MALIGNANT MELANOMA

A study of 283 cases with comments and suggestions on treatment.

by

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Introduction

From the time of its first description by Laennec in 1806, malignant melanoma has been the subject of controversy and dread. For nearly 100 years there was no firmly founded policy of treatment. The first rational surgical attack was described by EVE in 1902. SAMPSON HANDLEY, in the Hunterian lectures of 1907, based on this tumour the further development of his researches into the spread of malignant cells via lymphatic pathways. Since they were conveniently marked they traced their course from the primary site to the draining nodes and a regime could be planned to deal with all the expected treatable routes of spread. Handley confirmed Eve's recommendation of prophylactic lymph node dissection and described the en bloc operation which has been one of the accepted therapeutic standbys since.

While the techniques of surgery became well established quite early in this century, easily understandable and significant survival rates were not published until the third and fourth decades. These tended to confirm the pessimistic description of the tumour as the most malignant superficial neoplasm. Only one of BLOODGOOD's two hundred cases survived five years (1922). With improvements in case

selection, education of the general practitioner and the public, and the realisation of the dangers of inadequate therapy, the outlook improved through PACK's 9.6% 5 year results (1947) to PANAYOTIS' 1962 series of 170 patients, of whom 42.3% survived overall. Undoubtedly a higher proportion of patients are reporting at an earlier stage and surgeons are now treating all moles with respect. In certain sites, in females with disease confined to the skin, adequate excision has produced 5 year survival rates of 70% (LANE, LATTES and MALM; 1959). However in other sites, particularly in males, apparently equivalent lesions continue to cause the death of 4 patients out of 5 within 5 years and in some cases dissemination appears to follow attempts at removal with great rapidity.

In Europe this clinical impression was noted early and recourse was made to newer and less well tried modes of treatment. As early as 1903 Gassenbauer reported to the Vienna Medical Society twenty cases of "melanotic sarcoma" treated by exposure to radium, (reported by TRACEY, 1903). More recent results of radiological management have claimed very high survival figures at the three year period (MÜLLER-MINY, 1955) but since biopsy is forbidden their publications lack histological confirmation (HELLRIEGEL, 1952). In the

United Kingdom ELLIS (1939 and 1946) and TOD (1946) reported 53 and 21 cases respectively in which radiation was used. Their results in early cases, usually combined with surgery, were more than equal to those of surgery alone.

A combination of surgery and post-operative radiation was found useful in Scandinavia (SCHARNAGEL, 1933: JORGSHOLM and ENGDAHL, 1952: NITTER, 1958) although SYLVÉN (1949) had doubts about its efficacy. DICKSON (1958) carried this doctrine across the Atlantic. Preoperative radiation of the primary and post-operative Xray therapy of the block dissected nodes where these are involved is the current management in Russia (MEL'NIKOV and FEDOREYEV, 1961). The doses however are far higher than is acceptable in the West.

In America, COLEY reported regression in one or two cases treated with Xrays in 1903, but by 1916 called this mode of treatment "a most unwise procedure". Although no large series was produced to support the contention, malignant melanoma rapidly gained the reputation of being the most resistant neoplasm to radiation. Individual case reports (OWEN, 1924) and small series (KEITH and KEITH, 1922: QUIGLEY, 1924) contested this view but others (MORROW and TAUSSIG, 1924) reported complete failure. Cauterising doses

of Xrays were claimed by EVANS and LEUCUTIA (1931) to have produced good results but their illustrations of early primaries are open to other diagnostic interpretations of a more benign nature. On this rather uncertain clinical foundation statements are found in textbooks of dermatology (ORMSBY and MONTGOMERY, 1954) surgery (EDWARDS, 1949), oncology (RAVEN, 1959) and radiotherapy (PORTMANN, 1950) that radiation is contraindicated in the condition. RALSTON PATERSON (1948) goes so far as to say that a "malignant melanoma" which is locally cured by radiotherapy is probably not a malignant melanoma.

Much of the early controversy surrounding malignant melanoma lay in the field of histopathology. Unna, noting the epidermal origin of the lesion, dubbed it a carcinoma but RIBBERT (1897), basing his work on the morphology of the established tumour, differed. He attributed the origin of the "chromatophores" to the dermal histiocytes and defined the neoplasm as a sarcoma. Later works by DAWSON (1925) and ALLEN and SPITZ (1953) have clearly established the origin of the malignant process in the basal layers of the epidermis from the cell which is more correctly termed a melanoblast. In addition they showed the relationship of the neoplasm to

the benign naevi which has been lucidly and succinctly stated by HICKS, RANK and WAKEFIELD (1955). The derivation of the melanoblast from the neural crest and its migration to the peripheral epidermis are perhaps less clearly understood but appear to be reasonably well founded on comparative animal work (BECKER, 1948) and serial examinations of foetal skin (ZIMMERMAN and BECKER, 1959). MASSON (1951) has for many years propounded the dual origin of naevi from cutaneous and nervous tissue based upon the staining properties of the cells. Other Pathologists, principally ALLEN have rejected this hypothesis and produced convincing illustrations of fraying of the basal layers of the epidermis into tumour tissue. It may be that Masson's neurogenic theory has contributed to the stigma of radioresistance since nervous tissue, particularly such a highly differentiated cell functionally speaking as to continue producing pigment, was thought to be almost immune to damage from ionising radiation. DESJARDINS (1934) certainly classed the tumour among the least radiosensitive sarcomata.

DAWSON's exhaustive study of the histogenesis of the developing melanoma laid the foundation for ALLEN and SPITZ's later description of the various grades of malignancy although

no reference is given in the later work to Dawson's contribution. Although the more recent publication has been widely accepted as differentiating between "junctional naevi, active junctional naevi, superficial melanocarcinoma and invasive melanoma" the separation of these from the so-called juvenile melanomata is not universally acclaimed as explaining the very different prognosis in childhood and post-pubertal lesions. McWHORTER's thesis (1954) does however tend to confirm their findings and use has been made of their criteria of distinction in selecting the material for the present study. The more recent pathological "staging" (it would have surely been preferable to use the term "grading" since this is more commonly applied to pathological material) introduced by PETERSEN et al (1962), is perhaps more acceptable as a universally applicable definition but in no way really differs from Allen and Spitz's and as they have the prior claim their terminology has been adopted.

The present series, comparing radiation and surgery, in a very crude fashion, was made possible by the fact that the primary treatment of pigmented tumours in Melbourne was for many years in the hands of the radiotherapist. From 1928 when the present case recording system started, until the late 1940's

many cases of melanotic neoplasms were referred in the first instance to the Radium Department of the Royal Melbourne Hospital. During this period surgery became increasingly popular so that by the time World War 11 finished and plastic techniques were introduced only inoperable or recurrent cases were normally referred. With the establishment in 1956 of a radiosurgical unit at the Peter MacCallum Clinic which in the interim had supplanted the Radium Department, a reversal of policy was completed so that most treatable melanomata were subjected to operation. This reversal of policy will be evident in the numbers available for three, five and ten year assessment. No claim is made that the cases analysed represent all the melanomata presenting in Victoria or even Melbourne as many private patients were operated on in other units and at least three other teaching hospitals and two other radiotherapeutic groups were in operation.

Material

All cases registered as melanoma, malignant melanoma, melanosarcoma or melanocarcinoma, at the Radium Department of the Royal Melbourne Hospital and its successor the Peter

Table I

Discarded Cases

Wrongly registered : actually lymphosarcoma. 1

No histology or convincing clinical description. 5
3 cases alive and well, 22, 22 and 15 years.
1 untraced, 3 years.
1 died aged 97, 16 years.

Sclerosing angioma. 2
2 alive and well, 10 and 1 years.

Juvenile melanoma (Allen and Spitz,1953; McWhorter, 1954). 2
1 alive and well, 2 years.
1 untraced, 5 years.

Superficial melanocarcinoma (Allen and Spitz, 1953). 8
8 alive and well, 10 years to 6 months

18

Table II

Cases Accepted as Malignant Melanoma Without Review of Histology.

Surgery alone. 8
3 died of melanoma within 5 years.
3 died of melanoma, 5, 6 and 18 years.
2 died of other disease within 3 years.

Radiation first. 7
4 died of melanoma within 5 years.
1 died at 3 years, probably with disease.
1 discharged well and untraced after 5 years.
1 alive and well, 20 years.
All had convincing clinical descriptions and were implanted.

Surgery; recurrence; radiation. 6
3 died within 5 years of melanoma.
1 died of melanoma in the 7th year.
1 died of melanoma in the 9th year.
1 alive and well after repeated excisions and finally implant 10 years after first treatment.

Palliative therapy. 10
8 died of melanoma within 3 years.
1 died of other causes at 4 months.
1 untraced at 2 years.

No Treatment. 4
2 died of melanoma, 3 years and 1 month.
2 untraced within 1 month.

MacCallum Clinic up to December 1959 were reviewed. Of the total number of 301, 6 were excluded as wrongly registered or as having neither histology nor an adequate and convincing clinical description and history. 12 more were thought to be sclerosing angioma, juvenile melanoma, or superficial melanocarcinoma (Allen and Spitz) on reappraisal of the histology. All remain alive and well at the completion of the series and have been excluded from subsequent discussion. One case, originally diagnosed as superficial melanocarcinoma was found to be a true invasive melanoma and eventually died of melanoma. This case has been included. (Table I).

Histology was not always available for reconsideration in cases treated prior to 1955 and in some cases had not been examined at all. Reliance had therefore to be placed in a few cases upon the original pathologist's opinion or a convincing clinical description and history. Table II details the proportion and fate of these patients in each treatment group.

The 283 cases remaining fell into 5 groups according to the treatment they received. Many patients had already had some form of treatment before referral. 11 were offered no further treatment at the centre but were returned for more radical surgery and did not report again, were in extremis or

Table III

No Effective Treatment Group

Age	26 - 35	36 - 45	46 - 55	56 - 65	66 - 75	76 - 85	86 - 95	Unknown
	1	2	1	1	4	0	1	1

Sex: 6 males 5 females

Site	Head and neck	Arm	Trunk	Leg	Foot	Unknown (Nodes only or multiple)
	1	1	2	1	4	2

Size (cm.)	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	Unknown
	0	4	1	1	0	2	0	0	1	2

Stage and fate	I	II	III
	2 referred back for excision and untraced. 1 locally excised only but died 12 years later with multiple metastases.	1 untraced. 3 died 1, 2, and 36 months.	1 untraced. 3 died 1, 2, and 4 months.

refused treatment. These are recorded separately in Table III but are included in the overall basic data and survival rates. Only palliative therapy was possible in 55 patients either by reason of the extent of their disease or their age and general condition. 88 received surgery alone or surgery and chemotherapy for metastases. At no time was radiotherapy used so that to this extent they form a selected group. Most were referred to the Peter MacCallum Clinic after the establishment of a combined radiosurgical skin clinic in 1956 and hence are not available for survival studies. A further 47 cases were primarily treated by radical surgery but received radiation for recurrence or metastases. The remaining patients, 82 in number, were originally treated by radiation in one form or another, either alone or in combination with surgery. The surgery in most cases consisted of local excision of any remnant or radionecrosis following implant or Xray therapy. Post-operative radiation is included in this group where the radiation was administered within 4 weeks of operation and formed part of the planned regime.

Methods

In the treatment of the primary tumour, radiation most frequently took the form of a radon needle implant deep to the

Table IV.

Sex of Cases

	Males	Females
Surgery alone or with chemotherapy	40	48
Radiation first effective treatment	36	46
Surgery; recurrence; radiation	21	26
Palliative therapy	36	19
No effective treatment	6	5
	139	144

lesion. A biopsy was often taken at the time of insertion of the needles. Soft Xrays from a Chaoul tube were used when beds or sources were not available. The dosages used were in the region of 6,000 roentgens at 0.5 cm in 4 to 7 days with implants and 3,000 to 5,000 roentgens on the surface of the lesion in 10 to 15 sessions over 2 to 3 weeks with the Chaoul tube. Any remnant or radionecrotic ulcer was excised after a variable lapse of time up to several years after treatment. In a few cases local excision of the lesion usually by the referring General Practitioner was followed either by X-irradiation or a radon mould delivering much the same dosages.

Adequate surgery was deemed to have been performed if wide excision had been carried out with margins ranging from 2.0cm. to 4.0cm. In most cases skin grafting was required. Where the nodes lay adjacent an enbloc procedure was performed.

Prophylactic treatment of the nodes was often omitted. Block dissections were rare in the prewar period but became routine after 1956. They were usually "delayed" where the nodes lay remote from the primary area.

Clinical lymphatic metastases were more frequently excised than irradiated and more frequently implanted than treated externally. The numbers are small in both groups.

Results

Sex. There were 139 males and 144 females. This almost equal division of the sexes held for all subdivisions except the palliative where there were approximately twice as many males as females (Table IV). This may reflect the more advanced stage at which males presented.

Staging. Staging was determined according to the scheme adopted by several authors. (SCHARNAGEL, 1933; SYLVÉN, 1949). Stage 1: disease confined to the primary site on clinical examination. Stage 11: palpable but operable nodes in the immediate draining group present. Stage 111: inoperable nodes or distant metastases found on examination or Xray. Local recurrences were staged as 1 if they conformed to the definition given. Staging as 1, 11 or 111 applies to the patient's condition at the time of the first visit to a medical practitioner. This is modified in those cases who subsequently had radiation by substages A, B or C corresponding

to the same criteria but defining the condition as at referral for radiotherapy. Thus a patient whose melanoma was primarily excised and who subsequently developed nodes which were irradiated would be Stage IB if the nodes were operable and IC if they were fixed or distant metastases were found. Pathological findings do not alter the clinical staging as it felt that the separation of cases should be on clinical grounds alone if a different treatment policy is to be adopted for different stages or a comparison is to be made between procedures, one of which is not amenable to histological confirmation of staging.

Survival. No attempt has been made to estimate "Cure rates" (PACK, 1959) since this first gives a false impression of the value of treatment, second is inaccurate in that a not inconsiderable proportion of patients succumb to disease after apparent cure and third may impart a false sense of security in the patient's and the practitioner's mind. The only clinically observable and absolute fact about a patient is that he is alive or dead. No conditional statements are necessary.

"Determinate cases" only are used in the survival rates which are quoted (SYLVÉN, 1949). Cases lost to follow up or dying of unrelated causes within the period under consideration are omitted but are indicated in Table XIV under the end result

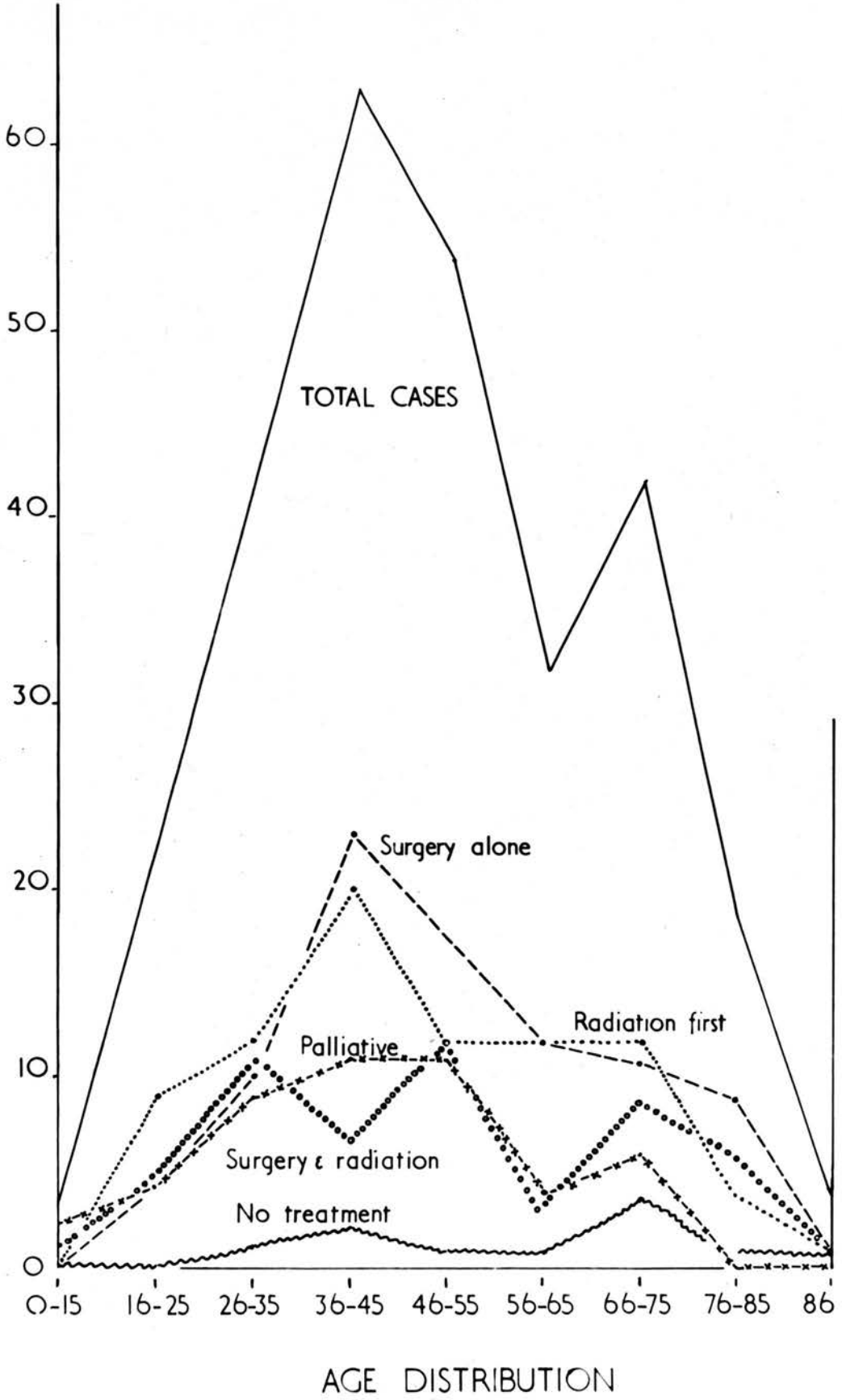

60
50
40
30
20
10
0
TOTAL CASES
Surgery alone
Radiation first
Palliative
Surgery & radiation
No treatment
0-15
16-25
26-35
36-45
46-55
56-65
66-75
76-85
86
AGE DISTRIBUTION

Table V

Age	0-15	16-25	26-35	36-45	46-55	56-65	66-75	76-85	86-	?
Surgery alone	0	4	10	22	19	13	11	8	1	0
Radiation	0	9	12	20	12	12	12	4	1	0
Surgery; recurrence; radiation	2	4	9	11	11	4	6	0	0	0
Palliative	1	5	11	7	12	3	9	6	1	0
No treatment	0	0	1	2	1	1	4	0	1	1
	3	22	43	62	55	33	42	18	4	1

Table VI

Stage Age Sex and Survival.

Age	0 - 15			16 - 25			26 - 35			36 - 45			46 - 55			56 - 65			66 - 75		
Sex.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.
Stage I	1/1	0	1/1	1/1	3/5	4/6	2/4	5/8	7/12	1/6	4/10	5/16	2/4	3/5	5/9	1/4	1/4	2/8	0/4	1/3	1/7
Stage II	0	0/1	0/1	1/2	1/1	2/3	1/1	1/2	2/3	1/2	0	1/2	0/4	0/1	0/5	0/1	0	0/1	0	0/1	0/1
Stage III	0/1	0	0/1	0/2	0	0/2	0/1	0	0/1	0/2	0/2	0/4	0	0/2	0/2	0/1	0	0/1	0/2	0/1	0/3
10 year survivors	1/2	0/1	1/3	2/5	4/6	6/11	3/6	6/10	9/16	2/10	4/12	6/22	2/8	3/8	5/16	1/6	1/4	2/10	0/6	1/5	1/11
Stage I	1/1	0	1/1	4/6	5/6	9/12	3/5	9/12	12/17	4/12	6/13	10/25	3/7	6/9	9/16	2/6	3/7	5/13	3/7	4/6	7/13
Stage II	0	0/1	0/1	1/2	1/2	2/4	1/1	2/3	3/4	2/6	0/1	2/7	0/5	0/3	0/8	0/1	0/1	0/2	1/2	0/1	1/2
Stage III	0/1	0	0/1	1/2	0	1/2	0/1	0	0/1	0/2	0/2	0/4	0/1	0/2	0/3	0/2	0	0/2	0/2	0/1	0/3
5 year survivors	1/2	0/1	1/3	6/10	6/8	12/18	4/7	11/15	15/22	6/20	6/16	12/36	3/13	6/14	9/27	2/9	3/8	5/17	4/10	4/8	8/18
Stage I	1/1	0	1/1	6/7	6/6	12/13	6/7	11/13	17/20	7/17	8/15	15/32	3/9	13/16	16/25	4/6	6/8	10/14	4/8	5/9	9/17
Stage II	0	0/1	0/1	2/2	1/2	3/4	2/2	3/5	5/7	2/8	0/1	2/9	2/5	2/5	4/10	0/1	0/1	0/2	1/1	0/1	1/2
Stage III	0/1	0	0/1	1/2	0	1/2	0/2	0	0/2	1/3	1/2	2/5	0/2	1/2	1/4	0/2	0	0/2	0/4	0/1	0/5
3 year survivors	1/2	0/1	1/3	9/11	7/8	16/19	8/11	14/18	22/29	10/28	9/18	19/46	5/16	16/23	21/39	4/9	6/9	10/18	5/13	5/11	10/24
Less than 3 years																					
Stage I	0	0	0	0	0/1	1/1	3/4	2/3	5/7	3/4	8/8	11/12	1/3	6/6	7/9	3/3	7/9	10/12	1/3	2/3	3/6
Stage II	0	0	0	1/1	0	1/1	0	1/1	1/1	0/1	0	0/1	3/3	1/1	4/4	0	0	0	0/1	0/1	0/2
Stage III	0	0	0	0	0	0	0/1	0	0/1	0	0	0	0/1	0/1	0/2	0	0/1	0/1	2/3	0	2/3
Survivors	0	0	0	1/1	1/1	2/2	3/5	3/4	6/9	3/5	8/8	11/13	4/7	7/8	11/15	3/3	7/10	10/13	3/7	2/4	5/11
Dead of other disease or untraced	0	0	0	0	1	1	0	5	5	2	1	3	1	0	1	2	0	2	4	3	7
Grand total	2	1	3	12	10	22	16	27	43	35	27	62	24	31	55	14	19	33	24	18	42

Table V(Cont.)

Stage Age Sex and Survival.

Age	76 - 85			86 +			?	M	F	Total	
Sex	M	F	Tot.	M	F	Tot.	M	Total Survival rates			
Stage I	0/1	0	0/1	0	0	0	0	8/25	17/35	25/60	
Stage II	0	0	0	0	0	0	0	3/10	2/6	5/16	
Stage III	0	0	0	0	0	0	0	0/9	0/4	0/13	
10 year survivors	0/1	0	0/1	0	0	0	0	11/44	19/45	30/89	(33.7%)
Stage I	2/2	0	2/2	0	0	0	0	22/45	33/52	55/97	
Stage II	0	0/1	0/1	0	0	0	0	5/16	3/13	8/29	
Stage III	0	0	0	0	0	0	0	1/11	0/5	1/16	
5 year survivors	2/2	0/1	2/3	0	0	0	0	28/72	36/70	64/142	(45.0%)
Stage I	4/4	3/3	7/7	0	0/1	0/1	0	35/59	52/71	87/130	
Stage II	0/1	0/1	0/2	0	0	0	0/1	9/21	6/17	15/38	
Stage III	0	0	0	0	0	0	0	2/16	2/5	4/21	
3 year survivors	4/5	3/4	7/9	0	0/1	0/1	0/1	46/96	60/93	106/189	(56.2%)
Less than 3 years											
Stage I	0/2	1/2	1/4	1/1	0/1	1/2	0	12/20	27/33	39/53	
Stage II	1/1	0	1/1	0	0	0	0	5/7	2/3	7/10	
Stage III	0	0/1	0/1	0	0/1	0/1	0	2/5	0/4	2/9	
Survivors	1/3	1/3	2/6	1/1	0/2	1/3	0	19/32	29/40	48/72	
Dead of other disease and untraced	2	1	3	0	0	0		11	11	22	
Grand total	10	8	18	1	3	4		139	144	283	

Table VII

Age, Stage and Survival	0 - 35	36 -	
Stage I	12/19	12/41	
Stage II	4/7	1/9	
Stage III	0/4	0/9	
Ten year survival rate	16/30	14/59	$x^2 = 5.2$
Stage I	22/30	33/67	
Stage II	5/9	3/20	
Stage III	1/4	0/12	
Five year survival rate	28/43	36/99	$x^2 = 6.0$
Stage I	30/34	57/96	
Stage II	8/12	7/26	
Stage III	1/5	3/16	
Three year survival rate	39/51	67/138	$x^2 = 5.4$

and in Table IX to allow assessment of the possible range of survival. The overall survival rates are shown as a check of additions at the end of each table. For males the 3, 5, and 10 year survivals are 46 of 96 patients (48%), 28 of 72 (39%) and 11 of 44 (25%). For females the figures are 60 of 93 (64%), 36 of 70 (51%), 19 of 45 (42%). The totals are 106 of 189 (56.2%), 64 of 142 (45.0%) and 30 of 89 (33.7%). These include all determinate cases presenting at the centre. Survival is dated from the first attempt at treatment whether this is adequate or inadequate since no other means can be used to gauge the natural history of the disease and compare this with the effect of treatment. The result may be to inflate the survival rates but the average delay between inadequate and adequate treatment was less than 6 months. The trend towards better survival for female cases tallies with that of most other authors quoted but is not significant.

Age. Age distribution is shown in Table V and figure I. The only deviation between sub groups is a not unexpected preponderance of elderly patients in those who received palliative therapy only. The survival rates are shown in Table VI according to age, sex and stage. Table VII shows that a difference between patients 35 years and under and 36 years and over exists at almost significant levels.

Table VIII

SITE

SITE	HEAD & NECK		ARM		HAND		TRUNK		LEG		FOOT		GENITAL		EYE		MENINGES		?	
SEX	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
	54	44	10	14	0	1	35	22	18	45	11	12	0	2	6	2	0	1	5	1
TOTAL	98		24		1		57		63		23		2		8		1		6	
%	34·6		8·5		0·35		20·0		22·3		8·1		0·7		2·8		0·35		2·1	

Table IX.

Site, Sex, Stage and Survival.

	Head and Neck				Trunk				Lower Limb				Foot			
	M.	F.	Tot.	%	M.	F.	Tot.	%	M.	F.	Tot.	%	M.	F.	Tot.	%
Stage I	3/12	7/11	10/23	43.5	0/2	3/7	3/9	33.3	3/4	6/9	9/13	69.0	0/3	1/5	1/8	12.4
Stage II	1/5	0/2	1/7		1/2	0/2	1/4		0/1	2/2	2/3		0/1	0	0/1	
Stage III	0/3	0	0/3		0/2	0/2	0/4		0/2	0	0/2		0	0/2	0/2	
Ten year Survivors	4/20	7/13	11/33	33.3	1/6	3/11	4/17	23.5	3/7	8/11	11/18	61.0	0/4	1/7	1/11	9.0
Stage I	9/19	10/15	19/34	55.9	2/8	5/8	7/16	43.7	5/7	13/19	18/26	69.0	2/6	2/5	4/11	36.5
Stage II	1/6	0/2	1/8		1/3	0/3	1/6		0/2	3/6	3/8		0/2	0	0/2	
Stage III	0/3	0	0/3		0/3	0/2	0/5		1/2	0	1/2		0	0/2	0/2	
Five year Survivors	10/28	10/17	20/45	44.5	3/14	5/13	8/27	29.5	6/11	16/25	22/36	61.0	2/8	2/7	4/15	26.5
Stage I	18/26	21/24	39/50	78.0	4/13	5/9	9/22	41.0	5/7	17/23	22/30	73.5	3/7	4/6	7/13	54.0
Stage II	2/7	1/2	3/9		2/5	0/4	2/9		2/4	4/8	6/12		0/2	0	0/2	
Stage III	0/3	0	0/3		1/5	0/2	1/7		1/2	0	1/2		0	1/2	1/2	
Three year Survivors	20/36	22/26	42/62	67.5	7/23	5/15	12/38	31.5	8/13	21/31	29/44	66.0	3/9	5/8	8/17	47.0
Less than three years																
Stage I	8/13	9/11	17/24		3/5	1/4	4/9		0/1	10/10	10/11		0	1/1	1/1	
Stage II	1/1	1/1	2/2		2/2	0/1	2/3		2/2	1/1	3/3		0	0	0	
Stage III	0/1	0/1	0/2		1/1	0	1/1		0/1	0/1	0/2		0	0/2	0/2	
Total	9/15	10/13	19/28		6/8	1/5	7/13		2/4	11/12	13/16		0	1/3	1/3	
Dead of Other Cause	3	1	4		1	1	2		1	1	2		0	0	0	
Untraced	0	4	4		3	1	4		0	1	1		2	1	3	
Grand Total			98				57				63				23	

Upper Limb			Eye			Hand	Meninges	Genitalia	Unknown			Determinate Total						Indeterminate Cases	
M.	F.	Tot.	M.	F.	Tot.	F.	F.	F.	M.	F.	Tot.	M.	%	F.	%	Total	%	M.	F.
1/1	0	1/1	1/3	0/1	1/4	1/1	0	0/1	0	0	0	8/25	32.0	17/35	48.5	25/60	41.6	4	4
1/1	0	1/1	0	0	0	0	0	0	0	0	0	3/10	30.0	2/6	33.4	5/16	32.0	0	0
0/1	0	0/1	0/1	0	0/1	0	0	0	0	0	0	0/9	00.0	0/4	00.0	0/13	00.0	0	1
2/3	0	2/3	1/4	0/1	1/5	1/1	0	0/1	0	0	0	11/44	25.0	19/45	42.3	30/89	33.7	4	5
2/2	1/2	3/4	2/3	1/1	3/4	1/1	0	0/1	0	0	0	22/45	48.8	33/52	63.3	55/97	56.8	1	2
3/3	0/1	3/4	0	0	0	0	0	0/1	0	0	0	5/16	31.2	3/13	23.0	8/29	27.5	0	0
0/1	0/1	0/2	0/1	0	0/1	0	0	0	0/1	0	0/1	1/11	9.1	0/5	00.0	1/16	6.25	0	0
5/6	1/4	6/10	2/4	1/1	3/5	1/1	0	0/2	0/1	0	0/1	28/72	38.9	36/70	51.4	64/142	45.0	1	2
2/2	2/4	4/6	3/4	1/2	4/6	1/1	1/1	0/1	0	0	0	35/59	59.3	52/71	73.2	87/130	67.0		
3/3	0/1	3/4	0	0	0	0	0	0/1	0	1/1	1/1	9/21	42.8	6/17	35.4	15/38	39.5		
0/2	1/1	1/3	0/1	0	0/1	0	0	0	0/3	0	0/3	2/16	12.5	2/5	40.0	4/21	19.0		
5/7	3/6	8/13	3/5	1/2	4/7	1/1	1/1	0/2	0/3	1/1	1/4	46/96	48.4	60/93	64.8	106/189	51.0		
1/1	6/7	7/8	0	0	0	0	0	0	0	0	0	12/20		27/33		39/53			
0/1	0	0/1	0	0	0	0	0	0	0/1	0	0/1	5/7		2/3		7/10			
0	0	0	1/1	0	1/1	0	0	0	0/1	0	0/1	2/5		0/4		2/9			
1/2	6/7	7/9	1/1	0	1/1	0	0	0	0/2	0	0/2	19/32		29/40		48/72			
0	0	0	0	0	0	0	0	0	0	0	0	5		3		8			
1	1	2	0	0	0	0	0	0	0	0	0	6		8		22			
		24			8	1	1	2			6	139		144		283			

Table X.

Size, Sex, Stage and Survival.

Size (cm.)	0 - 1			1 - 2			2 - 3			3 - 4			4 +			Unknown			Total		
Sex	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.	M	F	Tot.
Stage I	1/4	2/4	3/8	1/9	3/9	4/18	4/4	3/6	7/10	0/2	0/1	0/3	0	2/2	2/2	2/6	7/13	9/19	8/25	17/35	25/60
Stage II	0/1	0	0/1	2/5	0/1	2/6	0/2	1/2	1/4	0/1	1/2	1/3	1/1	0	1/1	0	0/1	0/1	3/10	2/6	5/16
Stage III	0/1	0/1	0/2	0/2	0	0/2	0	0/2	0/2	0/1	0	0/1	0/2	0/1	0/3	0/3	0	0/3	0/9	0/5	0/14
Ten year survivors	1/6	2/5	3/11	3/16	3/10	6/26	4/6	4/10	8/16	0/4	1/3	1/7	1/3	2/3	3/6	2/9	7/14	9/23	11/44	19/45	32/89
Stage I	3/8	8/11	11/19	6/17	8/14	14/31	4/4	3/6	7/10	1/2	0/1	1/3	2/2	2/3	4/5	6/12	12/17	18/29	22/45	33/52	55/97
Stage II	0/1	0	0/1	2/7	0/3	2/10	1/3	1/4	2/7	0/1	1/2	1/3	1/1	0/1	1/2	1/3	1/3	2/6	5/16	3/13	8/29
Stage III	0/1	0/1	0/2	1/2	0	1/2	0	0/2	0/2	0/1	0	0/1	0/3	0/1	0/4	0/4	0/1	0/5	1/11	0/5	1/16
Five year survivors	3/10	8/12	11/22	9/26	8/17	17/43	5/7	4/12	9/19	1/4	1/3	2/7	3/6	2/5	5/11	7/19	13/21	20/40	28/72	36/70	64/142
Stage I	7/10	13/13	20/23	10/21	13/20	23/41	5/7	5/8	10/15	1/2	0/1	1/3	2/3	3/4	5/7	10/16	18/25	28/41	35/59	52/71	87/130
Stage II	0/2	1/2	1/4	5/7	0/4	5/11	2/4	1/4	3/8	0/1	2/2	2/3	1/2	0/1	1/3	1/5	2/4	3/9	9/21	6/17	15/38
Stage III	0/1	1/2	1/3	2/3	0	2/3	0	1/2	1/2	0/1	0	0/1	0/4	0/1	0/5	0/7	0	0/7	2/16	2/5	4/21
Three year survivors	7/13	15/17	22/30	17/31	13/24	30/55	7/11	7/14	14/25	1/4	2/3	3/7	3/9	3/6	6/15	11/28	20/29	31/57	46/96	60/93	106/189
Less than three years																					
Stage I	3/4	9/10	12/14	4/6	16/18	20/24	1/2	0/3	1/5	1/1	0	1/1	0	0	0	3/7	2/2	5/9	12/20	27/33	39/53
Stage II	1/1	0	1/1	2/3	1/1	3/4	0/1	0	0/1	0	0	0	0	0	0	2/2	1/2	3/4	5/7	2/3	7/10
Stage III	0/1	0	0/1	0	0	0	1/1	0	1/1	0	0	0	1/1	0/3	1/4	0/2	0/1	0/3	2/5	0/4	2/9
Survivors	4/6	9/10	13/16	6/9	17/19	23/28	2/4	0/3	2/7	1/1	0	1/1	1/1	0/3	1/4	5/11	3/5	8/16	19/32	29/40	48/72
Dead of Other Disease	1	0	1	1	1	2	1	0	1	1	0	1	0	1	1	1	1	2	5	3	8
Untraced	2	1	3	1	3	4	1	1	2	1	0	1	1	0	1	0	3	3	6	8	14
Total	22	28	50	42	47	89	17	18	35	7	3	10	11	10	21	40	38	78	139	144	283

Site. All cases are divided as to site and sex in Table VIII. There is a significant difference at the 0.1% level of probability in the distribution of lower limb primaries between the sexes. An opposite trend but not of statistical significance can be seen in trunk primaries. Table IX breaks down the survivors according to site, stage and sex. It can be seen that trunk melanomata are more advanced and have a lower survival rate than most other sites. The difference between lower limb and foot primaries is not significant for 3 and 5 year results but approaches it ($x^2 = 4.4$) at the ten year point.

Size. The effect of the size of the primary on the stage of disease is more apparent in Table X than any effect upon the survival rate, if equivalent stages are compared.

The Extent of the First Treatment. Effective treatment was considered to be wide surgical excision, implantation of radioactive sources deep to the lesion, or Xray therapy administered under the direction of a radiotherapist. Ineffective treatment included local excision, carbon dioxide snow, bathing or the application of caustics. By far the greatest number of ineffectively treated patients had effective treatment later although in some, local recurrence took place before a correct diagnosis was made and effective therapy administered. Incisional biopsy was performed in a

Table XII

Biopsy and Survival.

Time between biopsy and effective treatment	0	-4 weeks	-8 weeks	-3 months	-6 months
Cases alive and well					
at 10 years	1	0	3	0	0
at 5 years	1	1	3	0	0
at 3 years	1	3	3	0	0
Alive with disease					
at 10 years	0	0	0	0	0
at 5 years	0	0	0	0	0
at 3 years	0	4	1	0	0
Dead of melanoma					
at 10 years	2	4	0	0	1
at 5 years	2	9	2	0	2
at 3 years	2	8	2	1	2
Dead of other causes	0	1	0	0	0
Untraced	0	0	1	0	0

Table XI

Nature of First Action and Survival.

Determinate cases only.	3 years	%	5 years	%	10 years	%
Effective treatment	48/71	(67.6)	31/59	(52.6)	16/38	(45.0)
Ineffective treatment	42/68	(61.7)	27/55	(49.1)	12/31	(38.7)
Biopsy before effective therapy	11/24	(46.0)	3/15	(20.0)	3/11	(27.0)

comparatively small number. Total excision was classed as ineffective treatment so that the effect of cutting into the tumour could be compared. Table XI reveals that only biopsy appears to have much of a deleterious effect upon the patient's survival. Ineffective treatment, so long as effective treatment follows, is not as fatal a step as many authors believe (PACK, 1947: SYLVÉN, 1949: CADE, 1957). It is however important to realise that all local excisions of pigmented spots for histological examination are included in this group and effective treatment in those followed fairly quickly. Further since survival is dated from this excision - since it was a form of treatment - they are rendered more comparable to those whose first medical attendant made a correct clinical diagnosis and instituted what is deemed to be correct treatment. Other series probably date their survival from the date of their referral to the centre by which time of course gross recurrence has often taken place.

For those cases who had biopsy it can be seen from Table XII that it makes little difference whether the biopsy was taken at the time of operation and reported by frozen section or a paraffin section is perused at leisure with a second more radical operation up to 4 weeks later. Table XIII reveals no significant difference between the survival rates of

Table XIII

Stage, Treatment and Survival.

Treatment policy	Surgery	Radiotherapy	Surgery; recurrence; radiotherapy
Determinate cases only			
Stage I or A	18/26 (69.2%)	39/55 (70.9%)	0
Stage II or B	2/5 (40.0%)	8/16 (50.0%)	5/11 (45.5%)
Stage III or C	0	0/4 (0.0%)	15/29 (51.7%)
Three year survivors			
All stages	20/31 (64.5%)	47/75 (62.2%)	20/40 (50.0%)
Stage I or A	7/11 (63.6%)	29/49 (59.2%)	0
Stage II or B	1/4 (25.0%)	4/13 (30.8%)	[illegible] (33.3%)
Stage III or C	0	0/4 (0.0%)	8/16 (50.0%)
Five year survivors			
All stages	8/15 (53.2%)	33/66 (50.0%)	11/25 (44.0%)
Stage I or A	1/3 (33.3%)	20/37 (54.0%)	0
Stage II or B	0/1 (0.0%)	4/8 (50.0%)	1/4 (25.0%)
Stage III or C	0	0/2 (0.0%)	2/9 (22.2%)
Ten year survivors			
All stages	1/4 (25.0%)	24/47 (51.0%)	3/13 (23.0%)

Table XIV

End Result. The State of All Cases at the Completion of the Survey.

Determinate group.	Alive and Well		Alive with disease		Dead of Melanoma	
	M	F	M	F	M	F
Less than 3 years	13	26	7	3	62	44
3 to 5 years	4	3	2	4	9	12
5 to 10 years	2	9	1	2	9	3
Over 10 years	6	10	0	1	5	5
Total	25	48	10	10	85	64

Indeterminate group.	Dead of other disease		Lost to follow up	
	M	F	M	F
Less than 3 years	4	3	7	8
3 to 5 years	0	0	2	3
5 to 10 years	1	1	4	2
Over 10 years	1	2	0	3
Total	6	6	13	16

Where the indeterminate cases are known to be alive at the appropriate interval they have been used in the survival rates.

Table XV

End Result and Size According to Treatment Policy and Site.

A. First effective treatment surgery: no radiotherapy at any time.

Site:	Head and neck	Arm	Trunk	Leg	Foot	Eye
Indeterminate cases	3	1	2	1	1	0
Survivors; Stage I	24/29	6/7	5/13	12/15	1/3	0/1
Survivors; All Stages	26/32	7/10	7/15	15/19	1/3	0/1
Size: up to 2 cm.	25	9	7	13	2	0
over 2 cm.	4	2	4	1	1	0
Unknown	6	0	6	6	1	1

B. First effective treatment radiation.

Site:	Head and neck	Arm	Trunk	Leg	Foot	Genital	Eye
Indeterminate cases	10	2	4	3	1	0	0
Survivors; Stage I	7/27	1/3	0/5	5/9	1/4	0/1	0/1
Survivors; All Stages	7/33	1/3	0/6	7/13	1/5	0/1	0/1
Size: up to 2 cm.	22	3	4	9	4	1	1
over 2 cm.	10	2	5	6	2	0	0
Unknown	11	0	1	1	0	0	0

C. Surgery - recurrence - radiation.

Site:	Head and neck	Arm	Trunk	Leg	Foot	Eye
Indeterminate cases	0	1	1	1	0	0
Survivors; Stage I	1/4	1/3	0/4	5/10	1/4	0/4
Survivors; All Stages	2/6	1/4	0/11	6/14	1/5	0/4
Size: up to 2 cm.	3	2	4	8	3	1
over 2 cm.	2	0	2	2	0	0
Unknown	1	3	6	5	2	3

D. Palliative therapy only.

Site:	Head and neck	Arm	Hand	Trunk	Leg	Foot	Genital	Eye	Meninges	?
Indeterminate cases	2	0	0	3	0	1	0	0	0	0
Survivors; Stage I	2/6	0	1/1	0/5	3/6	0/1	0	0	1/1	0
Survivors; All Stages	2/11	0/2	1/1	2/13	4/11	0/3	0/1	1/2	1/1	0/4
Size: up to 2 cm.	4	0	0	5	3	2	0	0	0	0
over 2 cm.	4	1	0	8	1	2	1	1	1	0
Unknown	5	1	1	3	7	0	0	1	0	4

radiation and surgery as the first effective treatment at 3 or 5 years. In spite of the wide percentage difference between those at 10 years the numbers are too small to attach any importance to them.

End Result. The state of all cases at the end of 1959 is shown in Table XIV. Although 283 melanomata are considered they represent only 282 patients since one female had two separate histologically proven primaries. The first, on the face, was implanted in 1931. She remained well and was discharged from follow up only to be referred back in 1958 well over 80 years old with a fresh subungual melanoma on the foot which had given rise to inoperable nodes. She therefore is recorded twice, once dying of other disease 28 years after primary treatment and once among the no treatment given group. Multiple primaries present simultaneously were noted in two cases. They are shown under "primary unknown" in Table VIII.

Any case known to have died of melanoma after an assessment year is shown as alive with disease in that year.

Table XV summarises site, stage, size and end result for the three radical treatment groups. Pure surgery has a spurious advantage in this table since most cases were operated on after 1956. The survival figures are shown in Table XIII.

Table XVI

Block Dissection.

Stage I cases (Prophylactic)	Alive and well	Alive with melanoma	Dead	Untraced
Nodes negative	18	4	7	0
Treated before 1957	2	1	6	0
Nodes positive	5	1	1	1
Treated before 1957	1	1	0	0
Stage II cases (Therapeutic)				
Nodes negative	3	0	1	1
Treated before 1957	3	0	1	1
Nodes positive	3	3	14	2
Treated before 1957	0	2	13	2

Average survival of dead cases.
Stage I : 33 months
Stage II: 26 months

Table XVIII

Radiation Treatment of Nodes.

Stage I cases (prophylactic)

Xray therapy: 1 case. 6 cm. primary on foot. Xray therapy to to popliteal fossa and groin. Well 3½ years later but lost to follow up.

Radon needle implant:

Primary on head and neck, size unknown. Implant to neck. Well 16 years later.

1.0 cm. primary on face. Died without recurrence in the treated area within 12 months. Ineffectual treatment 3 months prior to implantation.

Stage II cases (therapeutic)

Xray therapy: 5 cases.

2.0 cm. melanoma on upper limb. Axillary nodes resolved. No recurrence. Well 18 years later.

4.0 cm. primary on lower limb, recurrent 2 years after inadequate treatment. Xray therapy to primary and nodes in moderate dosage. Well 19 years after first attempt at treatment, 17 years after recurrence.

2.0 cm. melanoma on leg. Xray therapy and implant resulted in radionecrosis requiring skin graft (excised specimen tumour free). Well 2½ years later.

2.0 cm. tumour on trunk. Combined excision and Xrays to axilla. Recurred within 12 months. Died after chemotherapy and further excision within 2 years.

2.0 cm. primary on leg. Xray therapy at very slow dose rate to primary and nodes. Recurred at 3 months and died at 6 months.

Implant: 9 cases.

4.0 cm. primary on head and neck. Required 2 implants to clear persistent disease. Died of other causes at 2½ years.

2.0 cm. melanoma on leg. Died of other causes 1 year 11 months later.

Two cases with 4.0 cm. primaries on the head and neck died of disease but without recurrence in the treated area, 1½ and 3 years later.

3.0 cm. head and neck tumour, inadequately excised nodes implanted; died of disease 1 year 8 months later

Two on head and neck and two on leg and foot died 5 months to 3 years after a moderate response of the nodes in three and complete clearing in one. All of melanoma.

Treatment of Lymph Drainage Areas. Little attempt was made prior to 1956 to treat the lymph drainage fields if it was not clinically involved. "Prophylactic" block dissection of neck groins or axillae was seldom performed for melanocarcinoma but was more commonly used than radiation for the radical treatment of enlarged nodes. The results of surgery to the immediate drainage area are shown in Table XVI. The numbers are obviously too small to draw conclusions but it does appear that a negative pathological report on the draining nodes is not necessarily a sign that all the disease has been removed.

Therapeutic dissection was completely unprofitable in that of the four who remained alive and well at 3 years, none had tumour in the draining nodes. There was no obvious prolongation of the life of those who died when the average survival of the dead cases is compared with the whole series (Table XXI).

Table XVIII details the radiation treatment of nodes. Far too few cases were irradiated "prophylactically" to draw any sort of conclusion so that this form of treatment remains untried. Of the Stage 11 cases only those treated with Xray therapy show any reasonable survival and of course no proof

Table XIX

Speed of Recurrence and Survival

Recurrent in	Total	Died within that year	Survived twice this time	Survived four times this time
1st year	39	12	15	8
2nd year	27	5	9	8
3rd year	18	3	6	4
4th year	4	1	2	1
5th year	3	0	1	0
5 to 10 years	3	0	1	0
Total	94	21	34	21

is available that the nodes were involved. Patients with enlarged nodes implanted first all died within 3 years although two of the nine succumbed to intercurrent disease. One case obtained only a partial remission and one recurred locally.

Metastases and Recurrences. No tissue was immune from haematogenous deposits except apparently cartilage but the favoured sites were the subcutaneous tissues, brain, liver, lung and bone, in that order. At post mortem deposits were found in such uncommon sites as the spleen, skeletal muscle, cardiac muscle and thyroid. It may be that the apparent sparing of cartilage was not a real one since no routine sections were taken and microscopic metastases may have been present. The lack of gross tumour may have been related to the relatively poor blood supply.

A tumour which recurs quickly or in which metastatic deposits appeared shortly after treatment might be thought to be more rapidly fatal than others of a similar nature, but it can be seen that from Table XIX this is not necessarily so since an appreciable number of patients lived for over four times the period between treatment and the appearance of recurrence. In most cases this was local recurrence or the

Table XX

Treatment of Metastases and Recurrence Other than Nodes.

1. Surgery

6 alive and well 2-3 years after excision of metastases. One had Xray therapy to a supposed recurrent nodule.

6 alive with disease; 5 cases 1-3 years after treatment and one 7 years after first reexcision culminating in forequarter amputation. Two had Xray therapy in low dosage.

3 untraced immediately after surgery.

18 died of melanoma 1-5 years later.

2 died of melanoma 10 and 12 years after excision which had to be repeated.

Xray therapy was used at some stage in 17 cases for further recurrence

2. Implant

1 alive and well 14 years later.

1 alive with disease at 3 years.

1 dead of other disease 26 years after implant but a remnant was excised locally.

3 untraced 2, 3, and 4 years after retreatment.

15 died of melanoma 0-5 years.

2 died of melanoma over 10 years after treatment of recurrence.

3. Xray therapy

a) XRT - recurrence - implant

1 untraced after 12 months.

1 died of melanoma 3 years later.

b) XRT - recurrence - excision

1 alive and well 5 years after XRT and 1 year after excision.

c) XRT alone

2 alive and well 8 and 10 years after XRT to recurrent nodes.

5 alive with disease 1-3 years.

2 untraced at 3 months.

1 died of other causes but with disease present at 5 years.

20 died of melanoma 1-7 years after treatment.

Table XXII

Chemotherapy.

Responses

1. Cyclophosphamide. Complete remission for 12 months of cerebral metastases, groin and axillary nodes.

2. Nitrogen mustard. Shrinkage of an axillary mass but combined with Xray therapy.

3. Nitrogen mustard. Shrinkage of primary tumour but also had Xray therapy.

4. Thiotepa. Temporary relief of bone pain.

5. Tretamine. Objective partial remission on several occasions with combined local injections and systemic courses of treatment.

Failures

18 cases showed no response to any compounds of the nitrogen mustard group, Sarcolysin, Actinomycin D, "Tapazole", Sanamycin and various other cytotoxics on clinical trial for anti-tumour activity, either alone or in combination.

Table XXI

Duration of Life of Dead Cases.

	Stage I	Stage II	Stage III
No treatment	12 years (1 case)	1 year 4 mo.	0 year 2 mo.
Surgery alone	3 years 3 mo.	1 year 7 mo.	-
Radiation first	4 years 5 mo.	1 year 6 mo.	1 year 4 mo.
Surgery - recurrence -radiation	IB 3 years IC 3 years 7 mo.	IIB 0 year 8 mo. IIC 1year 10 mo.	-
Palliative therapy	IB 3 years 1 mo. IC 3 years 3 mo.	IIB 1 year 6 mo. IIC 0 year 11 mo.	1 year 4 mo.

enlargement of draining lymph nodes but it still indicates that treatment seems to modify the course of the disease assuming that the tumour's characteristic growth rate remains constant and differences in host resistance at different sites or at different times are discounted. Unfortunately this assumption is not always valid with malignant melanoma since this neoplasm is one of those known to undergo spontaneous regression. This may explain the long survival of the Stage I case who had no treatment but lived for 12 years.

The Treatment of Metastases and Recurrence. The methods used and their efficacy are set out in Table XX.

Survival of dead cases. Where survival rates are very similar a comparison of the value of treatments might be made by examining the duration of life of the dead cases. This is done in Table XXI. It will be seen that radiation has an apparent 33.3% advantage over surgery in this respect but this may be fallacious in that more irradiated cases are available for ten year assessment.

Palliation. Chemotherapy was used in 23 cases (Table XXII). 18 showed no response to a variety of agents. 2 others had Xray therapy as well as cytotoxic drugs with

Table XXIV

Pregnancy.		3 years S.R.	5 years S.R.
Malignancy appeared in relation to a pregnancy 3 of these had subsequent pregnancies between the apparent transformation and treatment without appreciable effect upon the primary.	13	5/8	3/5
Pregnancy following treatment	4 1 untraced after 2 years.	3/3	3/3

Table XXIII

Hormonal Therapy.

Females

1. Aged 30. Melanoma appeared during one pregnancy but subsequent pregnancies had no effect on the primary or later, her metastases. Radiation menopause with a temporary improvement in general condition. Alive with disease 3 years after treatment at end of series.
2. Aged 40. Regression of nodes and nodules at time of natural menopause but eventually died 11 years after implant and 9 years after appearance of metastases.
3. Aged 20. Ovarian irradiation given "prophylactically". Lost to follow up after 4 years but well at last report.

Males

1. Aged 40. Cross recurrence after forequarter amputation. No response to orchidectomy or hypophysectomy. Various forms of chemotherapy were equally unsuccessful. There was no recurrence in several areas treated by Xray therapy. Died 4 years after first treatment.
2. Aged 20. Pituitary irradiation had no effect on multiple nodules. Died 2 years and 7 months after ineffective treatment to the primary.

temporary response. Local injections into a perineal mass combined with a systemic course of "Tretamine" resulted in partial objective remission on three separate occasions in one patient, while another had subjective relief of pain from bony metastases following a course of "Thiotepa". The only worthwhile response was in a case with cerebral metastases, groin and axillary nodes who survived a further 12 months following the injection of a large single dose (40 mgms per kilo) of cyclophosphamide. Phenyl alanine mustard was not available for trial prior to 1959.

Hormonal therapy appeared to have some effect in 2 females although one of these may have been a spontaneous regression. It appeared in relation to her natural menopause and it is therefore classified as a hormonal effect. Two males failed to improve with orchidectomy and hypophysectomy or pituitary radiation. There was no obvious change in pigmentation following removal of the pituitary (Table XXIII).

Pregnancy. Although the primary lesion appeared in relation to a pregnancy in 14 cases, 3 of these had children subsequently without deterioration. A further 4 cases became pregnant after the treatment of their melanoma but without detectable effect on the progress of their disease (Table XXIV).

Table XXV

Response to radiation.

1. Implant	High dosage (over 6,000 rads)			Moderate dosage (3 - 6,000 rads)			Low dosage (0 - 3,000rads)		
	Comp.	Incomp.	None	Comp.	Incomp.	None	Comp.	Incomp.	None
	43	15	1	2	0	0	0	0	0
Radionecrosis	12	2	0	0	0	0	0	0	0

2. Xray therapy	(over 4,000 rads)			(2 - 4,000 rads)			(0 - 2,000 rads)		
	26	20	5	18	12	6	4	6	9
Radionecrosis	5	0	0	0	0	0	0	0	0

Table XXVI

Survival of radionecrotic cases.

10 year survival rate

Available for assessment	18	2 lost to follow up between 10 and 15 years. 1 died of a second primary melanoma, 28 years after the first (histologically proven in both cases).
Determinate cases	17	
Survivors	8	
Survival rate	8/17 (47.1%)	

5 year survival rate

Available for assessment	19	
Determinate cases	18	
Survivors	11	
Survival rate	11/18 (61.1%)	

3 year survival rate

Available for assessment	19	1 case alive with disease at 4 years 9 months.
Determinate cases	19	
Survivors	13	
Survival rate	13/19 (68.4%)	

Response to Irradiation. Implantation of radioactive needles was used on 61 occasions in which response could be observed. Postoperative and "prophylactic" irradiation of the node area is ignored unless recurrence took place within the treated area in which event the case is counted as no response. A breakdown of the total experience is shown in Table XXV with the incidence of radionecrosis. 106 courses of Xray therapy were assessable. Although the total dosage of some of these was high, several of the failures were treated over prolonged periods on a "growth restraint" basis aimed at damaging cells in mitosis. Complete response (Comp.) is clinical clearing of palpable disease in the treated area without recurrence within that area or adjacent to it. Incomplete response (Incom.) includes those which recurred after disappearance had been achieved and those in whom an observable and recorded diminution of the tumour mass was obtained but residual induration or tumour persisted. Persistence of pigmentation without palpable disease did not exclude a case from the complete response group.

Radio-necrosis was an inconvenient and sometimes distressing accompaniment of the high dose used on occasion. It was more common after implant than Xrays. The survival rates for these 19 cases are somewhat better than those for the radiation group as a whole. (Table XXVI).

Table XXVII

Recurrence in or within 1.0 cm. of the Treated Area.

After surgery	67
After radiation	23
After both	10

Recurrence in the Treated Area. After radiation 23 cases recurred in the treatment field or at its edge after clearing. If the incomplete and no responses are included 74 lesions showed an unsatisfactory local result from radiation out of a total of 167 courses. This can be compared with 135 cases treated by surgery of whom 67 have recurred in the dissected area in a shorter overall observation period. However there was no way of gauging the adequacy of the surgery in some of these as the excision was performed elsewhere and information was incomplete. An additional 10 cases showed reappearance of disease after both surgery and radiotherapy (Table XXVII).

Discussion.

Origin.

It is not proposed to enter the arena on the contentious issue of the embryological origin of the cell of malignant melanoma. Convincing demonstrations can be obtained from the varied histology of the tumour to support almost any contention. The fraying of the basal layers of the epidermis into the naevus formation and the implication of the epithelium in the advancing edge of the neoplasm pictured in DAWSON's monograph (1925) and ALLEN and SPITZ's work (1953) point to an epithelial origin, but the stained, teased specimens in that of PETERSEN, BODENHAM and LLOYD (1962) and the silver impregnated sections shown by MASSON (1951) are sufficiently reminiscent of nerve cells to lend support to MASSON's theory of two components in at least some naevi. This may explain some of the varied clinical behaviour of the tumour.

Pathology.

The pathologists have however drawn attention to the very different prognosis of the grades of melanomata described by ALLEN and SPITZ (1953) as junctional naevus, active junctional naevus, superficial melanocarcinoma, and invasive melanocarcinoma depending upon the depth of invasion

of the dermis. According to these authors and McWHORTER and WOOLNER (1954) juvenile melanoma is a relatively benign variant which is distinguishable histologically and occurs in adults although less commonly than in children.

Any lesion described as a malignant melanoma in a prepubertal subject must be suspected to belong to that category particularly if the patient survives. ALLEN and SPITZ even describe the occurrence of apparent lymph node metastasis in juvenile melanoma but claim the cells, which are shown in the peripheral sinus of a node, are not invading the node but rather are sterile emboli. Three patients in this series were 15 years or under. One girl of 15 died of disseminated melanoma 8 months after wide excision of a 3.0 cm. primary on her trunk. The second case, a 3½ year old boy died of a melanoma arising in the iris 4 months after enucleation. The last was also a 3½ year old boy at the time of diagnosis. A 3.0 cm. amelanotic melanocarcinoma on the leg was excised in March 1947 after being treated for 1½ years as a keloid scar. After wide excision and groin dissection nodes recurred in the groin and were implanted. He remains well 15 years later without further recurrence. The section has been reviewed on many occasions by several pathologists who all agree that it conforms to the criteria of malignant melanoma and is not a juvenile melanoma.

Some series (LUND and IHNEN, 1955: JAMES, 1958: PANAYOTIS et al, 1962) fail to state what proportion of superficial melanocarcinomas, if any, was found. Every effort has been made to eliminate all but the true invasive melanomata and hence they are comparable with Stage III melanoma (PETERSEN et al, 1962). These had a 5 year survival rate of 50% which is the same as those radically treated in the present series and 5% more than the overall survival rate.

Aetiology.

i) Pre existing naevi. It was not possible on the histories available to make any reliable estimate of pre existing lesions but from clinical experience, the impression is gained that most melanomata arise in association with pre existing naevi. This is confirmed by a survey of cutaneous melanomata conducted by the Anti Cancer Council of Victoria 1962. As the distribution of lentigines is almost universal among the white races, but melanomata are by no means common, some other factor or factors must be operative. Further the site distribution quoted by PACK, (1959) indicates a variation in the malignant propensity of moles according to the region involved.

ii) Sunlight. Evidence that one factor in the transformation to malignancy may be sunlight is given by

LANCASTER (1956 and 1957) who related the incidence of malignant melanoma to geographical latitude and the average daily hours of sunshine. The highest relative incidence recorded was in Queensland, Australia with a yearly death rate per million population of 23. This compares with an overall incidence in the U.S.A. of 10 per million, England and Wales 6, Scotland 4 per million and Eire 3 per million.

The distribution of primaries as regards site tends to bear this out. All series in which site incidence is quoted show similar trends. The head and neck and the lower limbs are the most commonly affected regions of the body surface. The lower limbs in CADE's 1957 series stands out as the most often affected region but most other authors (TOMPKINS, 1953: LUND and IHNEN, 1955: JAMES, 1958: VOGLER et al, 1958: PANAYOTIS et al, 1962: SCHARNAGEL, 1933: SYLVÉN, 1949: NITTER, 1956: JORGSHOLM and ENGDAHL, 1955) have quoted an almost equal incidence or a preponderance of head and neck cases. Only in the U.S.S.R. is this pattern disturbed. On the basis of the low proportion of head and neck lesions ultraviolet light has been specifically exonerated as an aetiological factor (MEL'NIKOV and FEDOREYEV, 1962).

Where the sex is given there are more females than males in lower limb primaries (JORGSHOLM and ENGDAHL, 1955) but the

difference quoted is far less than that found in the present series but no division into leg and foot cases is given. The difference is significant at the 0.1% level of probability. Trunk lesions are more common in males but this is not a statistically proven trend. Head and neck cases are approximately equally divided between the sexes but scalp lesions are reported to be more common in males (FOWLER, 1962). Similarly while the total lower limb cases contain twice as many females as males the preponderance is mainly due to lesions on the lower leg since buttock and thigh and foot and ankle lesions are almost equally distributed (FOWLER, 1962). This dissection of cases would indicate some modifying factor and it would appear reasonable to postulate clothing differences as an explanation. The loss of head hair in males would be a more acceptable theory than the relative frequency of hat wearing. In addition the proportion of melanomata arising on the trunk is somewhat higher than in the other series quoted corresponding to the national habit of males stripping to the waist both for work and recreation. National habitus may also explain the relative paucity of leg lesions in the series from Scandinavia.

iii) Trauma. Although only 8.1% of the melanomata in this series arose in the foot while other series quote

proportions double this figure (SCHARNAGEL, 1933: JORGSHOLM and ENGDAHL, 1955: PETERSEN et al 1962) this may only mean the swamping of this series by the more numerous lesions elsewhere. It may be that if it was possible to relate the number of foot lesions to the population at risk the proportion would be constant for Caucasians. The fact remains that for the area at risk the sole of the foot is a favoured site of origin. PETERSEN et al (1962) have attributed this to the role of trauma and have drawn attention to the increased proportion of melanomata arising below the ankles in Negro populations. There is however an alternative explanation for this latter finding in the relative sparseness of lesions elsewhere on the Negro body. However LEVENE (1958) in a survey of the actual site on the foot found 20 on the dorsum and 32 on the sole. Mapping of the lesions reveals that the melanomata were grouped quite distinctly around the non weight bearing instep so that the theory of pressure being related either to the incidence or the poor prognosis of melanomata on the feet requires re-examination.

Other trauma in the form of injury or "chronic irritation" is frequently cited both by patients and investigators as a cause of malignancy appearing in a hitherto innocent junctional or compound naevus. The data available on the records reviewed

was deficient in many cases on this point so that no evidence is presented either way. Deliberate trauma in the form of incisional biopsy is considered later.

iv) Pregnancy. GEORGE, FORTNER and PACK (1960) reviewed 77 cases of melanoma in which the onset coincided with pregnancy. The 5 and 10 year survival rates did not differ appreciably from those in whom pregnancy developed subsequently nor from a group of 330 controls. This reversed a previous opinion of one of the authors (PACK, 1948) that a melanoma developing during pregnancy inevitably led to an early death. No other controlled series could be found in the literature but SYLVÉN (1949) found pregnancy "affected the course of the disease" in 6 out of 341 cases only one of whom became pregnant subsequent to the development of her malignancy. McNEER (1958) claims that pregnancy does affect the growth without substantiating the statement. LANE, LATTES and MALM (1959) formed the reverse opinion in a series of 117 cases claiming that only the depth of pigmentation was affected by the hormonal changes.

In the present review, although 13 cases developed their malignant moles in relation to a pregnancy 3 of these repeated the supposed precipitating factor without further noticeable change. The only effect upon the survival rate appears to

have been an improvement. Four others had subsequent pregnancies following treatment of their disease. No latent metastases appeared as all remained well while under observation. Two were lost to follow up 2 and 11 years after treatment but the others remain alive and well 5 and 9 years later. The last patient had several pregnancies terminated because of fear of the effect upon her melanoma.

This would appear to indicate that while individual cases may appear to light up during a pregnancy, the coincidence of the exacerbation of the neoplasm and parturition is fortuitous. Had the patients not become pregnant the disease might well have run the same course. 64 women of the series were in the child bearing period (16 - 45 years). If 1947 is taken as a typical year in the period under review 7 births or stillbirths would have been expected in a random sample of this number. This is not significantly different since the numbers are so small but does tend to support the association of pregnancy with the development of malignant melanoma although the other findings refute the opinion that the prognosis is worsened.

Clinical Presentation.

It cannot be emphasised too often that any pigmented

lesion, with a history of rapid growth, particularly arising in a mole, must not be treated lightly. With experience as PETERSEN et al (1962) say, it is possible to diagnose malignant melanoma on clinical grounds alone but even the most experienced surgeon, dermatologist or radiotherapist may make mistakes (HICKS et al, 1955).

Many of the histories and clinical descriptions reviewed in this series were inadequate in their description of the primary lesion and unfortunately most of the clinical photographs in the period of greatest interest were destroyed so that no attempt has been made to study the frequency of modes presentation. However attention is drawn to the work of TOMPKINS (1953) and PETERSEN et al (1962) pointing out the grave prognostic significance of ulceration.

Where doubt exists in the mind of the experienced clinician it would appear that the prognosis is better since the lesion is more often of the superficial or juvenile variety if it is indeed a malignant melanoma. Other conditions mimicking malignant melanoma on clinical inspection alone include acanthotic naevi, junctional or compound naevi with superadded infection, pigmented basal cell carcinomata, sclerosing or ulcerated haemangiomata and pigmented papillomata. The rare unpigmented variety can be mistaken for virtually any ulcerated or

papular condition if the preceding naevus has been destroyed by the neoplasm. The prepubertal boy who survived was originally diagnosed as a keloid. The only clue to the correct diagnosis lies in the ring of pigment which is frequently present or in the pigmented lesion from which the tumour sprang.

HICKS, RANK and WAKEFIELD (1955) produced a review of clinical diagnosis in their series of 42 patients. Most were correctly diagnosed but the proportion of benign or relatively benign conditions mis taken for malignant melanoma is quite high. This would fall with more experience. In a paper assessing the accuracy of frozen section (MILTON and JELIKOVSKY, 1962) the clinical diagnosis was correct in the great majority of cases.

The formation of a red ring around a pigmented lesion is unfortunately more apt to be taken for supervening inflammation. The lesion is therefore more likely to be misdiagnosed in the presence of a "reactive halo" than without it. Its significance as far as the patient is concerned is obscure. No figures can be adduced from the series to prove the effect upon survival of the red zone surrounding the primary tumour or its metastases. Clinical experience of patients presenting subsequent to the

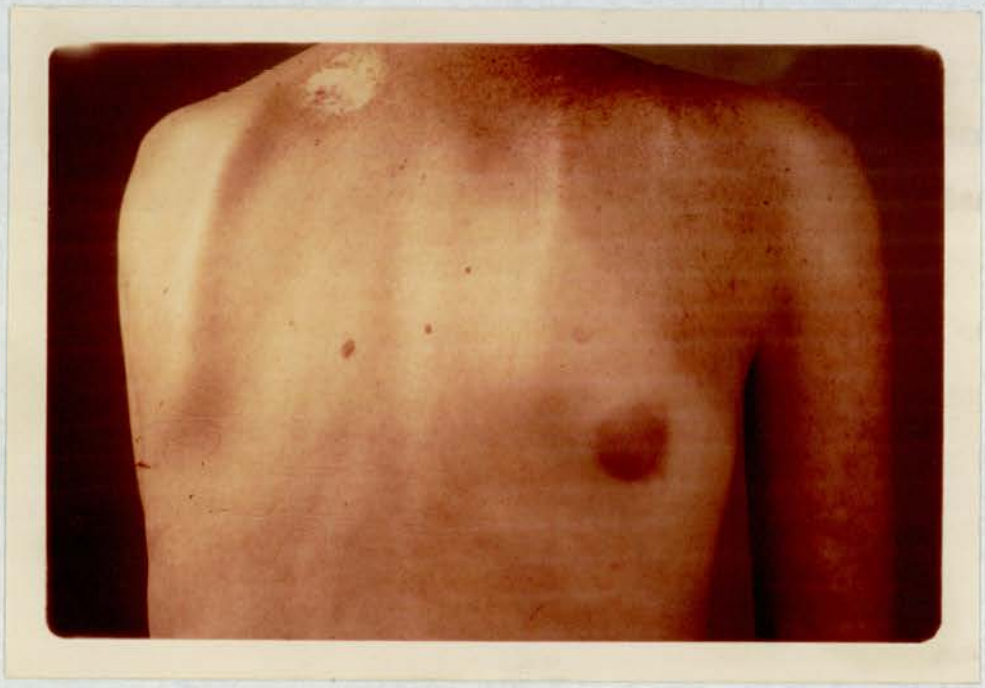


Fig. 2. The reactive halo. The lesion in the lower right corner is a subcutaneous metastasis which has had no radiotherapy. It lies below an area of radiation scarring from the posterior field applied to the right axilla. Over the left trapezius is a further circular radiation scar where a similar subcutaneous deposit with a reactive halo lay 18 months previously.

series tends to confirm that the reaction is rarely inflammatory even in ulcerated cases. It can appear around subcutaneous nodules (figure 2) and in one case involved the whole shoulder where axillary nodes had been invaded. It does not in my experience disappear rapidly with irradiation but can be abolished by the administration of corticosteroids. This latter finding was dictated by desperation in the patient whose shoulder was involved by an acutely painful red reaction. Only potent analgesics gave relief and prednisolone was prescribed as a trial. A dosage of 40 mgm per day gave prompt relief of symptoms.

Very little is said in the literature about the phenomenon. A "halo" is mentioned as a clinical feature but appears to mean a variety of things ranging from a zone of pallor around the tumour to the pigment halo around a compound naevus. In the present context the reactive zone described above is intended. No comment on its genesis, treatment or significance has been found. Too few cases are available for comparison or statistical analysis but in the few patients in whom it has been recorded the lesions have been only moderately radiosensitive. It appears sporadically around some subcutaneous metastases and not others. It has been noted in the patient mentioned above that those

lesions which presented a zone of hyperaemia have persisted sometimes unchanged but usually diminished in size after radiotherapy and chemotherapy to intensive levels while others without it have disappeared completely and have not recurred over 12 months.

No patient has died with the zone present so that in the absence of biopsy it is not possible to present any pathological findings on the cellular accumulation. It has not been noted in patients with what might be termed intradermal metastases so that it may represent a reaction to pigment in the subcutaneous tissues assuming that this pigment lies outside the normal macrophages which under more usual circumstances bear excess melanin away. Similarly it is found around lesions which are markedly pigmented. Some of them are more deeply placed so that the colour is largely hidden but pressure over the nodule thinning the overlying skin and blanching the reddened area will reveal the bluish tint of the underlying pigment. The inference is made that some metastases and some primaries allow pigment to escape from the tumour cells. This might well occur if avascular necrosis takes place in the tumour mass thus providing an explanation for both the halo and the radio - and chemo resistance. Since melanin is normally present in the

avascular epidermis and immediately it is released into the dermis it is taken up by the "chromatophores", no reaction would presumably take place.

Following irradiation or chemotherapy the halo slowly disappears taking a month approximately to vanish. The process may be masked by the radiation reaction but its evolution is visible following the administration of an effective chemotherapeutic agent. This would be compatible with the dispersal of the melanin crystals by the normal mechanisms and assumes that some effect of the treatment has been achieved since no more melanin is released immediately. If this is the case the disappearance of a halo can be used an an indicator of the effect of treatment even when little or no diminution of the tumour size is apparent. Equally it is an indicator of the relative radioresistance of the lesion under conventional conditions since the oxygen tension in such a nodule is almost certainly reduced. It cannot be taken to indicate resistance of the patient to the neoplastic process since it is more likely to be due to the presence of melanin or its breakdown products in an abnormal situation.

Prophylaxis.

Much has already been written by PACK (1959), CADE (1957) and others (BLOCK et al, 1961) on the relative incidence of

naevi and the supervention therein of malignant melanoma. The prevalence of lentigines estimated variously at 1 to 20 per adult Caucasian makes their routine removal impossible in all cases. However the transformation rate of these moles varies from region to region of the body so that even with an incidence of melanoma of only 6 to 23 per million population it becomes a worthwhile procedure to remove routinely all junctional naevi on the soles of the feet, the palms of the hands, the paronychial tissues and the mucous membranes. These areas have far higher malignancy rates per preceding naevus than any others in spite of the preponderance overall of the head and neck, trunk and lower limb primaries. In areas where chronic irritation is a factor such as the belt, shoulder strap, corset bone, and suspender regions, removal is also felt to be worthwhile, not solely because of the increased risk of trauma, which is as yet an open question, but the effect of the irritation in inflaming the naevus may mask malignant transformation or alternatively malignant transformation may be misdiagnosed as chronic irritation.

The effect of sunlight on the incidence of melanomata in particular and skin malignancy in general is one which has received too little publicity. In spite of the high incidence in Australia no warning is given to the young of the dangers of excessive sun exposure. The red haired, blue eyed adolescent

is unfortunately just the type to try hardest to produce a sun tan on a skin which more commonly than others gives rise to malignant melanoma (LANCASTER, 1957).

Biopsy.

Incisional biopsy is condemned in all early cases in almost every paper written on the treatment of this neoplasm. The present review bears out the wisdom of this advice and examines the effect of the time of biopsy in relation to subsequent treatment. Attention is particularly drawn to the finding that the proportion of alive to dead cases, although the numbers are very small, is the same whether the biopsy is performed at the time of operation (i.e. no delay between biopsy and effective treatment) or an interval elapses between the procedures. A frozen section to determine the extent of treatment is therefore just as injurious as a more accurate paraffin embedded one if the tissue is taken from the tumour while it remains on the patient's skin. A recent article recommends the procedure in clinically suspicious lesions (MILTON and JELIHOVSKY, 1962) but fails to emphasize that the lesion must be excised in toto and not cut into. Moreover a close analysis of the results in which clinical, frozen section and paraffin section diagnoses were compared reveals that in only one case was the surgeon about to perform less than what is accepted as adequate excision for a malignant melanoma which

he had diagnosed as a squamous celled carcinoma. The frozen section in this case was inconclusive between the two diagnoses. In two cases the frozen section would have led to under-treatment when the clinical diagnosis was in fact correct. In five, the patient was saved a more extensive operation than was planned but in one the surgeon was doubtful (3 basal cell carcinomata, one pyogenic granuloma, one seborrhoeic wart). Only the last two cases would have lost much and it is probable that with experience a more accurate clinical diagnosis would have been made. It would therefore appear that the technique provides little useful information and if carelessly applied it could have unfortunate consequences.

Ineffective Treatment.

The modalities listed under ineffective treatment include local excision, electrocautery, ablation by caustics of various kinds and bathing. Only the latter leaves the lesion in situ. The results of this group of cases in whom effective treatment was preceded by "tinkering" (CADE, 1957) are not significantly inferior to those in whom effective treatment was initiated immediately if survival is dated from the time of the first attempt at treatment. It would appear that much of the condemnation is due to the fact that the patient is not referred until recurrence has taken place which may be merely

a stage further on in the course of the disease. Indeed one is entitled to wonder how many melanomas are "cured" by local excision of a mole at the first sign of enlargement. PANAYOTIS et al (1962) refer to a patient who refused wider excision and block dissection of a locally excised melanoma which showed clear evidence of malignant cells in the lymphatics but survived without recurrence for 25 years.

This surprising result must be contrasted with the apparent effect of biopsy. In doubtful cases it would appear to be acceptable to excise the lesion with minimal margins and submit the entire tissue to the pathologist for decision on a carefully prepared paraffin section. So long as adequate treatment follows, the results should not be inferior to those whose tumours received adequate treatment ab initio. Indeed since the clinically obvious are usually ulcerated malignant melanomata while the doubtful are often equally dubious under the microscope the results in this group may even be better including as they will the superficial melanocarcinomata, the juvenile variety and the relatively more benign tumours mentioned previously. The important point is that anything excised from a patient should be referred for histological examination no matter what the clinician thinks it is.

Effective Treatment of the Primary Lesion.

The original purpose of this study was to ascertain the proportion of lesions which could be expected to respond locally to radiation but the results of this probably unique series were so surprising that a more complete examination was made. The several categories into which the cases are divided are not strictly comparable although age, sex and site distributions appear acceptably uniform between the radically treated groups. However comparisons will inevitably be made between surgery and radiation as to the results. These are very similar for 3 and 5 year survival rates. So similar in fact that the question must be raised of whether these figures actually measure a beneficial effect of treatment or merely reflect the growth pattern of the melanomata. The assertion has been made for carcinoma of the breast that treatment merely marks an incident in the course of the disease. This could well be said of malignant melanoma.

Such an argument cannot easily be refuted on these two groups alone. Indeed it is somewhat supported by the single traced Stage I case who refused treatment after diagnosis and died 12 years later with multiple metastases but no further medical attention.

It would appear to be more profitable to compare stage II cases since these are the ones at a clinically definable point in their progress. The primary lesion has declared itself by producing clinically enlarged mobile operable nodes. Before this the primary may only be in an inactive stage, or at a developing phase although every effort has been made to exclude this kind of case in this series. After this point treatment is seldom curative and often impractical. No Stage II case, who received no treatment and whose fate is known, lived for more than 3 years. Of those who received radical treatment 2 of 5 surgical cases and 8 of 16 radiation cases remained alive at the 3 year point. One of 4 and 4 of 13 respectively survived 5 years. At ten years there were still 4 cases alive in the latter group out of 8 available for assessment. It would appear therefore that treatment does exert some influence on the disease and this may be confirmed by a consideration of the span of life measured in terms of the time between first treatment and the appearance of further disease (Table XIX).

On the crude figures presented under survival rates it is impossible to say that one form of treatment is preferable to another although radiation appears to produce more long term survivors. The surgical group however were started more recently and may yet prove equal or superior to radiation. The apparent

advantage of radiation can be attributed to the fact that latent metastases or long delayed recurrences appear less frequently or later in the radiation group. More will be said about this later.

The group denoted as surgery without radiotherapy have few long term cases for assessment. The reason for this lies in the policy in vogue during the 1930's and 1940's. Obvious malignant melanomata were implanted. Doubtful cases only were referred for surgery. Since these will include the non ulcerated cases there will be a bias in favour of surgery in these cases. Further, since the recurrent cases treated by radiotherapy are grouped separately, the pure surgical cases are slightly more selected. A combination of the groups treated primarily by surgery leads to a 3 year survival rate of 40 out of 71 cases for surgery (56.3%) to compare with 47 out of 77 for radiation (61.0%). At 5 years 19 of 40 surgical cases (47.5%) survived while 33 irradiated cases out of 66 survived (50.0%). The ten year figures for surgery and radiation are respectively 4 of 17 cases and 24 of 47 (51.1%). In spite of this apparent doubling in the last figures the surgical group is too small to allow statistically significant comparison. The remainder are obviously very alike. PANAYOTIS et al (1962) report a total of 30 survivors at 10 years out of

116 cases treated (26%). A comparison of these with the present results gives a x^2 figure of 6.6 which indicates a statistically significant difference exists at the 1% level of probability.

The figure of 50% 5 year survival rate for radiation cases corresponds well with HELLRIEGEL (1952) series comparing surgery with irradiation. MULLER-MINY (1955) compiled the radiation results from 14 German centres. Of a total of 71 cases available for 3 year survival studies 67 were still alive, 3 having died of metastases and one of intercurrent disease. It is however impossible from this work to gauge the selection or staging of cases and histological evidence is specifically excluded since the author found this unreliable. This figure of 94% 3 year survivals must therefore be treated with caution. However it is unlikely that all but the 3 who died of metastases were benign. Chaoul radiation was employed but no details of technique or dosage are supplied. No later article has appeared giving later survival figures.

Russian experience was quoted at a scientific conference on vascular and pigmented tumours in February 1961 (MEL'NIKOV and FEDOREYEV). Their methods varied in detail from centre to centre but consisted mainly of pre-operative short focus Xirradiation directed to the primary followed by excision of any

remnants. In 53 Stage I cases KHMELEVSKAYA of Kiev reported disappearance of all tumour in 29, 17 of whom survived 5 years, 12 of them 5 year cures. 24 cases showed some remnant of pigment or tumour which was excised by electrocautery. Of these 18 survived 5 years, 15 of them without recurrence. These cases received 12,000 to 30,000 roentgens but no mention is made of prophylactic treatment of nodes. In Stage II cases, which includes ulcerated tumours and those with mobile nodes, 1 case of 10 who received Xray therapy alone survived 5 years and 4 of 21 where surgery followed radiation but only 2 of these were without recurrence. The conference concluded that pre-operative radiation was the treatment of choice.

This range, from PACK's condemnation of radiation to MULLER-MINY's complete faith in its ability to produce the best results, is most confusing. The present series confirms DICKSON's (1958) belief that radiation has a part to play in the treatment of malignant melanoma but has not conclusively established what that part should be. At a later stage in the argument specific suggestions will be made.

Size, Sex, Stage and Site.

Although the size of the primary tumour correlates well with the stage at which the patient presents, there appears to

be less effect upon survival than is apparent with other tumours notably breast carcinoma (McWHIRTER, 1957) particularly if equivalent stages are compared. The dimensions of the melanoma and hence its tissue pressures appear to be related therefore more to lymphatic metastases than blood borne since it is the latter which bring about death. LUND and IHNEN (1955) and PANAYOTIS, CHARALAMBIDIS and PATERSON (1962) did find a difference in 5 year survival between lesions below 2.0 cm. and above, viz. 46.7% and 27.5%. The relevant figures in the present series are 43.1% and 43.2%. It will be seen that the proportion of Stage I cases in the total falls steadily from 23/30 for primaries up to 1.0 cm. to 7/15 for primaries over 4.0 cm. From this proportion it could be inferred that most of the cases whose tumour dimensions were unknown were 2.0 cm. or less. Their survival rate matches this inference.

From Table X it can also be seen that males present at a later stage and with larger tumours than females. Combining Tables VIII and XV reveals that much of this anomaly is due to the preponderance of trunk lesions in males. Such a lesion, particularly on the back will escape notice for a considerable time while one on the face is obvious at its first appearance. Furthermore females naturally pay more attention to their skin. Males tend to postpone medical attention, minimise or even ignore blemishes or alternatively try home remedies such as

"blue stone", caustics or even red hot pokers before reporting to their medical attendant. PETERSEN et al (1962) note that 32.3% of lesions on the trunk had already spread elsewhere by the time the patient presented.

The site distribution in this series differs but little from most others. Omitting primaries in the eye, the meninges and the mucous membranes to confine the series to the cutaneous melanomata alters the site distribution figures by only 1 to 2% and improves the survival rates by a small margin. Few series break down the results of their cases according to the site involved and no-one has broken the site results into sexes. This dissection reveals that no significant difference exists between the sexes at any site although trends can be seen reflecting the overall slightly better outlook for females.

Prognosis according to site varies from series to series but in general head and neck and upper limb lesions carry a more favourable outlook (SYLVEN, 1949; JORGSHOLM and ENGDAHL, 1955; LUND and IHNEN, 1955; NITTER, 1956; VOGLER et al, 1958; DICKSON, 1958; PETERSEN et al, 1962; PANAYOTIS et al, 1962). However series differ on the outlook of primaries on the trunk and lower limb. Some find the leg the most favoured site

(eg. PETERSEN et al, 1962) some the worst (LUND and IHNEN, 1955).

Careful inspection of the 3, 5 and 10 year survival rates in Table IX reveals first the extremely good prognosis for patients with primaries on the leg and the poor outlook for those on the trunk. The lower limb results must be contrasted with those on the foot since the routes of spread should be exactly the same. If anything the greater distance between the primary and the nodes should, theoretically, be in the surgeon's favour. The intermittent pressure of walking has been put forward as the likely explanation but LEVENE (1958) has shown that the majority of lesions are on the non weight bearing portions of the foot and sole.

Secondly the difference in prognosis becomes more marked the longer the cases are observed. This effect is more noticeable in the foot and head and neck lesions than in trunk and lower limbs. The attrition between the 3rd, 5th and 10th years is extreme in the melanomata appearing on the foot compared to those on the leg. This may reflect a difference in the rate of progress of the disease at the various sites. Primaries on the trunk appear to cause early death. Those on the leg take much longer or are relatively more benign. One case exemplifying this was that of a male (not included in the

series as he presented after it ended) whose primary on the calf was excised in 1941. Grossly involved nodes were later incompletely removed from the groin and an incomplete course of radiation was given. Twenty-one years later he reported with tiny black epidermal recurrences adjacent to the graft on his calf. The groin remains clinically clear.

For mucous membrane melanomata the outlook is not so good. Two primaries arose on the female genitalia both proving fatal within 2 years of treatment. One male with a primary in the nasal cavity which proved to be very radio-sensitive finally succumbed at the age of 97, 17 years after his first treatment.

Age.

Although the excellent outlook of apparent malignant melanomata in childhood has been known for many years the literature does not contain many references to a difference in the survival rates of those occurring below the age of 36 and those after. LUND and IHNEN (1955) speak of a better survival rate in the younger patient while BLOCK and HARTWELL (1961) publish a similar finding but no other article makes much of a point of this. The differences (Table VII) border on significance at 3 and 10 years and are significant at the 1.0%

level for 5 year survival rates. This effect is not purely one of the older age group containing a higher proportion of advanced cases as perusal of Table VI will show that the trend is clear in Stage I and Stage II cases taken separately.

The Treatment of Nodes.

i) "Prophylactic." BLOCK and HARTWELL (1961) point out quite correctly that the so called "prophylactic" block dissection is in fact "therapeutic" since no element of prevention of the disease is present. The intention of the operation is to remove disease already present but not clinically detectable. However usage over the years has established the meaning of the word and it will be retained here to mean the dissection or treatment of nodes in a Stage I case.

It was clearly evident in the closing years of the last century that excision of a melanoma was not enough to eradicate the disease in the majority of cases. When HANDLEY's work (1907) on the lymphatics confirmed EVE's suggestion (1903) that spread from the primary might be encompassed by removing the draining lymph nodes, surgical treatment appeared to hold out new hope.

PACK (1959) in a review of the results of surgery over the years found an improvement from Adair's review of 267 cases in

1936 with a 12.0% 5 year survival through his own 1952 results (21.5% overall) to the 1959 figure of 39.1%. This improvement he attributes to earlier and more radical surgery, earlier diagnosis and the abandonment of radiation. The more radical surgery presumably includes more radical removal of the draining nodes. In 1952 he reported that 40.5% of 37 cases whose nodes were tumour free, and 14.1% of those with pathological involvement of the nodes (199 cases) survived 5 years. Of 204 cases who had wide local excision only 37.3% were 5 year survivors which is not significantly different from the 37 cases who had block dissection but had no pathologically confirmed nodal involvement. Similarly LANE, LATTES and MALM (1959) reported that 67% of 24 cases survived with only wide local excision. 14 cases were tumour free on block dissection and 71% survived. 49 cases showed nodal involvement pathologically and 20% survived.

LUND and IHNEN (1955) examined the question of the value of "prophylactic" block dissection and claim suggestive evidence that it does increase the survival rate but on the small numbers presented in their paper no firm conclusion is possible. BLOCK and HARTWELL (1961) go further in a detailed analysis of 88 adequately treated cases in a total material of 217. They claim a 50% 5 year survival if the nodes are clear and 25% if they are positive. They assert that it is possible

in 90% of cases to assess the clinical significance of nodes accurately and therefore advocate an observational policy in all but head and neck cases which can be shown to derive some benefit from the routine removal of the lymph drainage field. They rightly point out that most surgical series are deficient in the vital information of whether clinical nodal enlargement was present. There is no indication in the survival figures of those whose nodes are histologically positive of how many cases were clinically Stage I cases and therefore no estimate can be made of the proportion of cases which contain latent lymph node metastases.

The figures from this review are too small to clarify the question. Eleven Stage I cases were dissected "prophylactically" before 1957 (Table XVI). Six had died by the end of 1959 all having had apparently negative nodes. Two of the survivors had recurred and only 3 remained well. In one of these the pathologist had reported tumour present.

It may be argued that in many of the cases where nodes are reported tumour free there are in fact some cells present but they have not shown up in the sections cut. Serial sections of all the nodes in a clarified specimen have not been performed. However such an argument also strengthens the result of those

whose lymphatic barriers were not disturbed since their prognosis is not far different from those where nodes were reported to be free of tumour. There would have been an equal chance of these patients having minor deposits in their nodes, assuming an equal grade of malignancy. Dissection however is more likely to be omitted in non ulcerated small tumours of low grade malignancy so that this assertion may not be completely valid.

The nodes of only 3 cases were treated "prophylactically" by radiation. The results detailed in Table XVIII are quite inconclusive. Only SYLVEN (1949) and NITTER (1956) report prophylactic irradiation of the lymph drainage area although DICKSON (1958) advocates post dissection irradiation in all cases whether the pathologist can see involvement or not. Sylven reports no survivors of 4 treated with radiation alone (1,400 - 2,000r), 2 of 26 with surgery alone, 1 of 12 with pre-operative radiation, 3 of 10 with post-operative radiation. Nitter is much more encouraging, contrasting 11 survivors at 5 years of 24 treated with prophylactic radiation and 18 of 54 who had no irradiation (determinate cases 11/22 and 18/30 respectively). Again the dosage used is well below tolerance levels. The Russian work quoted previously is not clear on the results obtained by prophylactic irradiation but the dosages used for patients with clinically involved nodes are at the

other extreme (6,000 to 7,000 r). Prophylactic irradiation of the lymph drainage areas at tolerable but effective dose levels remains therefore a substantially untried method of treatment.

ii) Therapeutic. As mentioned previously most surgical series divide their cases according to histology and not on a clinical basis. While a small proportion of patients with clinically involved nodes in which the pathologist fails to find tumour, will be included in the histologically negative group a larger number will be transferred the other way i.e. clinically negative but histologically positive. This effectively will improve the results of both stages (McWHIRTER, 1957) without casting any light on the results of treatment by clinical stages.

In this study the clinical appearance of the nodes has been recorded in every case so that a clinical assessment is possible. More Stage II cases had a block dissection in the earlier years than Stage I. Nineteen cases are available for 3 year results. Fourteen had died by this time and 2 had recurred but were still alive. All 3 cases reported clear at 3 years were found to have no tumour in the nodes examined but of course small deposits could have been missed.

PACK (1959) quotes 20.0% 5 year survivors with histologically

Table XXVIII

Fate of cases with operable nodes.

No treatment to nodes.

4 died within 3 years

2 died at 3 years 3 months

1 died 14 years later of other disease

Surgery to nodes.

3 died within 3 years

1 lost to follow up at 11 years (nodes negative)

Radiation.

Implant	Xray therapy
5 died within 3 years	6 died within 3 years
2 died at 3 years	1 died at 5 years
1 died at 4 years	2 alive with disease at 3 and 4 years.
3 alive and well 13, 14 and 5 years after implant	4 alive and well, 19, 18, 8 and 5 years after Xray therapy.
2 died of other disease 1 and 2 years	1 lost to follow up at 1 year
1 lost to follow up at 3 years -	

1 alive and well 2 years after combined implant and Xray therapy.

5 year survival rate of determinate cases	3/11	5/11

positive nodes; LANE et al 20% and PANAYOTIS et al 13%. More radical surgery to the extent of major exarticulation has been recommended by PACK (1956) principally as the treatment of choice in cases with primaries on the extremities but the results he quotes for interscapulo thoracic amputation, hip disarticulation, and hemipelvectomy do not lend themselves to 5 year appraisal. Of 69 cases of melanoma treated in this fashion 22 were alive but only 4 were alive at 5 years. It is not stated how many were treated prior to 1951 for reporting in 1956. PACK and CRAMPTON (1961) report 3 cases of 20 melanomata surviving 5 or more years after a modified resection of the shoulder girdle.

Table XVIII also details the fate of those whose nodes were enlarged and were managed radiotherapeutically. If one includes all those whose nodes were enlarged at the time of referral to the radiotherapist (Stage B cases) a further table can be compiled (Table XXVIII) which will include palliative and no treatment cases as well as those whose original effective treatment was radiotherapeutic or surgery followed by recurrence. This shows that of 22 cases 8 survived over 5 years from the time of their first treatment. Four of these were proven by biopsy or local excision. This apparent doubling of the surgical rate is based upon too few cases to be significant but may be

suggestive enough to recommend that better results may be obtained in Stage II cases by the judicious combination of external radiation and either implantation or surgery for remnants.

Local Recurrence.

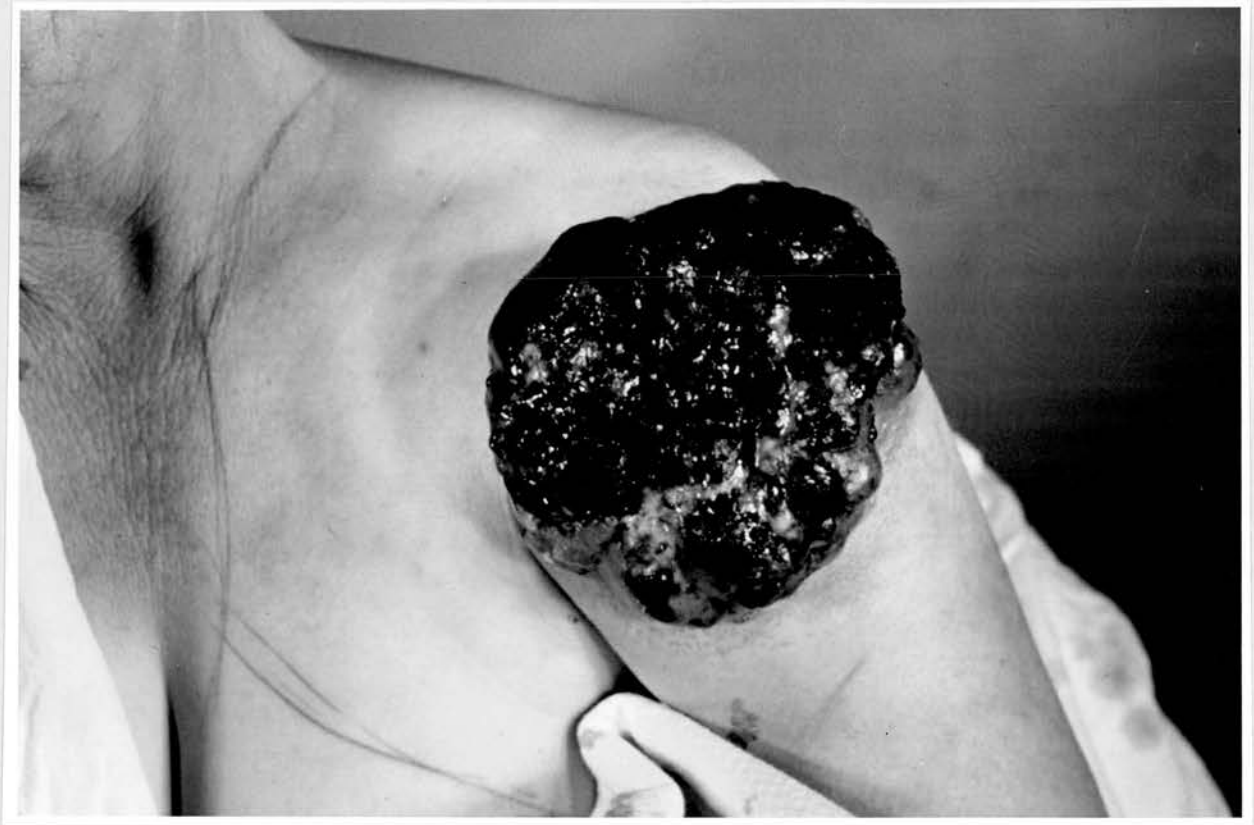
"Satellite nodules" frequently appear around the site of the excised primary. Whether this is attributable to direct spread of a carcinogenic impulse along the dendrites of the melanoblasts (PETERSEN et al, 1962) or lymphatic embolism in the dermal lymphatics appears to be a purely pathological issue. From the clinical aspect their importance lies in the determination of the margin to be included in any treatment of the primary. In so far as the satellite nodules appear much more frequently in the proximal side of the excision (well illustrated in CADE, 1957) there appears to be more evidence in favour of a lymphogenous origin for these recurrences than a neurogenic or "cytocrine" (MASSON, 1948 and 1951). This has determined the surgical margin as being wider towards the draining nodes than distally. The recommended margin in the more recent articles (PETERSEN et al, 1962) has increased from 2.0 cm. to wide flap reconstructions of the whole of the skin on the medial side of the thigh. However (HICKS et al, 1955) in a small series have been much less radical, modifying the skin

removal according to the site and availability of reconstructive tissue apparently without increasing the incidence of recurrence around the graft. VOGLER et al (1958) claimed only 3.0% local recurrence in 171 treated cases 95 of which had been observed over 5 years.

Two points are made here for discussion later. First, local recurrence is much more common following surgery than irradiation (Table XXVII). Second, satellite nodules are rarely seen around the untouched primary tumour. This may reflect a fundamental concept in the behaviour of melanomata and possibly malignant tumoursin general.

The confinement of a crop of nodules to an extremity appears to lend itself to a purely local and radical attempt at cure. It was on such cases that PACK (1956) and PACK and CRAMPTON (1961) performed the more radical operations reported above so that it is not surprising that the results were disappointing. However where the salvage was so poor it becomes difficult to justify the crippling which these procedures entail.

In an effort to save the limb yet confine treatment to the known metastases and hence apply more radical measures, perfusion techniques have been more commonly used in melanoma than other malignancies. IRVINE, NOON and BARNSTABLE (1962) have



Fig, 3. A massive primary melanoma on the shoulder arising 3 years prior to presentation with spread to the axilla only and one outlying subcutaneous nodule over the right costal margin. No "satellite nodules"around the primary.

reported a small series of 16 cases of whom only 4 showed any response and 2 died of the effects of treatment. The technique was used as a "prophylactic" measure at the time of excision of the primary in 5 cases and the results are more promising in that all 5 remained alive and well for an average of 12 months. No results of perfusion are available in the present study as the procedure only became widely known after the close of the series.

The Timing of Haematogenous Spread.

The question of the time of release of the cells from the primary site into the blood stream becomes of paramount importance in the planning of any attempt at radical treatment since it is this more than any local spread which will bring about the death of the patient.

Primary tumours with histories of obvious malignant change 3 years prior to reporting (figure 3) have been found with one solitary outlying subcutaneous nodule remote from the primary and its nodes. Other patients report with lesions probably less than a month old and apparently free of disease elsewhere, only to produce widespread metastases shortly after what was thought to be adequate surgical treatment. The swing away from surgery on this account in Germany has already been mentioned.

If this clinical impression is not correct then melanoma is a completely unpredictable disease with blood borne cells escaping from its inception and logically although unethically and inhumanly the patient who reports with an early tumour should have the minimum treatment and a completely pessimistic outlook on his future adopted. This policy of nihilism has been voiced (BLOODGOOD, 1922). If it is correct two explanations for this behaviour are available. Either metastatic deposits are sown at the time of surgery in a far higher proportion or with a higher growth potential than other tumours or the presence of a clinically obvious deposit of tumour exerts an inhibiting influence upon the growth of seeded cells. Evidence for the latter theory in animals with transplantable melanotic tumours exists in the papers of SCHATTEN (1958) and van den BRENK (1961). The former paper excludes experimentally the effect of the strain of surgery on the appearance of lung metastases as a factor in producing the results. Schatten took D.B.A. mice and inoculated S91 melanoma and DBA sarcoma 49 into one hind leg. He divided the successful tumour takes into 3 groups one of which was kept as a control. Of the other two one had the tumour bearing leg amputated and the other had the opposite leg amputated. The animals were all sacrificed at the same time. All the animals which had the primary tumour removed before death showed lung metastases in greater numbers and of a

larger size than the other two groups. A subsidiary study sacrificing animals one week apart showed that the pulmonary metastases in the animals which had the primary tumour removed were increasing significantly in number and size while in those which retained the primary or had the opposite leg amputated the pulmonary metastases were not actively growing as measured by the difference in multiplicity and volume over one week. Van den Brenk's experiment showed that it was much more difficult to get two tumours to take in animals unless they had been previously irradiated.

The immunological aspects of tumour control are not so clearly understood with spontaneous tumours which are more comparable with the situation in man but the experiments quoted would explain the "lighting up" of tumour activity following removal of a clinically obvious focus of melanoma. Ethically it is not practicable to transfer the experiment to human work with full control of the factors involved. The prohibition of biopsy would mitigate against histological confirmation until autopsy which is scarcely possible.

Spontaneous disappearance of disseminated metastases occurs too frequently to be dismissed lightly. Most series of any size contain one quoted case. In addition in 2.1% of patients in this series the primary was never found and in

other patients the site of presentation of enlarged nodes was the only clue as to the region involved. Subsequent excision of clinically innocent naevi proved them to be the primary, or the patient gave a history suggestive of malignant change in a lentigine which disappeared of its own accord. In such cases when did spread occur? What change either in the tumour or in the patient's metabolic or hormonal state occasioned the cessation of growth or even its complete healing at one site while at another, cells persisted to grow again later or even continued to grow while the parent tumour was being absorbed. Pure speculation might suggest that the metastases inhibited the primary, reversing the usual procedure. The converse occasion when removal of the primary is followed by regression of the metastases has not been reported in melanoma as it has with carcinoma of the kidney and some ovarian neoplasms.

Treatment of Haematogenous Metastases.

Once deposits of tumour become evident remote from the primary and its immediate drainage area, no cure is possible as the presumption that any blood borne focus is not solitary is much stronger than for other neoplasms such as hypernephroma. Dissemination in this fashion is usually followed by an early death with widespread melanotic tumours and in rare cases melanosis. If the metastatic focus appears long after the

treatment of the primary the potentiality for growth of that particular melanoma in that particular patient may be low. If so a solitary nodule may be the only sign of failure for several years and it behoves the medical attendant to treat it locally and radically. As these deposits are almost always on the trunk or in an internal organ perfusion becomes more hazardous or impossible. Infusion with a general cytotoxic agent is not without hazards of its own. Side effects are serious and uncomfortable, ranging from marrow aplasia to alopecia, nausea and vomiting. Local and "radical" treatment in the sense that the treatment is designed to eradicate the disease without recurrences as far as possible, could be excisional or radiotherapeutic. Deposits on the skin are surgically accessible and easily dealt with but affected internal organs entail risky exposures and particularly in brain metastases excision may seriously impair the patient's functional integrity.

Radiation therapy, particularly external radiation entails none of the risks of surgery but has been held to be a less sure mode of treatment and to carry risks of its own. Table XXI displays the respective methods and their results. It will be seen that Xray therapy and radioactive implantation are not inferior in prolonging life and are at least as effective as surgery in alleviating symptoms.

The risks associated with radiation are reputed to be the supervention of oedema in a closed space such as the skull, spinal canal or mediastinum and necrosis of the tumour or the surrounding tissues. Oedema in a tumour is caused by breakdown products of the dying cells. If this is the case the tumour has responded and will shrink. If the rate of shrinkage is the same or greater than the rate of accumulation of fluid no serious disturbance will result. If the tumour does not respond no breakdown products will be available to cause oedema. The only net swelling occurs when the radiation is not given sufficiently fast to cause rapid shrinkage. It is therefore more logical to give large dose fractions - in fact single doses or at most 2 to 3 doses spaced at weekly to fortnightly intervals than to space small increments at more frequent intervals. This policy has been used in intracranial metastases on several occasions without exacerbation of symptoms and signs. In all cases so far a prompt, if sometimes short-lived, improvement was obtained. Cerebral metastases appeared to be more responsive than subcutaneous deposits. Where surgery was used on supposed solitary metastases in the brain, both patients died with further cerebral involvement.

Necrosis of the tumour is of course inevitable with any successful treatment. In surgically excised specimens it occurs

after removal from the patient and occasions no harm. With radiation or chemotherapy the necrotic material is left in situ. If erosion of a vital organ or blood vessel has occurred this may precipitate a terminal event but this would appear to have been inevitable at an early date without treatment. No such terminal event was recorded in this series but one post mortem revealed a cerebro vascular accident in a young woman who was not suspected of having cerebral metastases. Necrosis of the surrounding tissues is acceptable if a radical cure is hoped for but should be avoided in palliatively treated cases.

Chemotherapy.

Five cases showed some response to cytotoxic agents. These are listed in Table XX. Only the nitrogen mustard group of drugs showed any promise in the control of the tumour. The most dramatic response was obtained with cyclophosphanide ("ENDOXAN", "CYTOXAN") in a large single dose intravenously (40 mgm per kilo body weight). Subsequent experience has confirmed that this appears to be the most effective way of administration. Not only was it the most effective drug used but the marrow depression associated with it affected only the Leucocytes to any great degree and that only temporarily. Thrombocytes were but little affected. White cell counts of

200 - approximately 2 weeks after injection usually recover to normal within a further week without supportive therapy. Alopecia is distressing at first since it occurs in about 80% of cases but most patients accept this eventually. Subsequent regrowth of hair is strong and well established in 3 months.

Phenyl alanine mustard ("MELPHALAN") was not available during the period under review but has been extensively reported as the most effective agent so far available.

Hormonal Treatment.

Factors suspected of indicating a hormonal dependency in melanoma are - 1. The paucity of prepubertal cases, 2. the apparent association with pregnancy, 3. the occasional case of spontaneous regression which might be associated with alterations of the endocrine status, 4. the isolation of a melanocyte stimulating factor from the pituitary related to the increase in pigmentation during pregnancy, 5. the hormonal control of pigmentation and pigmentary cells in animals, 6. the slightly better results in women. In an attempt to control disseminated melanoma manipulations of the hormone balance were tried in 3 females and 2 males (Table XXIII).

Although the menopause in one of the females was a natural one and therefore should not strictly be included, the regression at this time was so dramatic and the association with endocrine alteration so clear cut that she has been included under this category. Therapeutic ovarian ablation has not been tried in a sufficient number of cases as a single method of treatment to come to any conclusion about its efficacy (CADE, 1957). "Prophylactic" sterilisation in view of the previous findings on pregnancy has no place in the management of the disease.

In males the two cases included were not encouraging and until clearer evidence is available on the dependence of the tumour on male hormone no recommendation can be made as to the value of orchidectomy. Hypophysectomy is associated with so many sequelae that it would have to produce much better results to form a regular part of the therapeutic armamentarium.

The Survival of Metastatic and Recurrent Cases.

Mention has already been made of measurement of the effect of treatment by using the period between first treatment and the reappearance of disease as a yard stick. Table XIX is self explanatory. It is obviously possible to check the

progress of the melanoma even in recurrent cases. Prolonged survivals are achieved by both radical methods of treatment but it must be remembered that these are only truly effective when the deposit is a solitary one. Blood borne dissemination is normally associated with rapid deterioration but palliation of distressing symptoms is still possible.

The Duration of Life in Dead Cases.

Individual cases of malignant melanoma may show quiescence for many years before reactivation, recurrence and death. This appears to be more common if the prime therapy is radiation although this may be biassed by the shorter overall observation period available for the surgical cases. However a one third advantage would require a considerable improvement in the whole group to equal it. Reference is made again to the work of SCHATTEN (1958) to account for this.

If radiation can curtail the activity of a melanomatous tumour as it seems able to do, but leaves a sufficient amount of immunologically competent material which is not capable of reproduction it may restrain metastases which have already seeded. Although this may be commendable it cannot be denied that the surest method of cure is still surgical excision of all the disease. The difficulty arises in ascertaining if all

the disease is excisable, since there is, as yet, no available test which is universally applicable.

Response to irradiation.

Radioresistance is a relative term and not an absolute description. It is measured by recording the behaviour of a tumour following irradiation. One which shrinks rapidly is radio responsive. One which persists or grows during irradiation is radioresistant. However the shrinkage of an irradiated mass is to some extent dependent on the division rate of the cells since damage to the cellular metabolism may not be evident until it attempts division. Therefore a rapidly multiplying tissue under normal circumstances will shrink just as rapidly while a slower rate of division will be associated with a much diminished rate of regression. This phenomenon is seen daily in radiotherapeutic departments. The fact that a basal cell carcinoma apparently persists in an irradiated area for 3 months does not necessarily mean that the lesion is recurrent although the pathologist may report persistent tumour if the piece is removed. All that is being seen are the cells which have not divided since radiation was administered. This tenet may or may not be applicable to malignant melanoma.

If, as MASSON (1948 and 1951) suggests, the preceding

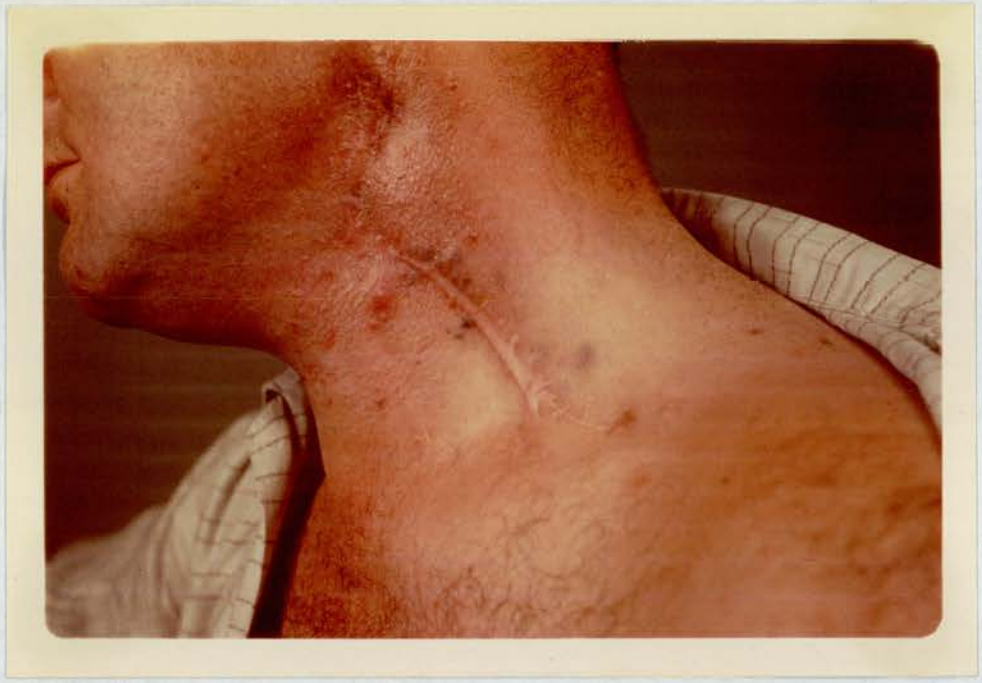


Fig. 4a. Recurrence immediately below the skin surface shortly after block dissection.

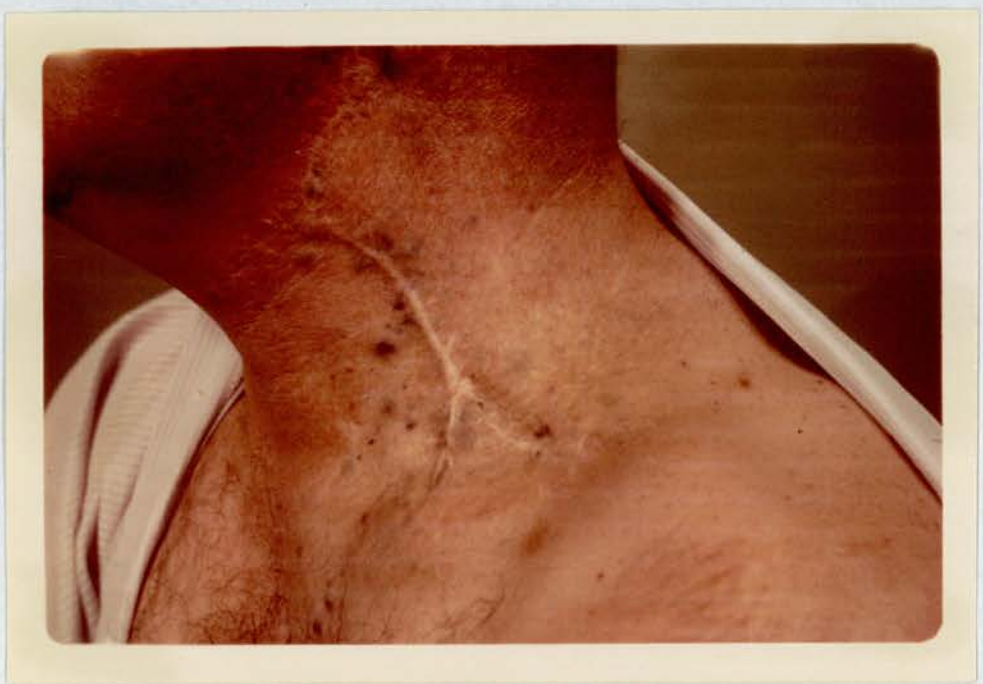


Fig. 4b. The same area after 4,500 rads. peak dose in 4 weeks. The lesions have increased in size and number.

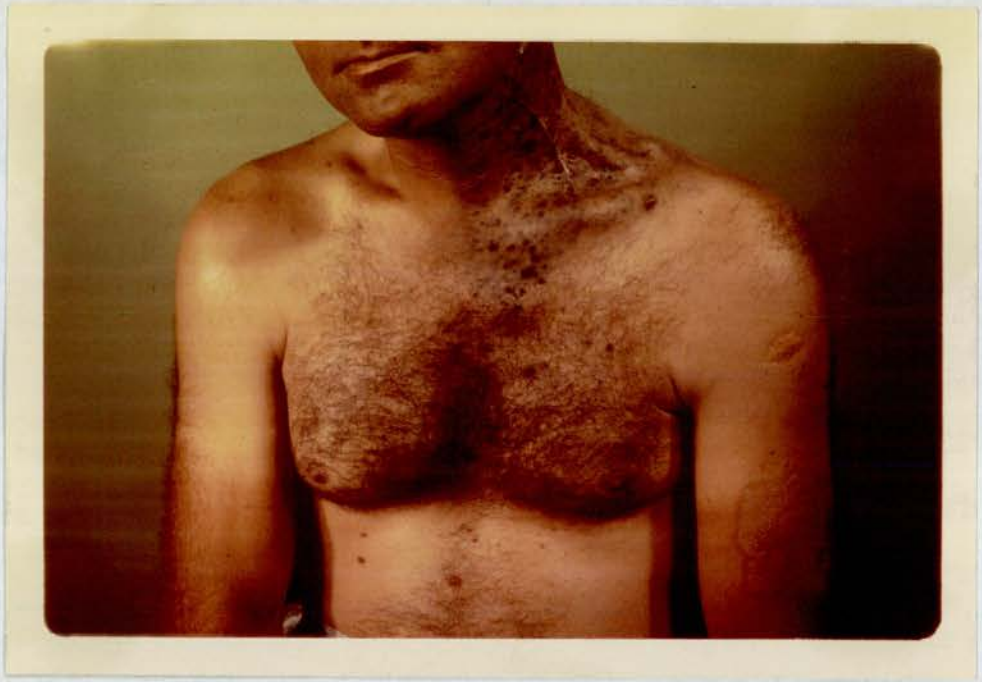


Fig. 4c. Six months after treatment there is an increased pigmentation visible on the face, below the mid humerus and especially in the Left neck where the radiation field is outlined by melanin.

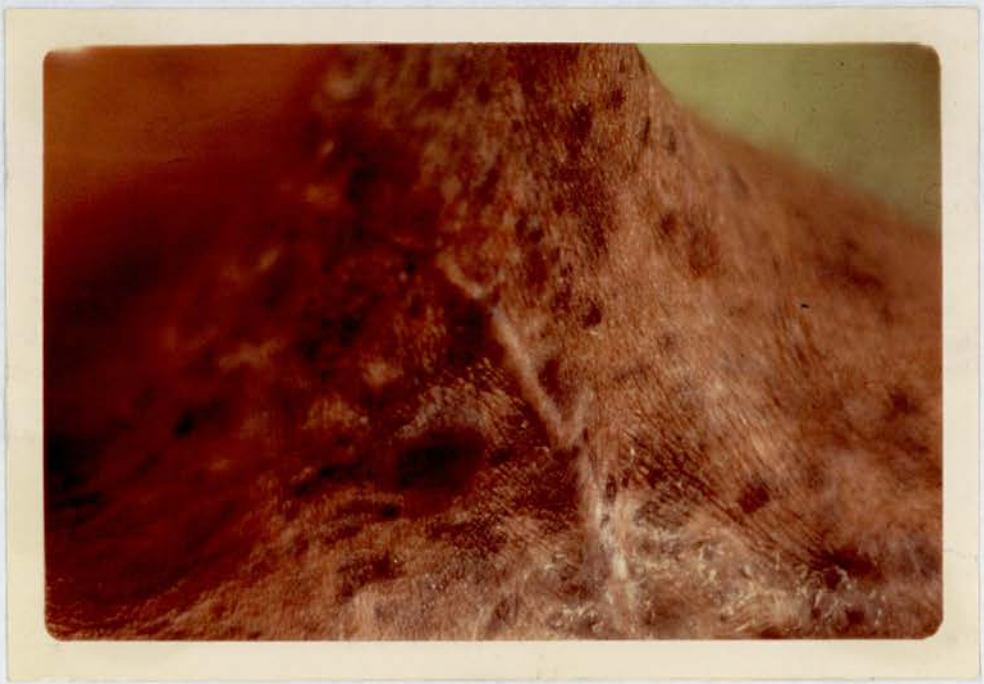


Fig. 4d. Close up of left neck showing that many of the deposits are not associated with palpable nodules.

naevus is composed of an epithelial and a nervous element the melanoma may have a dual type of malignancy. The rapidly dividing epithelial cells may be destroyed by radiation while the more slowly progressing neurogenic tissue may persist. The responsiveness of the tumour as measured clinically would therefore depend upon the proportions of each tissue within it. The metastatic deposits would be likewise composed of both types of cell although histologically they may be indistinguishable. It is also possible that the neural elements have the capacity to stimulate the local epithelial melanoblasts into uncontrolled growth. Such a neoplasm would be ideally adapted for metastatic spread since it not only makes use of the materials in its nidus but the cellular population as well. Cure by any means would be rare. Figure 4 illustrates a case which recently reported to the centre in whom adequate surgical treatment including block dissection was followed by rapid local recurrence (4a) which proved completely radioresistant (4b) and indeed showed more pigmentation in the irradiated area than elsewhere. The wide spread dissemination which subsequently occurred was associated with melanuria and pigmentation of apparently normal skin and this was more marked in exposed regions (4c). The metastatic deposits took the form of local increase in this pigmentation without nodule formation (4d) although section of one of these showed malignant melanoblasts

in the dermis. This widespread stimulation may be a hormonal effect of the tumour cells but it is the only example in which radiation was shown to exacerbate the disease in the area treated.

Persistence of a nodule in a treated area is much more common but in several instances in the series subsequent excision was performed quite locally. In the one case which is recorded as no response to a high dose implant the pathologist could find no tumour in the excised specimen although a pre-treatment biopsy had shown melanoma.

Theoretically all cells are equally likely to be damaged by ionising radiation under fully oxygenated conditions. The factors, apart from tumour type, which are usually quoted as affecting radio-sensitivity, such as previous surgery or radiation, site, infection and fibrosis all act through the intermediary of the blood supply to the part to reduce the oxygen tension within the tumour cell. It follows that if this is equalised the cells will be equally damaged and the division rate will determine the tissue destruction. If the number of viable tumour cells can be reduced below an as yet undetermined minimum the natural defences of the body will be able to complete the oncolytic process. It is not always easy to equalise the

oxygen tension in tumour cells and normal tissues but encouraging results have been reported by CHURCHILL-DAVIDSON et al (1955) and MADIGAN, (1962) who have increased tumour resolution following radiotherapy by exposing the patient to high ambient pressures of oxygen during treatment. Melanomata are reported in animals at least to have a relatively low oxygen consumption (BURK et al, 1948). This has been interpreted as a disturbance of the ratio oxidised to reduced cytochrome oxidase. Paraphenylenediamine has been reported to increase the oxygen consumption of Harding-Passey, Cloudman S 91 and Algire S 91A melanomata but the toxicity of this substance is such as to preclude its use in human tumours. The significance of the findings as regards the reported radioresistance of these tumours has not yet been established.

SUGIURA (1948) came to the conclusion that animal melanomata were "extremely resistant to radiation" but admits that definite inferences from his data are questionable. The dosage for radon tube implantation was given in skin erythema doses, the tubes contained a variable quantity of radon and the mice were not standardised as regards age and size. H.A.S. van den BRENK has kindly lent illustrations from unpublished work on the radiosensitivity of experimental melanoma which completely contradicts Sugiura's finding.

Fig. 5. (courtesy, Dr. H.A.S. van den Brenk). Harding-Passey mouse melanoma transplanted in Algire transparent chambers in CBA mice.

1. and 2. : Unirradiated transplant at 24 hours (1) and 5 days (2). (x 85)
3. : Migrating melanoma cells at the border of the transplant at 48 hours. (x 20
4. : Vascularisation of the transplant by host vessels at 4 days. (x 85)

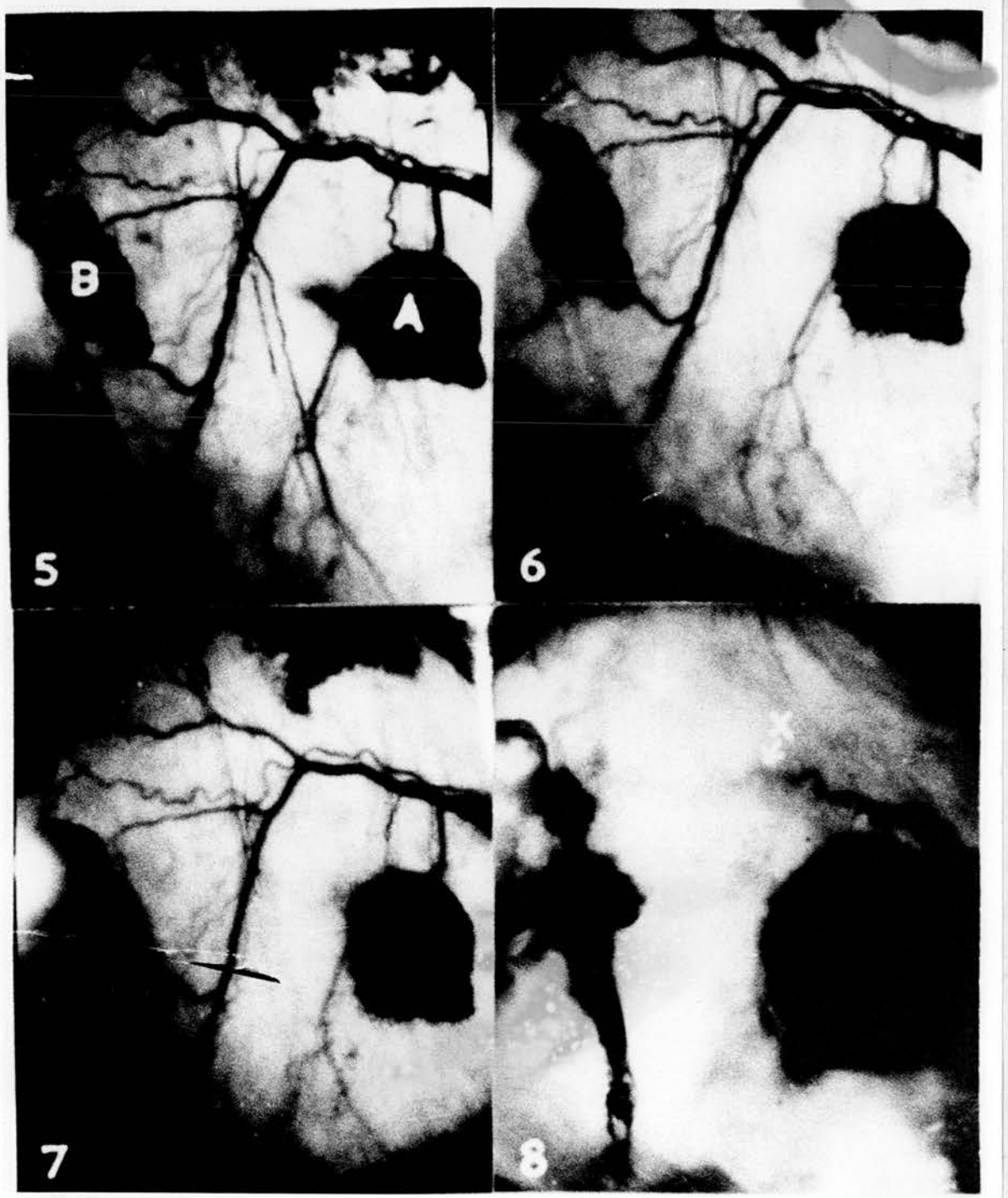


Fig. 5. (Cont.) Chamber implanted with two fragments of the same tumour, one of which (B) received 400 rads. ^{60}Co rays <u>in vitro</u> immediately preceding implantation. Photographs show progressive growth of the unirradiated fragment (A) and regression and degeneration of the irradiated portion (B) (x 8)
5.: day 7. 6. : day 10. 7. : day 13. 8. : day 17.

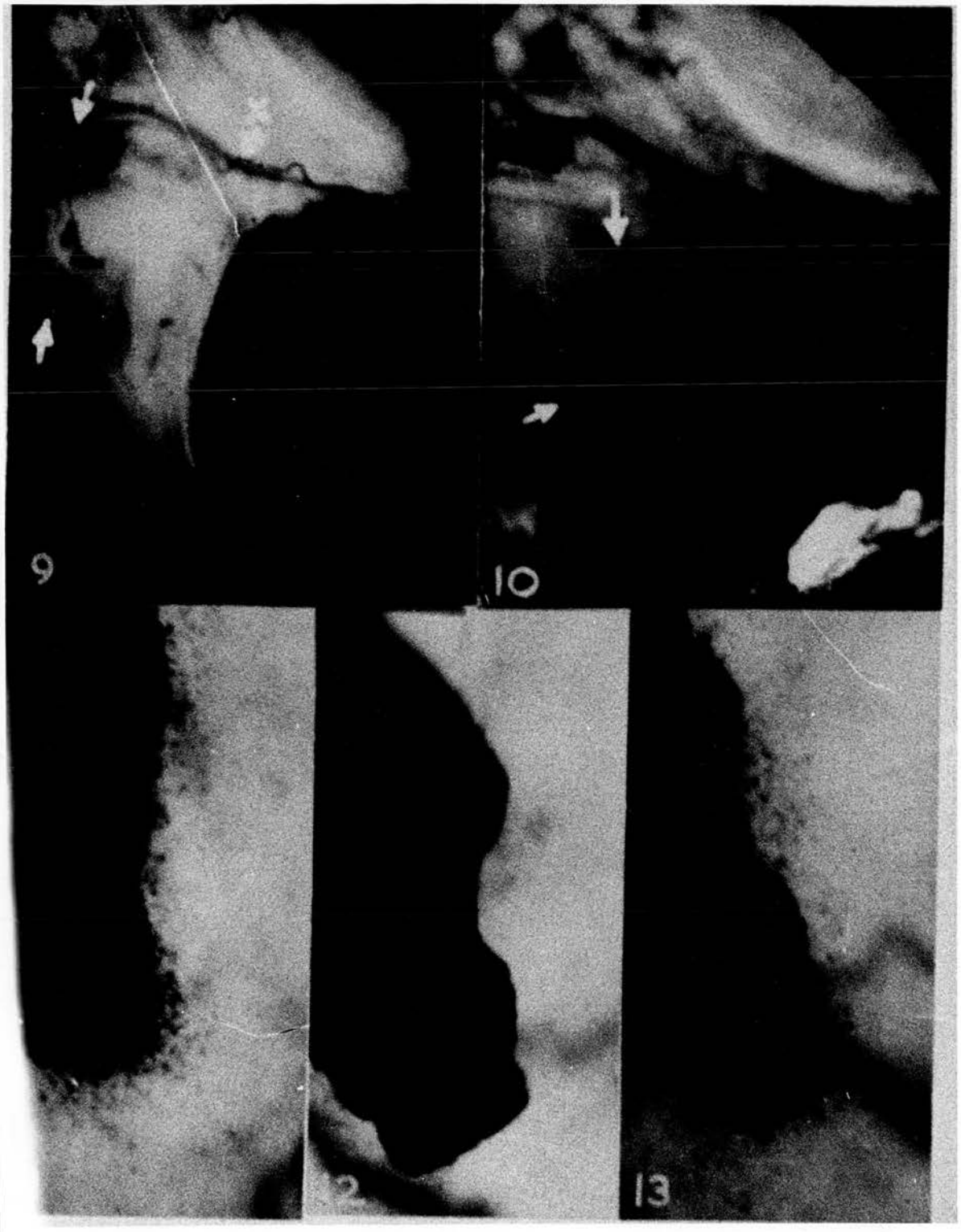


Fig. 5. (Cont.) 9. and 10. continue the previous sequence at day 27 and 45 showing the engulfing of the irradiated transplant by the growth of the control portion. (x 8).

11. : The edge of the unirradiated specimen showing melanoma cell migration at day 6. (x 40).

12. : The edge of the irradiated piece at day 6. No migration is visible. (x 40)

13. : As in 12. 4 days later showing pseudomigration due to degenerated cells and melanin. (x 40).

Figure 5 shows two inocula of Harding-Passey melanoma in a mouse back chamber. One half of the inoculum received 400 rads in air before implantation. It is obvious that its capacity to produce a tumour was markedly impaired. The edge of the tumours shown in higher magnification contrasts the active migration into the surrounding tissues of the unirradiated specimen with the smooth edge of the irradiated side. The later appearance of a stippled edge is due not to active cells but free melanin granules released from the degenerating neoplasm.

In the present series measurements of the tumour were available before and after treatment in all cases in which radiation response is recorded. Shrinkage of a tumour mass during or after radiation therapy is a reasonably good indication that some alteration has taken place but the presence of oedema within the mass from any cause prior to treatment makes this assessment difficult to appraise. Since surgery is frequently followed by oedema it follows that the only response which can be relied upon is one in which no incisional attack has been made upon the tumour or its surroundings. Infection is similarly a bête noir since it not only causes oedema but also interferes with radiosensitivity.

The response to radiation was strikingly high in implanted lesions. This may be related to the local dosage which is appreciably higher than for external therapy. Another factor to be considered is the continuity of irradiation with radioactive material. NITTER (1956 and 1959) has obtained good results with radium moulds. Recent reports (HALE, 1961) have suggested a periodicity of mitotic cycle in neoplasms which may be related to a variation in radiosensitivity which continuous radiation may be better able to utilise than discontinuous Xray therapy. Confirmation of this work is awaited with interest.

146 cases of 167 showed some measurable effect of radiation although of these 53 showed an incomplete response in that the tumour did not disappear entirely or recurred within the treatment area after a tumour free period.

Radionecrosis.

In the effort to force a response it is not surprising that dosages were carried to radionecrotic levels. This was commoner with interstitial implantation although subcutaneous fibrosis and restriction of shoulder movement following high doses to axillary nodes were noted in later years with Xray therapy. Since some disability as the result of treatment was

apparent although in most cases this was correctable by excision and graft, the survival of these cases should show some improvement over the remainder if the risk of radionecrosis is to be an acceptable one. It would appear that this is indeed the case although the numbers are too small to detect statistical significance.

Recurrence in a Treated Area.

Recurrence in the treated area or its immediate vicinity following surgery occurred in 50%. Only 23 cases irradiated showed recrudescence of tumour following clearing (13.8%). However it is only fair to include among the recurrences those where incomplete clearing had been achieved which leads to a 44% "recurrence rate". It has previously been pointed out that some of the persistent tumours did not in fact show malignant cells under the microscope and even of those who did, not all would have been able to reproduce. It is further pointed out that while radiation response is seriously interfered with by surgery the converse does not necessarily hold true. Many remnants can be removed locally without apparent ill effects.

End Result.

10 cases died of melanoma over 10 years after the first treatment. As there were only 30 survivors at 10 years this represents a further 33 1/3% attrition. Of 64 5 year survivors

22 died after this point. This runs counter to BLOCK and HARTWELL'S (1961) assertion that few cases die after 5 years and renders meaningless the 5 year "cure" rates published by PACK (1959) and many other authors, since some at least are harbouring latent disease. It is for this reason that no attempt has been made in this study to relate the figures to "cure". Any case dying of disease at a later stage is noted as being alive with disease at the point of assessment.

"Other diseases" causing death were carcinoma of the duodenum, carcinoma of the larynx, cerebro vascular accident proven at post mortem, post operative broncho-pneumonia, death during anaesthetic, and congestive cardiac failure. Several cases were clinically diagnosed as cerebral tumour or cerebro vascular disease. In view of the high probability of their death being due to metastases they have been counted as dying of melanoma unless post mortem evidence for such a cause of death was lacking. Many of the cases lost to follow up were in fact ill at their last visit or were reported to be ill by their local medical attendant. If all cases lost to follow up are counted as dead the 10 year survival rate becomes 30.6%, the 5 year survival rate, 44.0% and the 3 year rate 55.6%

Conclusions.

The first and basic result of this study is to show that radiation is by no means useless in malignant melanoma. Even as a palliative it appears to increase survival and certainly is a safer and more sure way of relieving local symptoms than any chemotherapeutic agent yet tried extensively. The fact that the established disease can respond in the great majority of cases has been obscured by the relative minority of spectacular failures.

In view of this and the disappointing results of surgery at least in certain situations, e.g. trunk and foot lesions it is perhaps worthwhile trying it in an attempt to improve the results in the elderly, unfit and more advanced case in whom the prognosis even with - or perhaps especially with - radical surgery is poor.

It would appear that any case with obviously involved nodes is beyond help by surgery alone. DICKSON (1958) has shown the improvement which post-operative radiation can achieve in early cases. It is postulated that in the advanced case intensive radiation may prolong the patient's life and preserve the functional integrity of his extremities with a better chance of so doing if surgery is not embarked upon.

The natural corollary is to advance this postulate further to the early case in whom nodes have not appeared. Difficulty is immediately experienced with the histological proof of the nature of the lesion since incisional biopsy has been shown to alter the prognosis for the worse. Local excisional biopsy removes the lesion for pathological confirmation and post operative radiation can then be administered. This scheme is followed in Norway (NITTER, 1956: 1959: EFSKIND and NITTER, 1962). However the problem of the draining nodes must be considered since in at least a proportion of cases the tumour appears to be confined to the primary site and the nodes. Radical block dissection in this series has been disappointing. The operation is not without mortality although this is small and becoming smaller. The morbidity is not negligible. Extending the operation to deal with further extensions into the internal mammary chain, iliac or para-aortic nodes increases both these disadvantages without promising much more in the way of salvage. Although subsequent radiation appears to be beneficial it cannot be used in these circumstances under ideal radiobiological conditions. It also cannot be denied that some cases derive no benefit from its use. The problem therefore is to select the best method or combination to suit each case.

McWHIRTER has advocated preoperative radiation for any

clinical thyroid carcinoma so that the few who are extremely radio responsive may be selected for radical wide field treatment to the neck and lungs. No biopsy is performed until the response has been assessed for fear of confusing the appraisal. Equally, in responsive cases, biopsy must follow clinical examination without delay since the tumour may disappear entirely. If this scheme is acceptable for thyroid tumours there is an equal claim for its employment in malignant melanoma although the stricture upon the time of biopsy is by no means as rigid.

The following policy is put forward as a practical regime for dealing with the disease. A clinical diagnosis of malignant melanoma is more frequently correct than not (HICKS et al, 1955: MILTON and JELIHOVSKY, 1962). Once a firm diagnosis has been made, careful measurements and photographs are taken. A single dose of 1,000 rads is given to the tumour and a 2.0 cm. margin of normal skin using superficial Xray therapy for thinner tumours and correspondingly greater half value layers for those in whom the tumour is too thick to allow 80% of the dose at the estimated base. This dosage can be delivered without delay, no waiting lists are involved and the promptness of treatment can only be beneficial. No biopsy is taken. At the end of one week a further measurement and photograph are recorded and a second

dose is given. If a response has been obtained by objective measurement it should be permissible at this stage to take a biopsy and proceed to a third dose one week later. If no response is noted at the end of the first week no further radiation should be administered after the second dose. Even in such cases some benefit can be expected from the radiation in sterilising the better oxygenated cells at the periphery of the tumour or around blood vessels may be expected. It is surely from this area that the dissemination of cells during surgery must come. The radiation may therefore assist in preventing or delaying the appearance of blood borne metastases. Wide excision removing all the irradiated tissue should follow. Block dissection in continuity if this is feasible or delayed block dissection should be performed. Whether this should be followed by post operative therapy or not is doubtful since the tumour has been shown to be radioresistant but if tumour is found in the draining nodes it may serve some purpose after surgery.

A responding case should be given a course of radiation to the draining nodes after a delay of 4 weeks since delayed treatment of the nodes has been shown to produce better results than immediate dissection (PETERSEN et al) presumably because tumour emboli released at the time of operation into the lymphatics have time to reach the node station. PANAYOTIS

et al, 1962 have shown this effect to be invalid for cases without nodal involvement but their figures reveal a slight improvement in those whose nodes are reported to contain tumour. Equally the same considerations should be applicable to radiation although irradiation in continuity since it will involve a change in the half value layer is seldom possible unless the primary lies immediately over the drainage field. In that event a risk of radionecrosis must be accepted if conventional voltage Xray therapy is all that is available. However the use of megavoltage equipment or telecobalt or telecaesium will allow some skin sparing while achieving adequate depth dosage with a single field and this factor may prevent subsequent necrosis. The dosage for irradiation of a clinically uninvolved field should be carried to skin tolerance for conventional voltages or subcutaneous or underlying tissue tolerance for supervoltage equipment. The 3 dose technique used for the primary is not applicable to wide fields placed over major joints, the abdomen or mediastinum.

The biopsy taken after the second treatment should not alter the prognosis in cases who respond and it is not performed in those who do not. It will probably show the effects of radiation but these are not sufficiently severe to obscure the difference between a melanoma and the more benign conditions which may be confused with it. It will probably not be possible one week

after a large dose of radiation to distinguish between juvenile melanoma, superficial melanocarcinoma and invasive melanoma but in the main these are clinically doubtful lesions and a firm clinical diagnosis is unlikely.

Where doubt exists as to the diagnosis wide excision is still the treatment of choice if the lesion is a naevus in the process of alteration. Where even this point is not clear local excision will allow the pathologist to use proper facilities and due consideration to come to a diagnosis without materially affecting the prognosis if the appropriate treatment, which may be radiotherapeutic, follows. This is the type of case which does best with surgery. It is the clinically obvious ulcerated lesion which produces the worst results.

For the case which has already produced regional nodes no delay should be allowed before administering radiotherapy to all the involved regions. It is in this case that barotherapy may have a part to play although the fractionation and intervals to achieve maximum tumour resolution with minimum tissue disturbance have not been finally settled.

If nodes persist in a drainage area after irradiation surgical excision may still be possible. Occasionally the

radiation changes in the skin and subcutaneous tissues or the situation of the residuum is such as to render the case inoperable. The implantation of local radioactive sources has much to recommend it in these circumstances since it confines further high dosage to the immediate vicinity of the tumour, and it utilises continuous irradiation which may be an advantage. Implantation as the initial treatment theoretically has the same disadvantages as surgery in disturbing the tumour bed and disseminating tumour. Certainly the few cases presented in this review have done better with Xray therapy first.

The risk of radionecrosis in such a case is of course high but it is felt that the possible benefits of this mode of treatment make this hazard acceptable.

The use of continuous external radiation for the primary tumour in the form of a radioactive mould would allow full utilisation of the effect previously mentioned but it is not such a decisive means of high dose irradiation and involves a delay between diagnosis and the institution of treatment. Much will depend upon the further investigations into P 32 uptake during the cell cycle and the prediction of radio sensitivity.

Persistent disease in the primary area has been safely

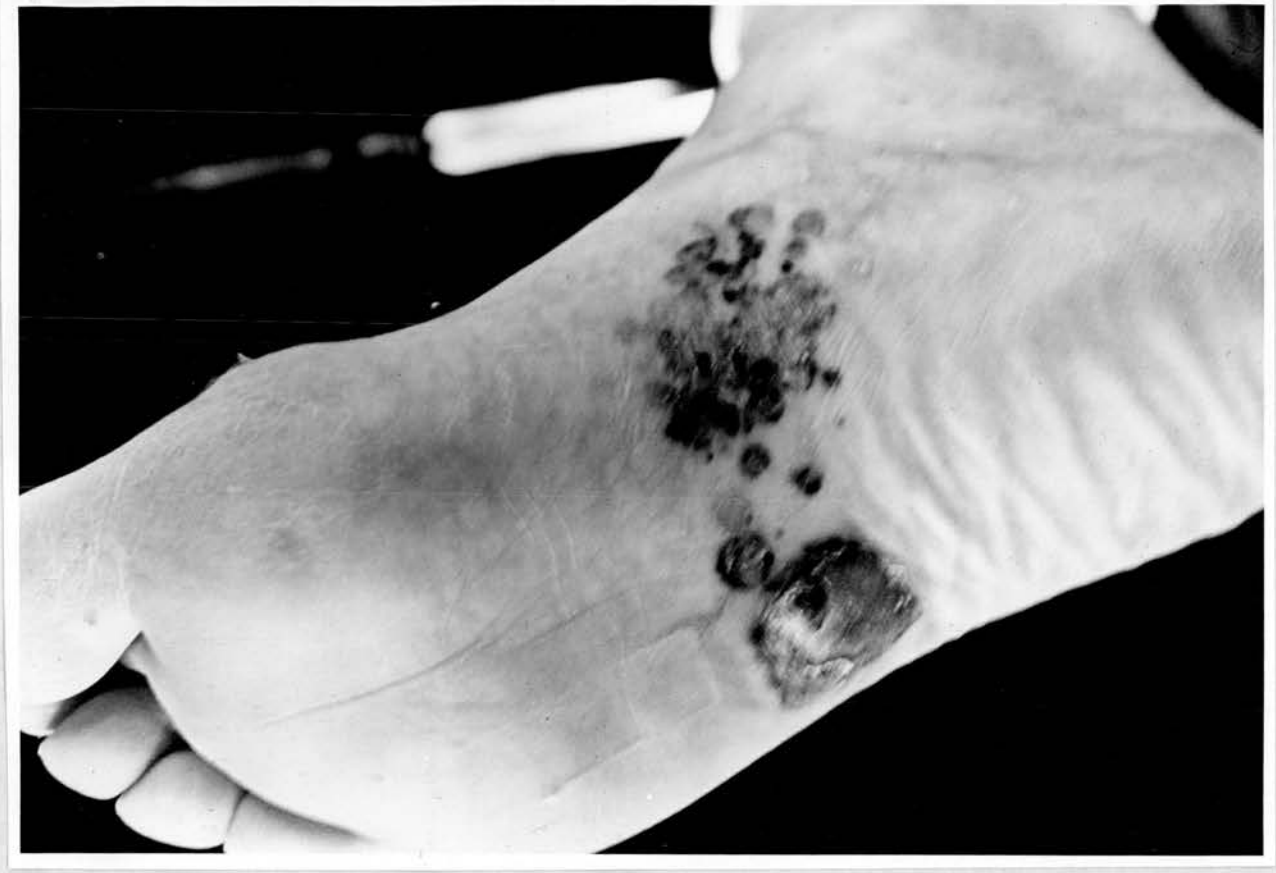


Fig. 6a. Malignant melanoma developing in an area of melanosis on the sole of the foot. Before treatment.

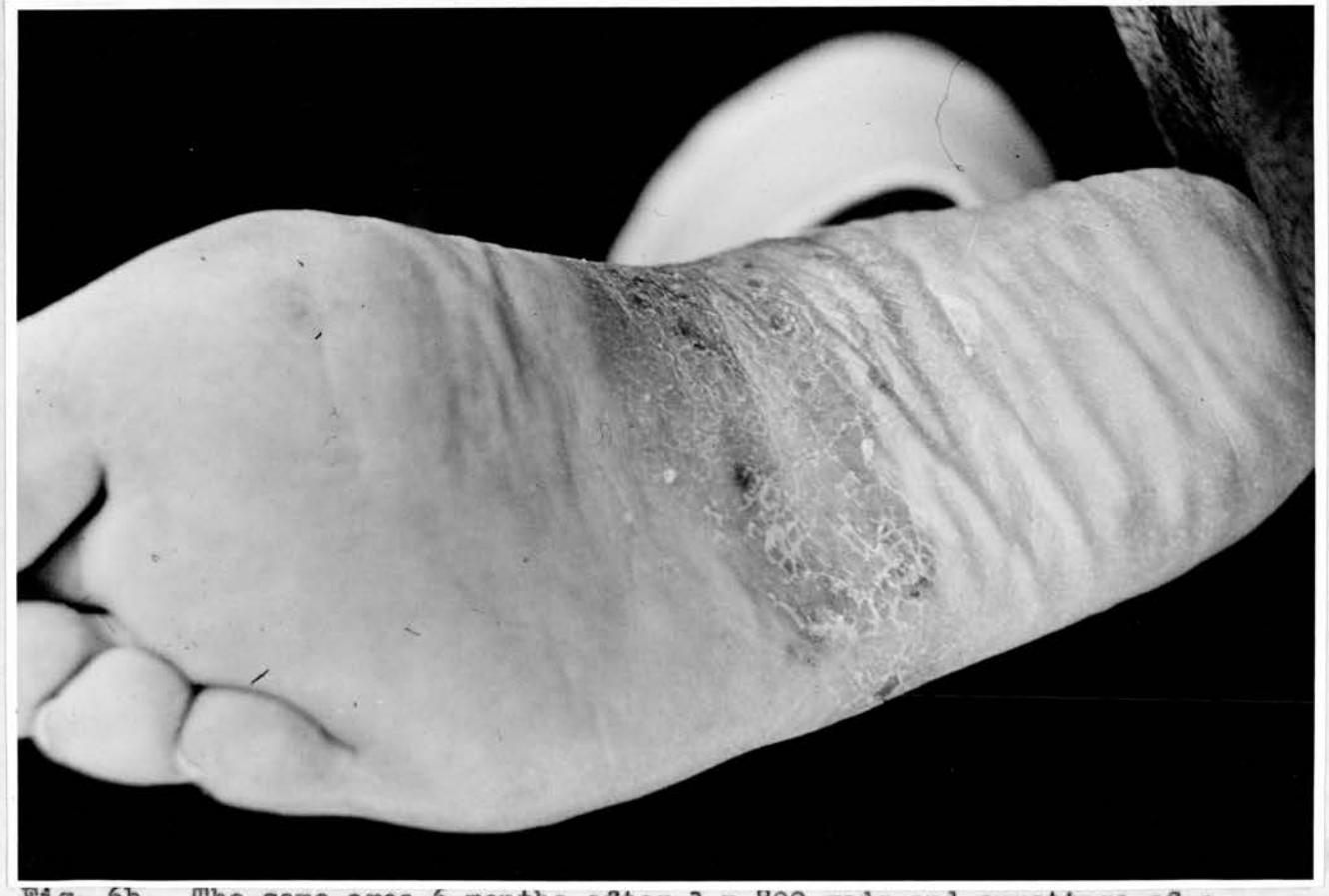


Fig. 6b. The same area 6 months after 3 x 800 rads and curettage of a residual nodule. The dose was reduced because of the poor circulation in the foo

curetted with complete healing in two cases one of which is illustrated in Figure 6. Both were elderly patients in poor general condition and presented after the instigation of this policy.

It is hoped that this proposal will go a long way to meeting the need, expressed editorially in the LANCET (1962), for "a line of therapy which is generally acceptable and widely applicable" although general acceptance would be a lot to ask without considerably more than the mere proposal. At least it is hoped that radiotherapy will be used more frequently to palliate advanced cases since therapeutic nihilism has resulted in 33% of Stage III cases being offered no treatment in one review (HEISE and KREMENTZ, 1961).

Acknowledgements.

I would like to thank Dr. R. Motteram and Dr. S. Were who traced and gave opinions on many slides, Dr. H.A.S. van den Brenk for his interest and encouragement and for permission to use figure 5 , and many of the clerical staff of the Peter MacCallum Clinic.

The cooperation of my colleagues at the Peter MacCallum Clinic and the honorary staff of the Royal Melbourne Hospital in allowing me to review their case material is gratefully acknowledged.

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