A STUDY OF 650 OBSERVED MALIGNANT MELANOMAS IN THE SOUTH-WEST REGION

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by

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ONE HUNDRED AND FIFTY YEARS after John Hunter recognized the ' Black Cancer ' it was still regarded as a rare and fatal disease. Since then, evidence has been accumulating to show that the incidence is rising, and many cases survive after treatment.

Six hundred and fifty consecutive cases occurring in the South-West Region are reviewed; all have been treated in one centre by an integrated team and of the first 150 cases 37 per cent have survived 10 years.

Variations in sex, site, and age incidence are discussed, together with corresponding variations in prognosis.

Studies have been made of disease patterns, local and systemic spread, spontaneous regression and unusual behaviour. The management of these cases is considered with special reference to skin and lymph node deposits.

Evidence of the rôle of the immuno-defence system is presented and the experience of chemotherapy and radiotherapy are reviewed.

INTRODUCTION

Among John Hunter's collection were two specimens of melanoma which have survived the hazards of the 175 years since his death. So far as I have been able to discover, his account remains the first to be recorded, and antedates Laennec's description of Melanosis published in 1819.

The first specimen (Fig. 1) in the Hunterian Museum was taken from the neck of a 35-year-old male from whom a similar lesion had been removed three years previously. Hunter describes it as being in two distinct parts: one white in colour and firm to feel, and the other spongy and dark-black in appearance. Recent microscopic examination of this specimen has confirmed that it was a round cell malignant melanoma, and this was probably secondary to a primary of the neck, which had previously been removed. The other example of melanoma he took from the neck of a horse. ' It was very dark in colour and when cut and squeezed a black fluid like ink came out.' This specimen is also in the Museum.

After John Hunter's death, William Norris—a general practitioner of Stourbridge and trained in the Hunter School—recorded in 1820 a most beautifully documented description of a man aged 59, who in 1817 developed a malignant change in an abdominal mole: the case was followed

through until death from widespread metastases, and concluded with an accurate description of the post-mortem findings. By this time the condition must have been well recognized, because Norris comments that, ' amongst the many cases of this disease on record, I am aware of none where its ravages have been so extensive '.

A century and a half later the malignant melanoma still preserves a reputation for mysterious and varied behaviour, and the speed with which it can sometimes kill.

All too often it has been a sad story with a painless growing tumour ignored by the patient, and often unrecognized by the profession, until the textbook picture of advanced disease was reached and, even then, only too often to be treated by some meddlesome and inadequate measures.

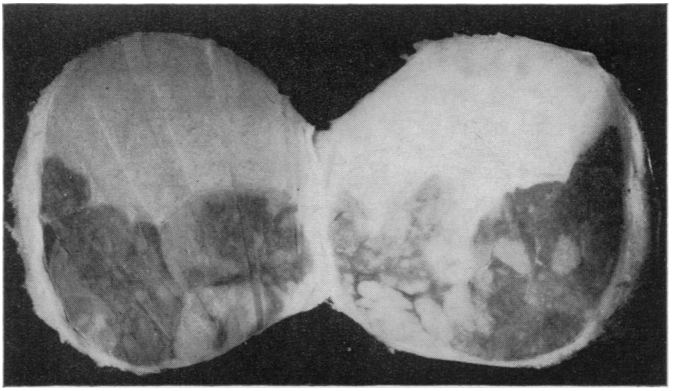


Fig. 1. Hunter's original specimen, No. P.219, from the Hunterian Museum.

Happily circumstances are changing and the melanoma is rightly receiving an increasing share of interest in the field of cancer research.

In this College we should pay tribute to Sir Stanford Cade for his leadership in the study of malignant disease and for all that he has contributed by stimulating the interest of others, and for his Bradshaw Lecture on malignant melanoma, given in 1960.

The melanoma is a most fascinating tumour; uncommon, yet possessing many natural advantages for study over other forms of malignant disease, identifying itself by pigment, and able to spread in the skin or disseminate widely. It can be observed at all stages, is subject to an infinite range of behaviour, and is liable to smoulder for many years or to regress spontaneously. Death, when it comes, is from secondary deposits and not from growth of the primary.

Statistically, by reason of the innumerable variables, many of the findings that come to light can be no more than trends or pointers, and regrettably only a few of the figures presented can satisfy the strictest

criteria of statistical analysis. On the same count, the majority of the published figures presented from other studies of malignant disease fail in the same manner, but by their publication new objectives can be visualized and very gradually the true picture will emerge. There can be no quick answer.

The geographical arrangement of the South-West corner of England offers particular advantages for study, being bordered on two sides by sea, with a population of 3,000,000, and it is favoured by having a single centre for plastic surgery to which the majority of cases of this disease are referred for treatment. For 20 years every specimen has been examined microscopically by the pathologist of this team (Dr. O. C. Lloyd) and every patient recorded has been personally observed, most of them by all members of the team.

Treatment throughout the series has been based on surgery, with wide excision of the primary. Radiotherapy and chemotherapy have only been used in a few cases.

THE LENGTH OF HISTORY

In this survey, particular care has been taken to assess in each case the time interval which has elapsed from the moment the patient first became aware of any change of size, colour or thickness, in a pre-existing lesion, or when he became aware of any new lesion in the skin and the time he reported for treatment. Although it must be apparent that the length of history would depend on the patient's own powers of observation, his memory, or his intelligence, it is a significant fact that there has been a considerable period before he reports to his own doctor. In fact, 71 per cent of all patients give a history of six months or more, and 53 per cent wait more than a year. Delay is rare once the patient has reported to his own doctor.

When the length of history is correlated with survival on a five-year follow-up there is a paradoxical situation in which it is apparently an advantage to report early or to wait 12 months, and a disadvantage to report between five and eight months, or delay for more than a year.

The only explanation for this paradox is that a rapidly growing tumour is more likely to alert a patient early, and a slowly growing tumour will be late in attracting attention. So it is that the group with a short history tend to be loaded with a higher proportion of rapidly growing tumours, and the longer history group contain a higher proportion of slowly growing and more favourable cases. Any advantage which might accrue from this selection is lost when the tumours are allowed to persist beyond 12 months.

It might be expected, with the increasing public awareness of the cancer problem, that there would be a gradual reduction in the length of history. Attempts to show this by comparing sequential groups of 100 cases over the last 20 years has so far failed to produce any evidence that patients are

reporting any earlier, but I am sure we now enquire more deeply into their histories than we used to, and this figure may be misleading.

On the other hand, we have shown that there has been a steady reduction from 25 to 15 per cent in the proportion of patients who present themselves with glandular metastases, and therefore there is to-day a higher proportion of patients now being referred with tumours in their earlier stages.

DISTRIBUTION

The preponderance of the disease in females (and in particular in the skin of the leg between the knee and ankle) was emphasized in the Bristol figures published in 1962 (Bodenham, 1962). It is significant that not only have these figures been endorsed by further experience, but at this site the ratio of females to males has risen from 3.5 : 1 to 11 : 1 in the two decades of the survey; the overall sex ratio is 2.5 females to one male.

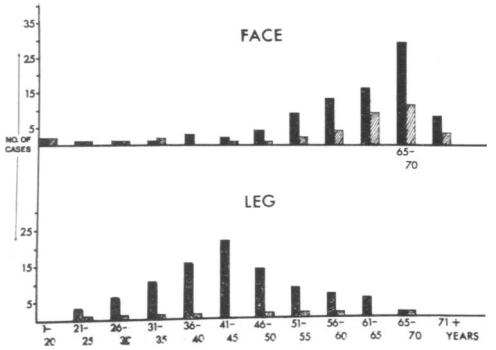


Fig. 2. Melanoma age incidence in two sites. Solid columns = female; hatched columns = male.

The breakdown for sex and site is also significant for age (Fig. 2, Tables I, II, III). Whereas the leg is affected in younger women, it is the older women in the 65/70 age group who are predominantly affected on the face. At other sites differences between the sexes are much less.

Figures from the Cancer Bureau of the South Western Regional Hospital Board show an incidence of 2.5 per 100,000 in females in the northern part of the region compared with 10 per 100,000 in Cornwall. This difference is accounted for by increased frequency of the disease on the leg in the south. The overall regional incidence is now 3.5 per 100,000.

Incidence of the disease in the legs of females has been rising for the last 20 years (especially in Cornwall and Devon) and it has been shown that this rise is statistically significant. A possible explanation for this could be exposure to ultra-violet light. Nylon stockings permit 75 per cent ultra-violet light to reach skin, whereas pre-war stockings offered a high level of protection. The rise in melanoma incidence corresponds in time to the increasing availability of nylon stockings.

In Queensland, Australia, the most recent unpublished figures reveal an incidence in excess of 16 per 100,000, so that there the melanoma is becoming one of the common major cancers.

In Australia and in America the disease is spread both more evenly over the body and almost equally between the sexes: perhaps this is due to habits and climatic differences.

TABLE I

SITE INCIDENCE 1948–1967: 620 CASES

Site	*Female*	*Male*	*Total*	*Percentage of all cases*
Leg	165	13	178	28.7
Face ..	114	61	175	28.2
Foot and ankle	45	27	72	11.6
Trunk	39	39	78	12.6
Arm	30	12	42	6.8
Head and neck			27	4.3
Thigh ..			22	3.5
Hand			19	3.1
Eye			7	1.1

TABLE II

SITE AND SEX INCIDENCE 1948–1967

Site	*Percentage of cases*	
	Female	*Male*
Leg	92.7	7.3
Face	65.1	34.9
Foot	62.5	37.5
Trunk	50.0	50.0
Arm	71.4	28.6

TABLE III

FIVE-YEAR SURVIVAL RATES 1948–1962: ALL STAGES, 296 CASES

Site	*Females*		*Males*		*Total*	
	Actual cases	*Per cent surviving*	*Actual cases*	*Per cent surviving*	*Actual cases*	*Per cent surviving*
All sites including arm and thigh	139/209	66.5	40/87	45.9	179/296	60.5
Face	51/65	78.5	17/24	71.0	68/89	76.5
Trunk	14/26	53.8	7/22	31.9	21/48	43.8
Leg	51/66	77.3	3/6	50.0	54/72	75.0
Foot	11/23	47.8	9/16	56.3	20/39	51.3

TUMOUR TYPES (clinical classification)

Broadly speaking, certain melanomas can be recognized at once as belonging either to a ' good ' or ' bad ' group.

The ' good ' tumours remain localized and rarely metastasize

1. Facial melanoma arising in a lentigo, the pre-cancerous melanosis of Dubreuilh.

2. Slow-growing coherent tumour which produces little mass in relation to surface area.

3. Ring melanoma.

The ' bad ' tumours metastasize early, often, and are a systemic problem

1. Non-pigmented melanoma.
2. Ulcerating melanoma.
3. Growing with bulk out of relation to surface area.
4. Diffuse tumour, with satellite formation.

THE ' GOOD ' TUMOURS—a local problem

Examples

Malignant lentigo

This form of malignant melanoma appears on the face of the elderly. It starts as a perfectly smooth, pigmented patch (Fig. 3*a*), gradually spreading, later slowly developing one or more foci of greater activity

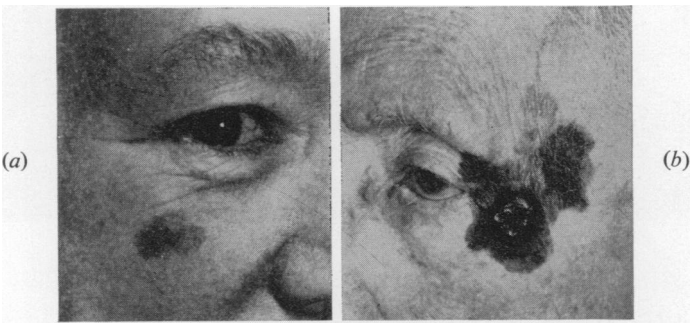


Fig. 3. Early and late lentigo with well-developed tumorous malignant melanoma.

which lead to tumour formation (Fig. 3*b*). There is invasion of the dermis and then later spread through the lymphatics to the lymph nodes, as the lesion develops.

The manner in which the disease extends and spreads is similar to melanomas occurring at any other site, but differs in respect of the time factor. The typical lesion may remain coherent for 10 or 15 years to reach a large size before invasion takes place, but it cannot always be relied upon to develop so slowly and it is capable of spreading and metastasizing within 12 months. Under the age of 50 malignant melanomas occurring on the face develop either in a pre-existing mole or in apparently normal skin. They tend to grow faster and are more malignant than those of lentigo origin.

Mishima (1967) claims distinct differences between these two types—the former he calls melanocytomas: the latter, naevocytomas, which arise in junctional naevi, grow faster and metastasize more freely. Our experience is that there are many exceptions to the distinctions he draws.

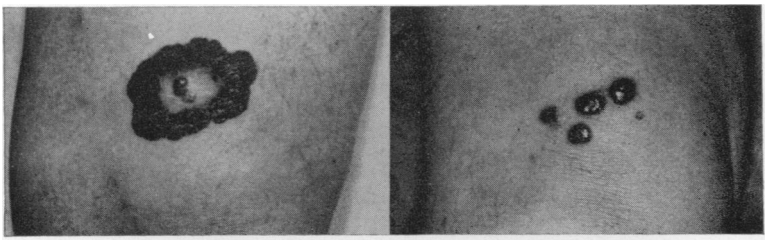
For example, wide variations in growth rates, in the inhibition of melanocytes in the pigmented flare and variations in pigment content ranging from excess to very little can be found in both types.

Slow-growing coherent tumour

This type is commonly found on the female leg and has a five-year survival rate of over 80 per cent. The lesion often itches, as if to attract attention, remains relatively flat and is mainly a local disease responding well to local treatment.

The ring melanoma (Fig. 4*a*)

This somewhat unusual type accounts for only 1 per cent of all cases, but is of particular interest. It grows slowly, reaches a large size without tumour formation and as it enlarges the pigment fades from the centre; ulceration is rare, and it does not metastasize. Microscopically there is round cell infiltration and inhibition of the melanocytes in the centre.



(*a*) (*b*)

Fig. 4. (*a*) Ring melanoma. (*b*) Melanoma with satellite formation.

THE 'BAD' TUMOURS—a systemic problem

Examples

Non-pigmented melanoma

This is a relative term, pigment being identifiable microscopically in nearly all primaries, but the more actively growing melanocytes have a diminished capacity to form pigment which is not present in sufficient quantity to be readily visible to the naked eye. At first it appears skin coloured and later ulcerates to look more like a squamous carcinoma than a melanoma. On close inspection with a hand lens some pigment can usually be identified at the edge; it is a highly malignant tumour and metastasizes early. Lymph node deposits can be either black or white, or both, as in the case of John Hunter's original specimen (Fig. 1). Generally, however, a non-pigmented primary produces non-pigmented recurrences and metastases.

Ulcerating melanoma

The melanoma will ulcerate if it is damaged, usually healing again if it is uninfected and left alone; it will ulcerate spontaneously when growing

fast, because the overlying epithelium becomes attenuated and necrotic. Pigment is scanty, but usually present in any part of the tumour not ulcerating, and at the edges.

Tumour with bulk out of relation to surface area

In contradiction to the flat, slowly growing lesions, this type rises steeply from the surface of the skin, and is often mushroom-shaped. The characteristic pigmented flare of many melanomas is often absent. Though small in area, it tends to metastasize early and often spreads directly to distant organs, missing out the regional nodes.

Tumour with satellite formation (Fig. 4*b*)

Satellite formation can be due either to epidermal spread in continuity, or may be due to cell emboli or direct spread within the dermal lymphatics. Aggregates of cells lead to tumour formation, the satellites from the epidermal spread appearing within 0.5–1.0 cm. of the primary, and the others a little farther afield. Though these lesions are all highly malignant they exhibit some tendency to remain limited to the limb or region before reaching the distant organs.

Lloyd has always searched out for microscopic evidence of local spread in the dermal lymphatics before it has become visible to the naked eye, and positive findings in this series are associated with a 20 per cent reduction in the number who survive five years.

CELL TYPES (pathological classification)

When the epidermal melanocyte becomes malignant, first it enlarges, then it loses some of its dendritic processes and may become fusiform or spindle shaped, or round.

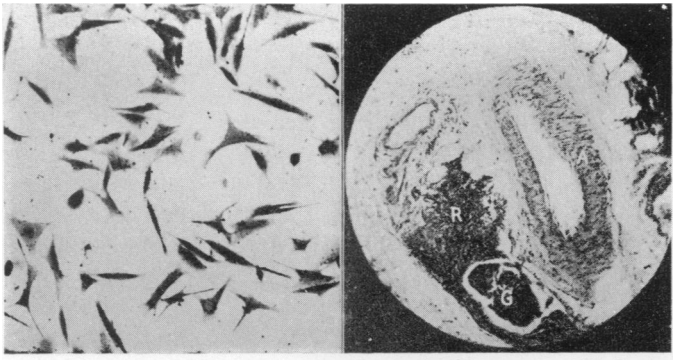
In different tumours one or other cell type may predominate or there may be a mixture of the two.

It was thought that there might be some relation between cell type, site and prognosis.

In a series of 252 cases which have been followed up for five years, it appears that males are more likely to present with the spindle-cell type and are least likely to have a round-cell type, but in females the case is the reverse. In both males and females the mixed-cell type has the best prognosis and the round-cell the worst—the differences vary by 13 per cent.

Comparison by site shows a significant preponderance of the spindle-cell type in facial lesions, and of round-cell lesions on both the trunk and the leg; since the trunk carries a poor prognosis and the leg a good prognosis, and both types affect the same age group, it is apparent that site and sex are a more important factor than cell type in determining prognosis.

It is of interest to speculate on the explanation for these cell types: it is possible that the stromal reaction determines cell type, though it could be that cell type determines the amount of stroma. However, on tissue



(*b*) *reproduced by courtesy of* The Lancet

(*a*) (*b*)

Fig. 5. (*a*) Photomicrograph of melanocytes in tissue culture growing from case of malignant melanoma. (*b*) Reproduction from *The Lancet* (1907) of Samson Handley's illustration drawing attention to the reparative process of round cell infiltration and fibrosis (see text).

culture where there is no stroma, most cell types develop to the dendritic or stellate form (Fig. 5*a*) and look similar, though some fusiform cells may be seen; it should be remembered, however, that growth takes place on the glass surface of the culture chamber.

BEHAVIOUR

The stormy, sometimes short, sometimes lengthy and (it seems) often unpredictable behaviour of the melanoma can be visualized most easily in graphic records.

Events preceding and following treatment are recorded by symbols and these can be clearly seen in the magnified portion of a chart in the lower half of Figure 6. Each patient is allotted space to record a period of up

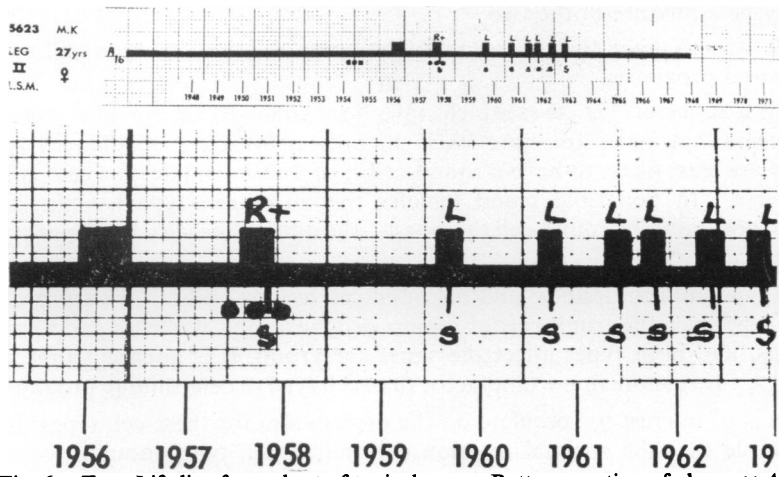


Fig. 6. Top: Life line from chart of typical case. Bottom: section of above × 4.

to 30 years. Particular types of recurrence, methods of treatment, pregnancy or other important events being easy to record and read off.

The form of the chart has been chosen to set out a linear presentation of the life-span of 500 cases, and a study of these has revealed definite patterns of disease. Since, however, the story will not be completed until all these have died—some have already survived 20 years—this will only be an interim report on the first 220 cases who can be followed up for seven years or more.

SPONTANEOUS REGRESSION

Spontaneous regression has been defined (Everson and Cole, 1966) as a regression in a proven case, or cure following inadequate treatment or no treatment at all. In this category seven patients qualify out of 220. Amongst these, two patients who developed recurrences after removal of their primaries were observed to regress following a refusal of operative treatment, and had no further trouble. Two patients had developed multiple recurrences in the leg and have been observed to regress while attending as out-patients, and three patients have had totally inadequate treatment for a long sequence of recurrences and have been free from further trouble for a period of five years or more: all have been females. No common factor has been found—two have had tumours present during pregnancy, but none has been pregnant during the regression. Regression occurred between one and $3\frac{1}{2}$ years of first treatment.

Spontaneous regression is being increasingly reported in the literature, and we have occasionally removed a tumour for examination in the act of regressing. The histology shows how most of the melanocytes have disappeared and only a few remain. It seems very likely that these freak cases which present with lymph node deposits without an identifiable primary have, in fact, had a primary which has fully regressed.

In 1907 Samson Handley, in his Hunterian Lecture on melanotic growths, illustrated with the photomicrograph shown in Figure 5 (*b*). I quote: 'The reparative process which occurs even in very malignant growths. **A** is a normal artery, **G** a mass of growth lying in a space without definite walls representing a ruptured lymphatic or vein. The growth **G** is surrounded by a very dense collection of inflammatory round cells.'

I believe Samson Handley was amongst the first, if not the first, to recognize the nature of the local defence mechanism which can lead on to regression, characterized by diffuse infiltration with lymphocytes and plasma cells, and found altogether in four categories of lesion:

1. Benign halo naevus (Sutton) undergoing regression.
2. Benign juvenile melanoma of Spitz.
3. Parts of malignant haloes undergoing inhibition.
4. Tumorous malignant melanomas undergoing regression.

SMOULDERING DISEASE

Seven per cent of cases would appear to exhibit such a measure of control over their disease, even though it may have reached an advanced stage of spread and dissemination, as to qualify for this term of ' smouldering'.

An extreme example is illustrated in Figure 7, showing how the disease, having spread rapidly from a primary of the calf to become stationary

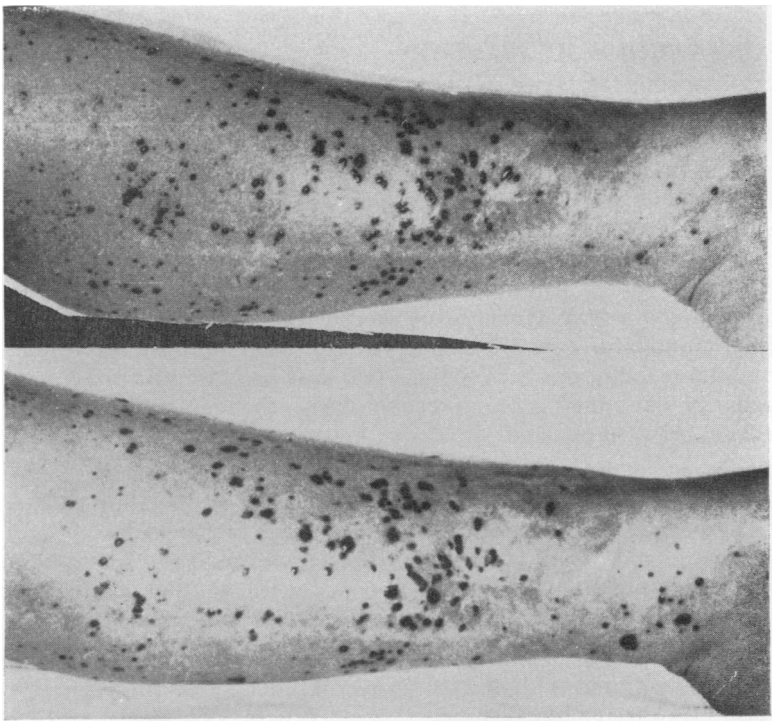


Fig. 7. Photographs taken at an interval of twelve months in a case of smouldering disease. Some lesions have faded, other new ones have appeared (female aged 60).

during a period of observation extending over one year, shows no really significant change—as seen in the upper and lower pictures. In this case we have observed that from time to time the surface of some of the tumours dries up, falls off and leaves behind a pinkish, flat patch which fades, to leave virtually no visible mark, but at the same time other spots appear and ultimately pass through the same cycle.

POOR RISK CASES

Thirteen per cent of all cases die within two years of their first symptom —6 per cent dying within the first 12 months—but if survival is related to

the time of treatment the figures are much higher. On the other hand, 6 per cent of those who present with particularly rapidly growing tumours, which have spread to lymphatics or lymph nodes, survive without intermediate trouble for five or more years after treatment, even though they seemed hopeless at the time.

The percentage of those who, on experienced clinical judgement, should do well and who, in fact, do badly is very small.

In others, after an apparently steady extension of the disease, growth rate speeds up, becoming in some cases reminiscent of a fulminating infection with tubercle bacilli with rapid miliary spread.

There is evidence, therefore, of some retarding influence which some patients possess, acquire or even lose, over which the clinician has no control; a point not to be forgotten when assessing the merits of some variation of treatment which could only be correctly determined in a large series followed up for a long period.

TREATMENT

Since 1947 it has been general practice to excise the primary tumour with a margin of 5 cm. of healthy skin all round, but on the face the margin must be less for physical and anatomical reasons and, because the prognosis has been proved to be more favourable, the margin has often been taken as low as 1 cm. On the trunk, where the outlook is poor, the margins have been as much as 15 cm.

The problem of management of the regional lymph nodes is discussed later but, at this point when discussing excision, it can be said with reasonable certainty that there is no justification at present for advocating routine prophylactic dissection.

Treatment of skin and subcutaneous recurrences

It has been our practice to treat all excisable recurrences, wherever they occur, by pure surgery as a matter of urgency, and generally with the same safety margin of healthy tissue as if they were a primary growth.

Not infrequently, multiple recurrences present simultaneously; as many as 17 separate deposits of up to 1 cm. diameter have been removed in this way, to be followed by another crop shortly afterwards (Fig. 9*a*) which were similarly treated. At times the disease appears to be controlled without further treatment, and five years and over elapse without trouble. Events like this occur often enough to justify an optimistic attitude and make it difficult to compare the effectiveness of any adjuvant or alternative treatment which might be given.

Large and rapidly growing recurrences which crop up at intervals later in the course of the disease, which suggest that the case is becoming hopeless, have sometimes been treated by quite limited excision and there have been some surprising results. A 42-year-old female, first treated in 1960 for a primary of the leg, developed in 1962 deposits in the groin,

in 1964 developed recurrences in the opposite thigh, all being treated by surgery. During this time she was also treated by heavy doses of nitrogen mustard for six months, leaving her with a bone marrow depression still present in February 1966, when she produced in rapid succession three quickly growing deep deposits in the thigh and buttock. These were removed quite locally with primary suture, and there has been no further trouble in two years, and no other treatment was given; she has already survived eight years.

This and many other cases highlight the extraordinary capacity of some patients to survive for prolonged periods by limited surgery, and for this reason very radical measures, such as amputation, cannot be generally recommended.

The melanomatous deposits tend to bleed spontaneously; one patient (J. G.) with axillary and pectoral deposits was observed over a period of 10 years. During this time there was a slow but regular cycle of waxing and waning, as presumably haemorrhage occurred then absorbed. No treatment was given and, in spite of the tumour, she was fit and led a normal active life until she died of cerebral metastases.

Other patients develop a slowly growing miliary type of deposit under the epidermis from spread along the dermal lymphatics, the clinical behaviour indicating the presence of a natural retarding influence or immunity mechanism. Earlier these were treated by wide excision, but in three cases the individual seedlings have been dealt with by diathermy puncture; where the disease appears to be scattered, limited local treatment of this sort can be considered a possible alternative to more extensive surgery.

I am of the opinion that there can be no standard treatment; at present only clinical judgement can suggest which cases will fare as well or better with less treatment. Until such time as histological and biochemical means of selection are perfected, the quantity of treatment remains empirical, guided only by experience and guesswork.

Treatment of deposits in main organs and cavities

Solitary deposits occurring in the stomach and lung have been dealt with surgically with short-lived, but worthwhile, benefit.

All too often the deposits make themselves known with dramatic suddenness as bleeding occurs in the growth; brain secondaries are common and coma is a frequent herald of death, though there may often be temporary improvement as the haemorrhage absorbs and the cycle repeats itself.

Chemotherapy

Chemotherapy has been reserved for advanced cases and used on 29 occasions only. Intra-arterial perfusion with Melphalan has been found effective in generally reducing tumour size, and sometimes causing the deposits to flatten completely, but in use it suffers from three limitations.

1. It can only be given to an area defined by arterial considerations which may not coincide with the extent of the growth.

2. It has a high general toxicity.

3. Tumour growth has been found to recommence soon after treatment ceases—the gain in time is less than three months. When given as a pre-operative measure it has not prevented recurrences developing later in the limb.

Infusion with methotrexate into the femoral artery has similar effects, but owing to toxicity it has not been possible to maintain sufficient dosage long enough to achieve more than a slight, temporary reduction in tumour size. The lower limb has too large a bulk to allow infusion with the same high concentration of the drug that has been successful for malignant disease of the head and face.

Systemic treatment with a variety of nitrogen preparations, including Degranol, Chlorambucil and Cyclophosphamide, have been tried: the results are disappointing. Whilst patients have been on full treatment, tumours have been observed to appear and grow rapidly, even though the blood count had been depressed to less than 2,000 white cells.

Once treatment ceases the bone marrow usually recovers. Infection has not been troublesome but it seems that the melanoma is never less, but generally more, robust than the bone marrow.

It may be that there is a place for chemotherapy, but it is difficult to reconcile the use of such potent and toxic immuno-suppressive agents in the light of current experience of the immunity reaction to tumour growth.

Radiation treatment

External radiation is never justified for routine primary treatment. The majority of melanomas resist a dosage high enough to destroy normal tissues and on the leg particularly the intolerance of the skin to radiation precludes its use due to its poor vascularity.

Only the melanomas arising in a lentigo may be sensitive, but surgery is quicker and more positive. Age to-day is no contra-indication to surgery, which in these cases can be carried out equally well under local anaesthetic.

Radiation has not proved effective in dealing with deposits unless they are very small and accessible. In less than full dosage it may actually enhance tumour growth by lowering local tissue resistance.

Endolymphatic treatment with radio-active isotopes is a recent measure which has not yet earned a regular place in management.

For clinical stage I melanomas of the leg, results will have to be better than 80 per cent 5-year survival, and for clinical stage II better than 30 per cent for there to be any advantage over treatment by surgery alone.

SURVIVAL RATES (Tables IV and V)

The survival of the first 150 cases in graph form (Fig. 8) shows that the fall is steep at first, then flattens out, 66 per cent surviving five years and 38 per cent surviving 10 years. Females have approximately 15 per cent advantage over males.

The female preserves her advantage even when sites are considered separately. This is not due to earlier treatment, but must be due to having a more slowly growing tumour. On the leg and face, the five-year survival rate is over 75 per cent for females and over 50 per cent for males; on the trunk, the next most common site, the female has a 50 per cent chance, but the male only a 30 per cent chance of living five years.

TABLE IV

FIVE-YEAR SURVIVAL RATES 1948–1962

Clinical Stage I			*Clinical Stage II*		
	Male and female			*Male and female*	
Site	*Actual cases*	*Per cent surviving*	*Site*	*Actual cases*	*Per cent surviving*
All sites including arm and thigh ..	165/224	73.7	All sites including arm and thigh..	15/72	20.9
Trunk	21/34	66.7	Trunk	0/14	0
Leg	49/58	84.5	Leg	5/14	35.7

TABLE V

RECURRENCE RATE IN THOSE SURVIVING FIVE YEARS OR MORE 1948–1962

Site	*Male and female*		
	Actual cases surviving	*Number that recurred*	*Percentage recurred*
All sites including arms and thighs	179	45	25.4
Leg	54	17	31.5
Face	68	12	17.6
Trunk	21	6	28.5
Foot	20	7	35.0

Death comes from cerebral, chest and liver secondaries, and the indications are that the disease was systemic from the time of its first treatment. Material improvement in prognosis is only likely to come from some treatment equally capable of dealing with the remote, as well as the accessible, foci at the same time.

Broadly speaking the results of local excision fall into three categories:

1. There is complete cure.

2. There is cure of the local disease, but the tumour reappears in lymphatic pathways, lymph nodes or in other organs.

3. There is recurrence of the tumour most often at the junction of the skin graft with normal skin, and very rarely deep to the graft itself.

In the first category primary excision achieved its purpose; in the second, the disease had already spread beyond the zone of treatment although the local cure was complete. In the third category, local treat-

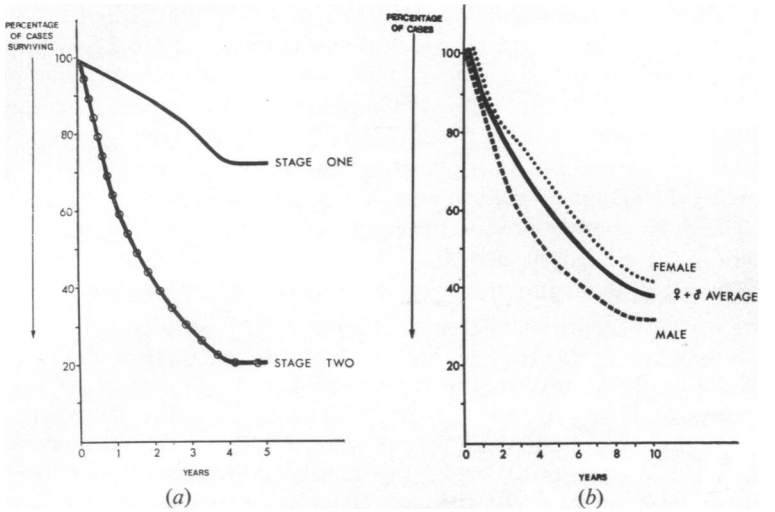


Fig. 8. (*a*) Five-year survival rate with or without lymph node metastases (296 cases). (*b*) Ten-year survival rate (150 cases).

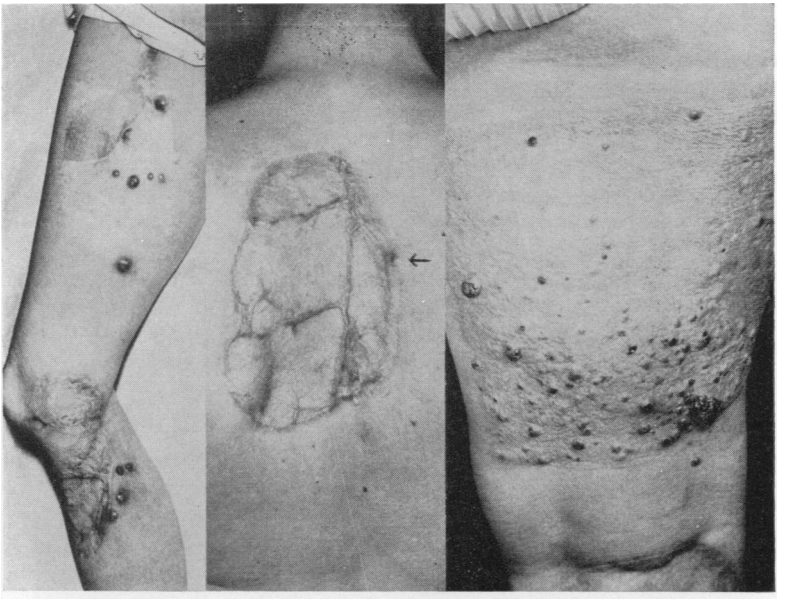


Fig. 9. (*a*) Multiple recurrences. These were removed and later a trio of deposits appeared in the skin of the upper thigh, which were observed to regress spontaneously. The patient has remained fit and is free of further trouble five years later (female aged 48). (*b*) Typical marginal recurrence following excision of melanoma of back six months before (male aged 35 years). (*c*) Multiple deposits growing preferentially within area from which skin graft was taken.

ment failed to prevent a marginal recurrence (Fig. 9*b*), which is often multiple. The mechanism by which deposits appear so precisely at this site is mysterious and fascinating: there are four possible explanations:

1. The cells migrating through lymphatics at the time of operation may be held up, since cutting the pathways slows up the lymph flow.

2. The repair process during healing may provide a growth factor encouraging the malignant cells to grow at this particular site.

3. The inflammatory process of repair may provide favourable vascular conditions for malignant growth.

4. The act of damaging tissues may impair local tissue defences.

It is perhaps significant that in three cases, where inadvertently the skin graft was taken from the same limb as the primary, there was seen a remarkable localization of multiple deposits (Fig. 9*c*) limited accurately to the zone of damaged skin. There are strong reasons, therefore, for believing that trauma in some way promotes cell growth and there is no reason to believe that wider excisions will necessarily prevent such trouble, and may even increase the risk of encouraging tumour growth over a much more extensive area. It may well be shown in time that equally good results will follow smaller excisions, but in the present state of our knowledge the 5 cm. margin should continue to be recommended as being the best compromise, except on the face, where the commonly occurring lesions in the elderly are generally cured by a 1 cm. margin, and experience has shown a high rate of local cure even in the younger age group.

Results of prophylactic lymph node dissection

The malignant potential of the melanoma led to the natural conclusion that elimination of regional lymph nodes, before they became clinically involved, would lessen the risk of further trouble. Examination of excised specimens confirmed the presence of microscopic deposits in 25 per cent of cases, and supported the belief that the correct management was being conducted. It would, however, be wrong to accept this without further questioning, and records are now accumulating in sufficient numbers to give an idea of the morbidity which follows prophylactic dissection. The operation on the groin itself adds 14–21 days of hospitalization and leads to a high incidence of oedema in the leg and ankle, some 30 per cent of the patients developing enough swelling to limit their activity or produce discomfort.

The present series of comparable cases is still too small to be statistically significant; nevertheless, a close scrutiny of the charts of 35 patients who have had the operation prophylactically, compared with 24 patients who did not have the operation over four years ago, has failed to reveal any difference, either in the survival figures or in the incidence of recurrence. Since, however, the prognosis of female patients with a leg melanoma in a clinical stage I has already shown to be good, with 80 per cent five-year survival, it is unlikely that anything but a major difference in prognosis

would have shown up in this series, and that it will be necessary to follow up not less than 50 cases in each group over a 10-year period to provide statistically significant results.

Results of therapeutic lymph node dissection

In a study of 296 cases at all sites, there is a 55 per cent difference in five-year survival between those patients who did not (stage I) and those who did have the lymph node involvement (stage II) at the time of the first treatment. Of the former group 73 per cent survive five years against 20 per cent of the latter. No patients who had a primary on the trunk with axillary or inguinal node metastases have yet survived five years.

Radical node dissection is therefore a relatively unsuccessful operation, for the reason that the spread has often taken place to brain, chest or liver by the time the operation is performed.

Nevertheless, in the present state of our knowledge, a node dissection is justified on the following grounds:

1. Removal of a mass is beneficial to the patient's sense of well-being.
2. The reduction in the quantity of growth present in the body may reduce the bulk to the point at which natural defences may be able to operate successfully against any remainder which cannot be reached therapeutically.
3. The clearance may eliminate the growth completely. But one can say with reasonable certainty that there is no justification, at the present time, for advocating prophylactic dissection.

Sartorius transposition

When groin dissection must be carried out the morbidity is lessened when the sartorius muscle is detached at the upper end and swung medially to cover the main vessels, not only protecting them but eliminating the dead space.

Skin flaps are more likely to survive if the edges are cut back by 1–2 cm., an amount which can well be afforded. Then, in the unlikely event of there being a breakdown, skin grafts can be placed at an early date on a bed of muscle, hospital time is saved and post-operative oedema is reduced.

SOME OBSERVATIONS ON FACTORS CONCERNING PROGNOSIS

It has become increasingly apparent during the survey that the degree of malignancy of the tumour is pre-determined at the time of diagnosis, and falls into one of three broad groups:

1. Slow growing with a high cure rate.
2. Fast growing with early death.
3. Intermediate between 1 and 2.

The issue, however, is complicated by the apparent capacity of a melanoma to change from one group to another, though it seems as if the pattern is constant in 50 per cent of cases.

It therefore becomes pertinent to examine other factors which might lead to an early assessment of the degree of malignancy and consequently more precise treatment, which at present tends to be standardized.

The matter will be discussed under the following headings:

1. Tumour and skin temperatures.
2. The immuno-defence mechanism.
3. Pregnancy.

Tumour temperature

During the last two years the tumour temperatures have been taken using a micro-sensor with a multi-channel electric thermometer on 80 occasions, and the temperature related to the average skin temperature taken at four sites, 5 cm. distant in each direction from the centre of the tumour. Excluding these tumours which have been injured or infected, temperature differences up to 3° C. have been recorded. It will be many years before the final assessment can be made, and at this stage it can only be said that, generally, slowly growing tumours, which experience would suggest have a good prognosis, are within 1.5° C. of skin temperature. The ' hot ' tumours—those 1.5 to 3° C. above skin temperature—have been more actively growing tumours.

Tumour cell activity with increased vascularity is the principal cause of this raised temperature, but may not be the only explanation. Recent work by Riddell and Symes (1968) has shown that it is possible to induce an elevation of tumour temperature over that of surrounding skin by the administration of immunologically competent spleen cells, and thus it is possible for a cellular defence mechanism to produce increased vascularity which is, in fact, favourable and not adverse.

Tumour temperatures have been found to be a useful, but not necessarily a reliable, guide to tumour activity and prognosis.

The temperatures of normal skin have been taken on both sexes and it has been observed that the ambient skin temperature of the calf is 2.5° C. below that of the back in males, and 4.5° C. below in females: also, the temperature of male skin is generally higher than the female at the same site.

The effects of temperature differences on metabolic and tissue growth rates are well known and the recorded differences offer some explanation for the site and sex differences in prognosis.

The immuno-defence mechanism

There is no lack of evidence for believing that the course often taken by malignant disease is due to some natural influence present in the host:

for example, the spontaneous regressions, those cases that smoulder on, and those who survive for long periods and then later develop recurrences.

There is therefore ample evidence to justify the laboratory work now being carried out to enquire into the mechanism (Mansell, 1968).

Melanomas grown under standard conditions of tissue culture, irrespective of their previous rates of growth in the patient, all ultimately grow at the same rate, even though some begin to grow more slowly than others. Cells from the tumours that grow more slowly in the patient are more difficult to culture than cells from florid lymph node metastases, but in the end all seem to grow alike. It can only be concluded, therefore, that there are specific and individual retarding factors which control, at least to some extent, the clinical behaviour and so explain the individual pattern of the disease.

It has been shown that in many animal cancers, whether induced by chemical means or by viruses, detectable antigens are present. During the last six months a search has been going on for both antigens and antibodies in cases of melanoma. So far they have only been found by agglutination tests in three out of 22 tests, and in two out of 16 tests by the immuno-fluorescent method.

On most of these occasions the tumour tissue has come from patients with massive growths who are near the end of their survival period and would not clinically be expected to have antibodies in any concentration. Favourable cases who might be expected to have a good defence cannot usually provide enough material for the present methods of testing and micro-methods need to be worked out. Nevertheless, their presence in detectable concentration in a few cases is encouraging.

It is of interest to appreciate that to-day we require no less than six separate portions of the original specimen for laboratory work, namely for: routine histology; tissue culture; extraction of antigens; immuno-fluorescence; virus study; and some in low temperature storage for reference purposes.

Pregnancy

No conclusive evidence has yet been produced to suggest that pregnancy occurring at any time adversely affects the course of the disease.

In our series 29 patients have been pregnant, either at the onset of the disease or have become pregnant subsequently. This series could not be considered sufficiently large, nor has it been studied long enough, to be statistically significant. All that can be said at present is that the most careful scrutiny of their records fails to reveal any noticeable difference in their behaviour from comparable non-pregnant patients. Therefore, in the present state of our knowledge, there is no justifiable reason on the grounds of malignancy to prevent or terminate pregnancy. A mother with advancing disease, who is pregnant, might possibly be considered

for termination on the grounds that treatment by chemotherapy or irradiation methods could not be carried out, but the evidence is that these measures would not be life saving.

CONCLUSIONS

The rising incidence of melanoma, particularly on the female leg, and also the lapse of time which takes place between the patient noticing the tumour and seeking advice, are both matters for concern.

Whereas adequate surgery can generally cure the local disease, systemic involvement remains untreatable by methods at present available.

The fate of most patients suffering from malignant melanoma is predetermined, and the defence mechanism dominates the outcome. A parable in contemporary form explains the progress of the disease. The clinician can be likened to a referee in charge of the contest between the patient and the tumour. By participation at the opportune time, he can generally arrange for a win for the patient against the ' good ' tumours, but against the ' bad ' tumours he can only prolong the match.

The supporters' club of chemotherapy, radiotherapy and hormone therapy have little or no influence on the outcome of the match.

The greatest need is to improve the playing standards of the patients, and to avoid weakening them by harmful and suppressive measures, whether these be chemical or physical. No agents at present available fulfil these requirements.

The most profitable immediate step which could be taken would be to reduce to less than three months the time most patients wait before they seek advice—the average time is over one year.

The melanoma, as a research project, has enormous advantages over many other tumours, both for clinical and laboratory research; if sufficient resources were directed towards intensive investigations of the melanoma riddle, the way might be opened to a breakthrough in the management of other forms of malignant disease.

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