying within six months of manifesting this stage of the disease.

Tumour invaded the regional lymph nodes in 67 cases. This occurrence, while slightly less serious than dissemination, reduces the five year survival rate by between two-thirds and five-sixths. We believe that much of this increased mortality could be obviated by the wider use of elective nodal dissection. Therapeutic nodal dissection must always be the product of failure; failure of the patient to present at a treatable stage or failure of the surgeon to control the primary tumour. Isolation perfusion may slightly reduce the mortality at this stage of the disease but the paramount aim must be to prevent patients reaching this stage of the disease.

Local recurrence was noted in 24 cases. Where this is the only manifestation of recurrent disease, the prognosis remains similar to that of patients with no recurrence. When local recurrence is associated with any of the more serious forms of metastasis the outlook is that appropriate to the coexistent metastasis. The appearance of locally recurrent disease is a timely warning that treatment has not totally eradicated the tumour and that the possibility of further spread is a very real one. Urgent wide local excision with appropriate treatment of the regional lymph nodes and intervening lymphatic plexus is mandatory. Dermal secondary deposits of tumour developed between the primary site and the regional lymph nodes in 9 instances. Their significance has already been discussed.

It has been noted that certain clinical features of patients with malignant melanoma appear to have an influence on prognosis. Female

patients had a better survival rate than their male counterparts and were less prone to all forms of metastasis, with the exception of locally recurrent disease. A heightened reluctance of surgeons to practise very wide local excision on their female patients, in view of the risk of scarring and disfigurement, may explain the higher incidence of local recurrences in female patients. Several factors appear to combine to produce the favourable female prognosis. Women seem to present with their disease at an earlier stage, their tumours tend to occur on relatively favourable sites and the specific female hormonal milieu appears to be less favourable to the growth and spread of this tumour. The prognosis for patients with malignant melanomas appears to worsen with increasing age. Women under 50 have a better prognosis than any other sex/age group. It is of interest to note that most of the tumours in this especially favoured group occur on the calf - shin area and that these women have a hormonal milieu quite distinct from all other age/sex groups.

Tumours on the head and neck and limbs have a relatively favourable prognosis, while tumours on the trunk, the ano-genital area, the mucosal surfaces and tumours arising beneath the nail have an unfavourable prognosis. Tumours in which the primary could not be demonstrated had a uniformly fatal outcome. The regional lymph nodes were invaded least frequently with tumours on the head and neck. This is surprising in view of the short lymphatic plexus involved but may be due to early treatment of tumours on the readily observable

areas and possibly to some inherent quality of these tumours (Catlin, 1954). Tumours on exposed sites had a better prognosis than those on covered areas. This is probably due to early diagnosis and the fact that the majority of patients with tumours on exposed sites were women.

Patients undergoing incision biopsy had a worse prognosis than the study group as a whole. This seems to be due, at least in part, to the type of tumour treated in this way. Such tumours tended to be large and occurred on unfavourable sites in older patients, the majority of whom were males. While these facts are undoubtedly important it is not possible to exclude the dissemination of viable tumour cells by the mechanical interference of subtotal excision as an important factor in the determination of the unfavourable outcome of these cases. The presence of obvious nodal involvement or of disseminated disease has the most unfavourable effect on prognosis (vide supra). Clinical features which had no apparent effect on prognosis included the presence or absence of a previous pigmented lesion at the primary site, the degree of pigmentation of the tumour, pregnancy coexisting with or preceding the development of a melanoma and minor degrees of delay in initial treatment. Surprisingly, inappropriate treatment did not appear to influence the prognosis provided effective definitive treatment was instituted within a reasonable period of time. This latter finding is markedly at variance with the experience of Tod (1944).

Certain histological features appeared to have a definite effect on prognosis. Favourable features were location of the tumour above the level of the epidermal appendages, melanocyte-like tumour cells, a mitotic rate of less than one mitosis per high power field, an intact epidermis and the presence of a predominantly lymphocyte aggregation at the periphery of the tumour. The depth of tumour invasion into the dermis has been noted by previous authors to influence prognosis (Allen and Spitz, 1953, Lund and Ihnen, 1955, Kragh et al., 1960, Block and Shattuck, 1961 and Bodenham and Lloyd, 1963). The depth of invasion with heightened risk of lymphatic or vascular invasion appears to increase with duration of symptoms. In a few tumours, however, rapid downward spread occurs and this appears to reflect an inherent aggressive quality of the tumour cells. The suggestion of a favoured prognosis for tumours in which the cells are morphologically similar to melanocytes is interesting since this type of tumour must represent the most minimal degree of dedifferentiation. The worsened prognosis associated with high mitotic rates is in line with the findings in most tumours. In the present state of knowledge of the functions of lymphocytes it is not easy to explain the favourable effect of a lymphocyte response as opposed to a plasma cell response.

Unfavourable features included deep dermal invasion, spindle cell cytology, a mitotic rate in excess of one mitosis per high power field, evidence of lymphatic and/or vascular invasion, ulceration, melanocyte

pattern B (vide supra) and a mixed plasma cell/lymphocyte reaction to the tumour. Histological features with no apparent effect on prognosis included the various tissue patterns, e.g. packets, sheets, pseudoalveoli, microscopic evidence of a previous naevus, lateral junctional change, the amount of pigment in the tumour, a tumour free zone beneath the epidermis and the various connective tissue patterns. We believe, on the basis of these findings, that careful histological examination of a malignant melanoma does allow some assessment of prognosis (vide infra).

It has been noted that there are numerous morphological similarities between simple and malignant pigmented tumours. There are, in addition, marked differences in relative cellular constitution and in the nature of the cells composing these tumours. We believe that most of these tumours are readily separable on histological examination but that a few present real difficulty in diagnosis. We have experienced difficulty most often in separating active compound naevi and superficial malignant melanomas in adults. It is suggested that careful examination of the number and distribution of the basal melanocytes over and adjacent to these tumours may reduce the number of tumours in which confusion occurs.

A small group of ocular tumours was examined, primarily to parallel and contrast the cutaneous primaries. The findings in this small group of tumours mirror the experience of previous authors. Ocular melanoma appears to differ from its cutaneous counterpart only

as a result of the mechanical limitations to spread imposed by the sclera. Once this boundary is transgressed the behaviour and course of ocular melanoma are not very different from the cutaneous tumour.

The technique described for assessing the incidence of melanocytes in the stratum basale is simple and not unduly time consuming. Comparison of the results obtained by this technique with those obtained by counting the area incidence of melanocytes suggests that the linear counting technique is of comparable accuracy to the more time consuming area counting method. The incidence of melanocytes relative to epidermal cells in the stratum basale was noted to be about 1 in 10. There is relatively wide variation in incidence from area to area within the individual and between individuals. We have found a marginally higher incidence of melanocyte in females than in males. It is suggested that this may provide a quantitative basis for the observed higher incidence of malignant melanoma in females. Snell and Bischitz (1963) reported a decrease in melanocyte incidence with increasing age. The figures from this series confirm this finding. This is regarded as a part of the process of skin atrophy associated with ageing. The main regional variation in melanocyte incidence was noted to be between the upper limb and all other areas. Billingham (1948) and Szabo (1954) noted a high incidence of melanocytes around the face. Since the main source of material for this part of the study was post mortem tissues, it has not been possible to gather a statistically significant group of specimens from the face.

Occasional very high values for melanocyte incidence were obtained from random samples of normal skin. It is suggested that a punctate distribution of areas of relatively high melanocyte density may exist in the human skin. Species variations in melanocyte distribution and density are well recognised. Such areas of increased melanocyte density may well be the site of origin of malignant melanomas which arise from apparently normal skin.

Examination of a group of simple pigmented tumours reveals that there is an increase in the incidence of melanocytes in the epidermis over and adjacent to them. The degree of increase appears to vary with the proliferative activity of the lesion. It is suggested that this raised incidence of melanocytes may explain the frequency with which malignant melanomas arise adjacent to more or less longstanding cutaneous pigmented tumours. Examination of primary malignant melanomas shows a considerable increase in melanocytes in the epidermis adjacent to the tumours. This increase appears to be proportional to the degree of coexisting junctional activity. No increase in the incidence of basal melanocytes was noted in the epidermis overlying and adjacent to dermal deposits of secondary malignant melanoma. This is important in the separation of primary malignant melanomas and superficially placed dermal secondaries which may abut on the epidermis.

The melanocyte patterns in relation to a group of simple and malignant tumours of the skin, derived from sources other than the melanocyte, were examined. No increase in basal melanocytes was noted

in relation to any of these tumours. The presence of a raised incidence of melanocytes in the epidermis overlying or adjacent to a tumour is strong evidence in favour of the origin of that tumour from the melanocytes. This observation may be of value in separating ulcerated skin tumours of ambiguous morphology.

The primary aim of this study was to ascertain which, if any, of the clinicopathological features of malignant melanoma were of importance in forecasting prognosis. With the possible exception of the clinical stage of the disease, no individual feature taken in isolation was found of value in the assessment of prognosis. Several clinical and histological attributes were noted which, taken together had apparently some bearing on prognosis. An attempt was made to assess the relative importance of each of the features, and a "score sheet" was compounded on the basis of the relative significance of these features. Application of this scoring technique to the individual cases provides a considerable degree of separation of good and bad prognosis cases. The score may be usefully assessed at the point in time when clinical and histological assessment and diagnosis are complete. This we have referred to as the "Initial Prognostic Score". The separation of good and bad prognosis cases using assessment at this time is reasonably good but by no means complete. Patients with low scores - less than 25 - had a 1 in 5 chance of dying of melanoma; patients in the middle range - 25 to 39 - had a 1 in 2 chance of dying of melanoma; patients with high scores - over

34 - had rather less than 1 chance in 10 of NOT dying of melanoma.

It is assumed that patients with malignant disease should be under continuous outpatient review. If this is the case, the assessment of prognosis need not be tied to an arbitrary moment in time but will be based on the month to month clinical status of the patient. Accordingly, the Prognostic Score will be altered as and when metastases become apparent. Using this type of technique a more satisfactory separation of patients with good and bad prognosis was achieved. Of 57 patients whose prognostic score never exceeded 30 none are known to have died of melanoma. Seventy four patients had scores in excess of 30 and 63 of these are known to have died of melanoma to date.

We believe that this technique may be of considerable value in the prospective assessment of prognosis in malignant melanoma. In order to test the technique it is proposed to review the malignant melanoma patients from other hospitals and apply the technique to them. The availability of the LEKTON system and access to a computer should allow the analysis of a large number of cases. The technique will also be applied to new patients with malignant melanoma who present in the next year or two. It seems possible that modifications of this scoring technique may be applicable to other forms of malignant disease.

SUMMARY

An analysis has been made of the clinical and pathological features of patients with malignant melanoma who attended the Western Infirmary, Glasgow between 1952 and 1961. These patients have been followed up to date and the effect of the various features on survival was considered. A large group of simple pigmented tumours has been examined and compared with the malignant melanomas. The distribution of melanocytes in normal skin and around cutaneous tumours has been examined. A method for the assessment of prognosis in malignant melanoma, based on the results of the above studies, is described.

APPENDIX I

The following staining techniques are currently in use in this Department and have been found reliable.

1. Regressive haemalum and eosin

Section to water	1.	Xylol	5 mins.
	2.	Alcohol	3 mins.
	3.	Spirit	3 mins.
	4.	Water	Rinse
Treat for mercuric deposit	5.	Lugol's Iodine	5 mins.
	6.	Water	Rinse
	7.	5% Hypo	5 mins.
	8.	Water	5 mins.
Stain nuclei	9.	Haematoxylin	5-10 mins.
	10.	Water	Rinse
Blue	11.	Scott's Tap Water Substitute	2 mins.
	12.	Water	Brief Rinse.
	13.	Examine under the microscope & assess the degree of differentiation required.	
Differentiate	14.	1% Acid Alcohol	2-3 secs.
	15.	Water	Rinse
Re-blue	16.	Scott's Tap Water Substitute	2 mins.
	17.	Water	Rinse
	18.	Examine for adequate differentiation. Repeat stages 14-18 if necessary.	
	19.	Water	5 mins.
Counterstain	20.	Eosin	10 mins.
Dehydration	21.	Spirit (will differentiate Eosin)	Rinse
	22.	Alcohol	Rinse
Clear	23.	Xylol	1-2 mins.
	24.	Mount in D.P.X.	

RESULTS:

Nuclei	-	Blue
R. B. Cs.	-	Usually bright red
Muscle	-	Deep pink
Connective tissue	-	Paler pink

2. Haematoxylin/

2. Haematoxylin and eosin for frozen sections

Sections in water

1.	Stain Haematoxylin	½ time
2.	Rinse in water	
3.	Differentiate in ½% Acid Alcohol	Briefly
4.	Wash in water	
5.	Blue in Scott's tap Water Substitute	
6.	Wash in water	
7.	Examine microscopically	
8.	Repeat step 3 if necessary	
9.	Stain in Eosin	5 mins.
10.	Rinse in water	
11.	Mount on microscopical slide	
12.	Blot dry (Whatman's No. 1 filter paper)	
13.	Differentiate in Meth. Spirit	
14.	Complete dehydration in Absolute Alcohol	
15.	Clear in Xylol	
16.	Mount in D.P.X. mounting medium	

RESULTS: Nuclei - Blue
R. B. Cs. - Yellowish
Other tissue - Pink to Red

3. Perl's Prussian Blue Reaction for ferric salts

1. Paraffin or frozen sections to Distilled water
2. Transfer to a fresh solution or equal parts of
   2% aqueous solution Potassium Ferrocyanide and
   2% Hydrochloric acid
   Time - 30 mins.

   or

   Above solution heated to 60°C.
   Filter on to section Time - 30 mins.
3. Wash well in running water or Distilled water
4. Counterstain - Carmalum or Neutral Red
5. Wash in Water
6. Dehydrate, clear, mount in D.P.X. or H.S.R.

RESULTS: Ferric Iron containing Pigments (Haemosiderin) - Blue
Nuclei - Red

5. Fontana's/

5. Fontana's Melanin Stain

1. Deparaffinise block
2. Section to water
3. Place in Fontana's Melanin Silver Solution* at 37°C. for 6 hours or at 60°C for 3 - 5 hours.
4. Wash in water
5. Flood slide with equal parts of solutions A and B for 30 minutes.
6. Fix in "Hypo". for 5 minutes
7. Wash well in water
8. Counterstain with carmalum or unblued haematoxylin

*Reagents

1. 5% solution of Silver nitrate in distilled water. Add ammonia drop by drop until the silver precipitate dissolves. Add more silver until the solution is just opalescent. No scum should remain.

2. Ammonium thiocyanate or sulphocyanate 3g)
Sodium hyposulphite 3g) Solution A
Distilled water 100 mls)

3. Gold chloride 0.2% aqueous solution - Solution B

APPENDIX 2

THE DISTRIBUTION OF MELANOCYTES IN ADULT HUMAN SKIN. ANALYSIS OF 139 SPECIMENS FROM 27 INDIVIDUALS (INCIDENCE OF MELANOCYTES EXPRESSED AS %GE OF ALL CELLS IN STRATUM BASALE)

Number	Age	Sex	Scalp	Upper Leg	Chest	Abdomen	Forearm	Upper Arm	Foot	Genitalia	Mean Incidence Basal Melanocytes	Range
1	-	M	12	10	8	5	22	-	-	12	13.5%	5-22
2	62	M	11	9	9	51	-	-	10	-	8.8%	5-11
3	75	M	10	10	-	6	7	8	7	-	8.1%	6-10
4	55	F	-	9	12	6	8	8	7	-	8.3%	6-12
5	78	F	9	7	9	9	12	9	10	-	9.25%	7-12
6	70	F	9	10	9	11	15	13	9	-	10.7%	9-15
7	44	F	9	9	26	10	16	22	8	-	14.4%	8-26
8	66	F	9	7	23	11	9	14	10	-	11.75%	7-23
9	68	M	10	11	16	16	23	15	11,15	-	14.7%	10-23
10	61	F	14	16	9	13	13	13	-	-	12.9%	9-16
11	73	F	15	12	10	14	22	14	12	-	13.9%	10-22
12	65	M	4	7	6	4	7	-	4	-	5.3%	4-7
13	82	M	4	6	5	8	8	-	5	-	6.0%	4-8
14	69	M	-	4	8	5	5	-	5	-	5.4%	4-8
15	61	F	-	7	4	5	8	-	6	-	6.0%	4-8
16	69	F	-	10	8	-	11	-	5	-	8.5%	5-11
17	75	F	-	9	7	4	7	-	6	-	6.6%	4-9
18	47	F	8	8	10	6	17	-	7	-	9.3%	6-17
19	78	M	-	4	6	6	10	-	7	-	6.6%	4-10
20	57	M	7	4	6	6	-	5	4	-	5.3%	4-7
21	-	F	7	8	8	9	6	-	5	5	7.2%	5-9
22	-	F	7	4	5	8	6	-	4	-	5.7%	4-8
23	33	F	-	-	-	7	-	-	-	-	-	-
24	77	F	-	-	-	9	-	-	-	-	-	-
25	40	F	-	-	-	10	-	-	-	-	-	-
26	50	M	-	-	-	8	-	-	-	-	-	-
27	60	F	-	-	-	11	-	-	-	-	-	-

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