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Current Management of Melanoma

H. F. SEIGLER, M.D., B. F. FETTER, M.D.

From the Departments of Surgery and Pathology, Duke University Medical Center, Durham, North Carolina

EVEN THOUGH CARSWELL first used the term melanoma in a treatise in the early part of the 19th century, Hippocrates is credited with the first recorded clinical observation of cutaneous melanoma. During the seventeenth century several reports appeared in the literature referring to the "fatal black tumor." In 1806 both Laennec and Dupuytren published on melanosis; however, it was not until 1864 that Sir James Paget stated that cancer could develop in a mole. In 1892 Hutchinson published his *Archives of Surgery* in which he carefully described the senile freckle which we now call Hutchinson's melanotic freckle. A decade ago Clark[2] formulated the classification utilized throughout the world today. He described three separate types: 1) melanoma, Hutchinson's melanotic freckle type (lentigo maligna melanoma), 2) melanoma, invasive with adjacent intraepidermal component of superficial spreading type (superficial spreading melanoma), 3) melanoma, invasive, without adjacent intraepidermal component (nodular melanoma).

Etiologic Factors

The etiology of melanoma has been complicated by the diffuse distribution of the melanocyte to tissues throughout the body. It is felt that the malignant tumor arises from melanocytes or their antedecents and differentiates in a manner similar to that of its benign pigmented nevus counterpart. Stegmaier[32] has reported that nevi may appear as early as the fourth fetal month and then proceed through an active life cycle ending in involution during the ninth decade. Interim stages include the first appearance of junctional nevi during the first few years of life, followed by compound nevus formation in the prepubertal years with enlargement and darkening at puberty. Further enlargement and darkening may occur during the second decade of life and during pregnancy. A gradual loss of pigment and decline in number of nevi takes place during the fifth, sixth, seventh and eighth decades of life. Any variations from this life cycle may be indicative of the development of a melanoma in a previously benign nevus. However, only about one-fourth of melanomas seem to arise from a previously benign nevus. Most caucausian adults over the age of 40 have approximately 100 nevi and with the low incidence of malignant change, approximately 250,000 benign nevi would have to be removed to prevent a single melanoma.

Irritation and trauma such as elastic injuries, blunt trauma, x-ray changes, and old burn scars have been indicted in approximately one-third of the cases reported. Sunlight as an etiologic agent remains debatable. Individuals of Celtic heritage who have migrated to areas close to the equator have a high incidence of melanoma. Following American independence, Great Britain utilized Australia as a penal settlement. A large proportion of those deported were of Celtic decent. McGovern[16] has reported that skin cancer and melanoma are very common among this

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population. The frequency of melanoma increases as one proceeds north to Queensland, near the equator. Lane-Brown[10] has shown that the incidence of melanoma among people who are one-half or more Celtic is double that of the non-Celtic portion of the population. A similar report from this country gives corresponding results.[11]

In the United States melanoma is 80% more frequent in the caucausian population than in the black population. The most common primary site in the American black is the skin of the foot. Lentigo maligna is extremely rare. In Africa plantar melanoma comprises from 60–70% of the reported cases in blacks. Lewis[13] clearly documented prior junctional nevi of the plantar surface of the foot with the development of malignant melanomas. Other primary sites found in the black population include oral cavity, nasal cavity, palmar surfaces of the hand and conjunctival surfaces of the eye. Intra-ocular melanoma is practically unknown in the African black and is only slightly more frequent in the American Black.

Melanoma is a complication of xeroderma pigmentosum and chiefly affects females at an average age of 17 years.

Clinicopathological Presentation

Cutaneous melanoma develops at the site of a previously benign nevus in only one out of four cases. Giant pigmented nevi are potentially malignant whereas the hairy nevus has a much lower potential. Reed[24] has reported a 30% instance of malignancy in the giant nevus, and the incidence is 4% in Hutchinson's freckle. Thirty-five per cent of superficial spreading melanomas occur in a previously benign nevus. Twenty-five per cent of nodular melanomas occur in a previously pigmented site.

Melanoma arising in Hutchinson's melanotic freckle is the least common of the principal histogenic types of melanoma, yet it has the best prognosis. The lesion is macular, irregularly pigmented, (Figs. 1 and 2) and wanes and waxes over the years. It has been reported on occasion to disappear completely only to return after several years. Its most common location is in the sun-exposed area of the malar and temporal regions of the face, but it may appear in other areas such as the hands and feet or, very rarely, in the conjunctivae. Changes of rather marked solar damage are always present and the invasive characteristics do not usually appear until the sixth, seventh, and eighth decades. The development of melanoma is characterized by the formation of nodular areas in the lesion. The nodules represent foci of proliferating melanocytes which may be invading the dermis.

Superficial spreading melanoma is more pagetoid in nature and usually begins as a spreading pigmented macule that is more circumscribed than Hutchinson's freckle. The color may be brown, black, red, or pink. This lesion grows far more rapidly than Hutchinson's freckle and has usually reached between one and two centimeters in diameter after a 12–18 month period. Melanoma of this type occurs in both covered and exposed parts of the body as well as in mucosal surfaces such as the oral cavity, nasopharangeal cavity, vulva, vagina, penis and anal canal. Figure 3 shows the typical appearance of such a lesion. In Fig. 4 the pigmented cells appear in small groups at the basal layer and also extended upward through the epidermis.

Melanoma without an adjacent intraepidermal component is commonly referred to as nodular melanoma. There is usually no preliminary spreading pigmentation and the growth is more frequently dome-shaped or polypoid. Color variations may be similar to superficial spreading melanoma. Figure 5 gives the gross appearance of a typical nodular melanoma. The nodule is formed by proliferation of the melanocytes in the dermis. The overlying epithlium is usually thinned. In Fig. 6 the prominant mass of proliferating pigmented cells has elevated the epidermal surface producing a nodule.

Melanoma constitutes between 1–3% of all malignancies. It is slightly more common in males than in females with a ratio varying between 1:1–1:1.3. Primary tumors occurring on the head and neck and trunk are more common in the male, whereas lesions in the lower extremities that are exposed to solar rays are more common in females. Thirty-three per cent occur in the head and neck region, 29% lower extremity, 19% trunk, 15% upper extremity, 4% subungal, and the remainder are distributed throughout different locations of mucous membrane. In approximately 2–4% of the cases multiple primary cutaneous melanomas are found. Documentation that the melanoma is indeed primary requires demonstration that it arises from proliferating melanocytes in the basal layer of the dermis or that it has arisen in the dermis as a malignant blue nevus. If doubt exists, one should regard the lesion as metastatic and not as a new primary growth, since cutaneous metastases are common.

There seems to be rare familial or genetic predilection for this form of the disease. The most common type of melanoma to demonstrate multiple primary tumors is the superficial spreading type. Multiple lesions are indeed more common if the melanoma is associated with xeroderma pigmentosum.

Roentgenological Findings

In our own series of over 600 melanoma patients treated during the past 6 years, stereoscopic chest

x-rays done routinely demonstrated an incidence of pulmonary nodules of 7%. If, however, one considers only those patients who died of causes secondary to their disease, the chest x-ray was positive in 40% of the cases. Total body gallium scan has not proved to be of benefit, whereas liver/spleen scan, bone scan and brain scan have been helpful. If patients gave a history of unusual visual problems or headache, the brain scan was diagnostic in 24% of the cases studied. If, however, the patients demonstrated findings of systemic melanoma the brain scan was positive in 56% of such cases. We have elected to do bone scans only in symptomatic patients, in favor of routine metastatic bone surveys. Bone scans done routinely without bone pain symptoms were positive in only 12% of the cases, whereas, if the patients had symptoms, the scans were positive in 57% of the cases. Liver/spleen scans with focal defects compatible with metastatic disease should be differentiated from a shift of tracer activity from the liver to the spleen. This shift may reflect only the reticuloendothelial stimulation of the tumor itself, or may be reflective of different chemotherapeutic or immunotherapeutic regimens. We have documented a shift of tracer activity in 20% of 697 liver/spleen scans completed. The liver/spleen scan was helpful in only 2% of the cases done in patients without documented evidence of metastatic disease. The scan was positive 25% of the time, however, if the patient's disease was widespread.

The female breast is a site of metastatic disease, but routine mammography should not be relied upon to distinguish benign from malignant disease if this is the clinical suspicion. The xeroradiographic interpretation will most consistently be interpreted as benign fibroadenoma. If the clinician suspects metastasis to the breast, this should be confirmed by biopsy.

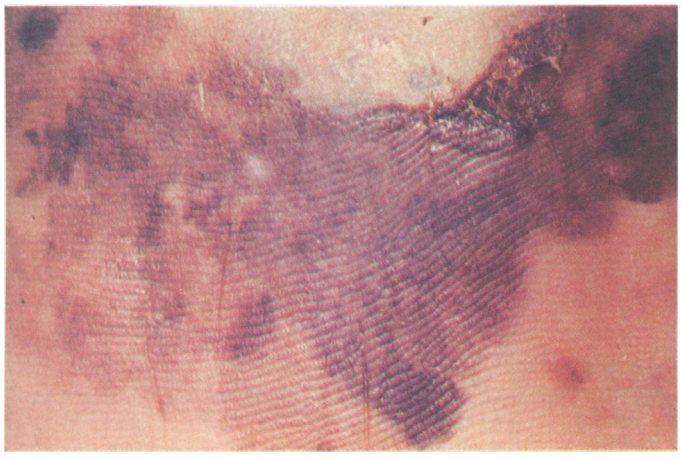
A favored site of metastatic disease in melanoma is the small bowel. At this medical center, half of the metastatic lesions to the small bowel are secondary to melanoma. This lesion may be missed by routine upper GI series and small bowel follow-through examination. The diagnosis should be suspected if the patient has a prior history of melanoma and develops clinical symptomatology compatible with intermittant intestinal obstruction. This is secondary to the polypoid metastatic lesions acting as a focal point for intussusception. The clinician should work in concert with his radiological consultant, and a primary tube, small bowel x-ray series should be obtained. The column of barium can be followed down and very small lesions may be demonstrated. Figure 7 represents a typical radiologic finding of small bowel metastases and Figure 8 is the gross specimen.

The question concerning the timing of routine chest x-ray in patients with a past history of melanoma is a practical one. In the 638 patient series at this medical center, 156 have converted their chest x-ray from negative to positive for an instance of 24%. This finding in conjunction with the report by Spratt[31] of a 43 day doubling time for a metastatic pulmonary nodule, indicating that one should obtain routine stereoscopic chest x-rays at four to 6 month intervals. In the absence of a clinical indication, the various scans are not positive with sufficient frequency to warrant routine usage. If, however, the patient has a clinical or chemical suggestion of disease, an appropriate scan should be obtained. Also, if major surgical intervention is entertained beyond removal of the primary lesions, stereoscopic chest x-ray, indicated pulmonary tomograms, radioisotope scans, and primary barium small bowel x-ray should be obtained.

Levels of Invasion, Clinicopathologic Staging, and Prognosis

Many factors such as age, host response, sex, location of primary, degree of differentiation, mitotic activity and size of tumor are important for predicting long-term survival rates for most neoplastic disorders. For melanoma, an overview clearly reveals that Hutchinson's melanotic freckle has the most favorable prognosis, nodular melanoma the least favorable and the superficial spreading type an intermediate prognosis. Clark et al.[2] have reported a mortality rate for Hutchinson's freckle as 10%, superficial spreading 31% and nodular 56%. McGovern[17] has correlated mitotic activity and five year survival rates, and has demonstrated that fewer than one mitosis per five high-powered fields is attendant with an 80% survival rate while between one to five mitosis per five high-powered fields is attended by a 55% survival rate, and if five or more mitosis are seen per five high-powered fields the survival rate is only 41%.

Clark[2] very clearly demonstrated that the level of invasion of the primary has a great deal of prognostic significance. The five levels of invasion as defined by Clark are depicted in Table 1. Utilizing these criteria, Clark has reported an 8.3% mortality with Level II lesions, 35% with Level III, 46% with Level IV, and 55% with Level V. McGovern[18] had similar findings with 80%, 50%, 50% and 20% 10 year survivals with Levels II–V respectively. The level of invasion of extremity lesions can also be linearly correlated with the likelihood of positive regional lymph nodes for metastatic disease. Wanebo[40] has reported 4%, 7%, 29%, and 70% for Clark's Levels II through V respectively. Pre-invasive melanoma has not been demonstrated to have metastasized and polypoid melanomas cannot be accurately staged since the entire tumor may be confined to the papillary layer distorted into the



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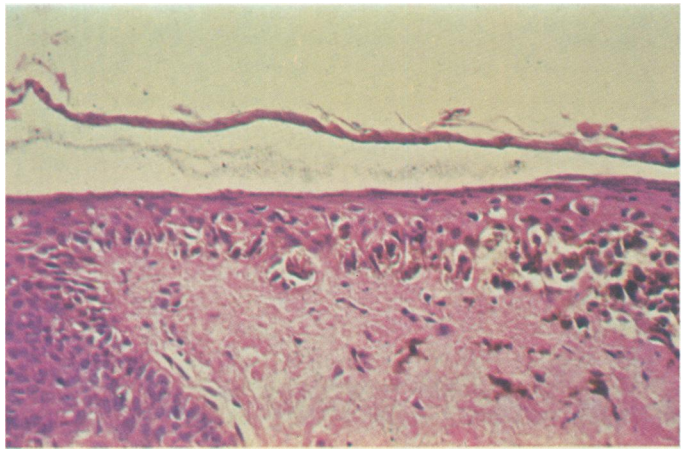

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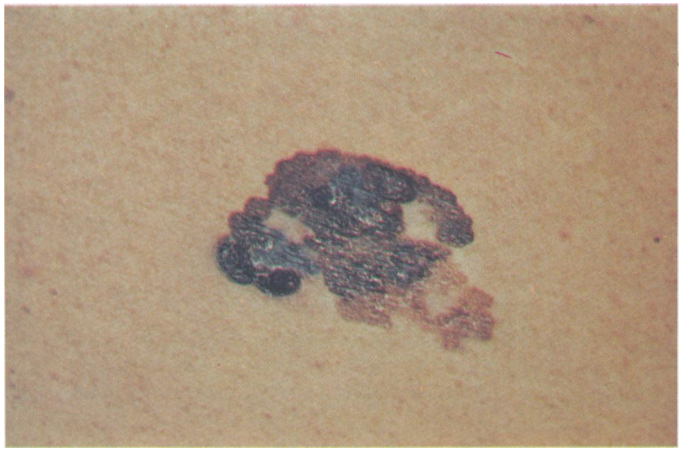

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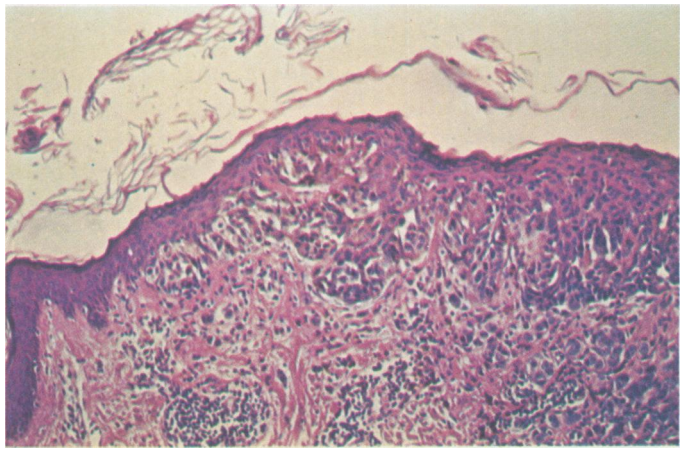

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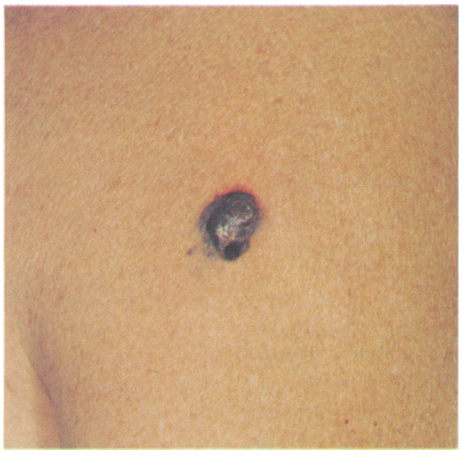

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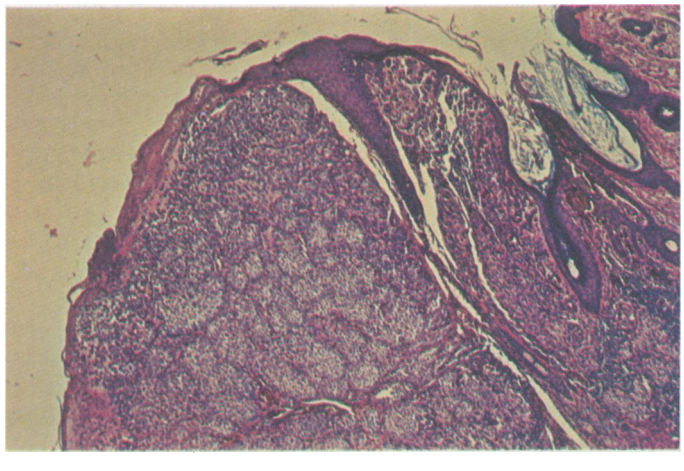

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FIG. 1. Hutchinson's freckle appearing on the malar region of a 78 year old female.

FIG. 2. In this microscopic section pigment laden cells are in the region of the basal cell layer of the epithelium. Some of the pigment is phagocytized in the dermis. This is a common feature of Hutchinson's freckle.

FIG. 3. Superficial melanoma appearing on the back of a 37 year old caucausian male.

FIG. 4. As in Figure 2 the pigmented cells in the superficial spreading melanoma are in the region of the basal layer. They also extend upward through the epidermis. The pigmented cells tend to be more polygonal than the cells of the Hutchinson's freckle.

FIG. 5. Nodular melanoma appearing on the upper arm of a 45 year old caucausian male.

FIG. 6. The epithelium is thin and elevated. The dermis is occupied by a mass of proliferating melanocytes.

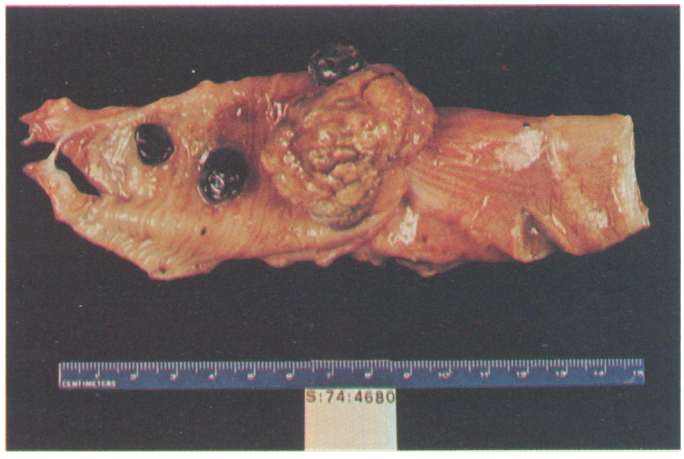

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FIG. 8. The gross specimen revealing metastatic melanoma to the jejunum with the polypoid lesion acting as the focal point for the intermittant intussusception.

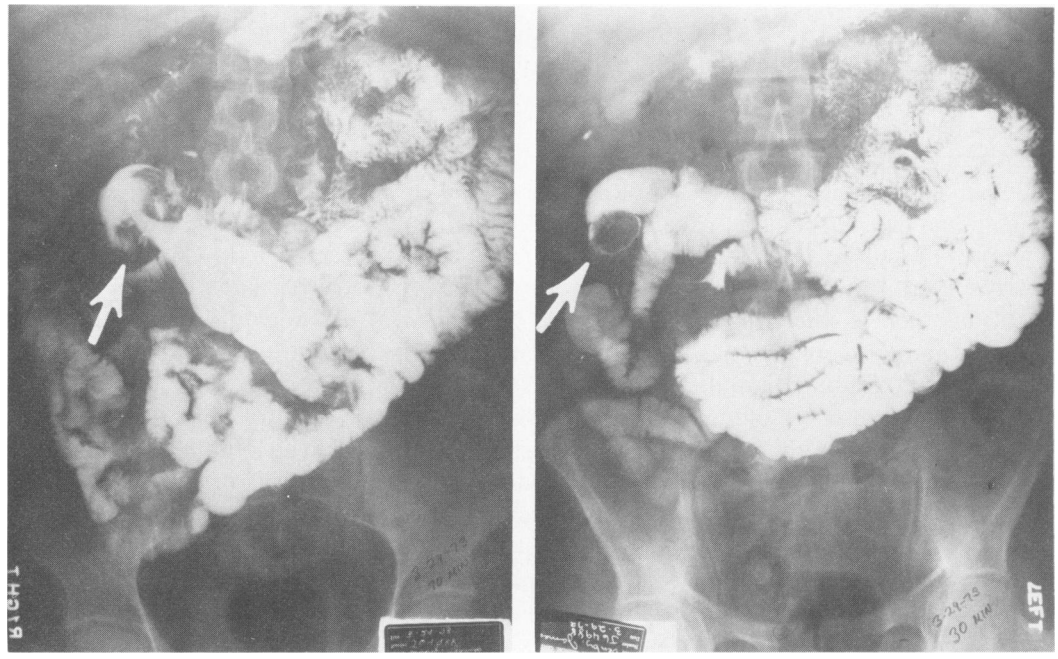

FIG. 7. Radiograph (right) showing an intralumenal polypoid defect in the jejunum. The radiograph (left) demonstrating the intussusception documented by a barium small bowel x-ray.

polyp formation. Little[14] states that polypoid melanomas have a high mitotic activity and poor survival rate.

Breslow[1] has reported that a more accurate way of predicting the biological aggressiveness of the tumor and the likelihood of regional lymph node disease is attained by accurately measuring the area of the lesion, its depth of penetration and its maximal cross-sectional area. His data indicate that the chance of developing recurrent disease appears to be directly proportional to the tumor thickness. He further states that prophylactic lymph node dissection doubles the rate of survival for patients with lesions greater than 1.5 mm. in thickness but has no protective effect for those with lesions less than 1.5 mm.

The Surgical Approach

The unpredictable biologic behavior of melanoma requires the surgeon to have an operative plan for control not only of the primary lesion, but also of local recurrent lesions, metastatic disease to regional lymph nodes, and for removal of selected disseminated tumor involving visceral organs as well as distant lymph nodes and distant cutaneous lesions.

Wide surgical excision is generally proposed for gaining adequate control of a primary melanoma. Different reports have expounded upon the necessity of removing 3 cm, 4 cm, or up to 6 cm in all directions from the lesion. These measurements would have a devastating effect if the primary lesion was on the face, or ear, for example. Also, it has been stated that closure of an adequately excised wound must, of necessity, be managed by placement of a split thickness skin graft. Much argument based on very little data has taken place as to the necessity of removing the deep fascia. A more logical approach should include not only the location of the primary, but also the identification of the type of melanoma involved. In regard to superficial spreading melanoma and Hutchinson's melanotic freckle, there seems to be a field effect with lateral extension and, therefore, this lesion should have a wider margin of excision than melanoma with no adjacent intraepidermal component as seen in most nodular melanomas. Excision of local recurrent disease involving the skin should generally be handled more aggressively with 4 cm margins in each lateral direction and closure by split thickness skin grafting. Recurrent subcutaneous nodules should most probably be managed by simple local excision. Treatment of plantar or palmar melanomas should be treated by

TABLE 1. *Level of Invasion in Malignant Melanoma (From Clark[2])*

Level	Description
1	All tumor cells above basement membrane
2	Invasion into loose connective tissue of papillary dermis
3	Tumor cells at junction of papillary and reticular dermis
4	Invasion into reticular dermis
5	Invasion into subcutaneous fat

wide local excision and split thickness skin grafting. Subungal melanoma should be managed by an amputation procedure with no attempt at local excision and coverage.

A continuing controversial issue, concerning management of malignant diseases in general and of melanoma in particular, revolves around regional lymph node dissection. Much of the argument could be resolved if the clinician would consider prognostic goals as well as therapeutic possibilities. If a single lymph node is positive, the possibility or indeed, probability, exists that the patient has systemic disease. Institution of therapeutic or adjuvant chemotherapy or immunotherapy may well depend upon a knowledge of the status of the lymph nodes. If, for example, one considers the real therapeutic benefit of combination adjuvant chemotherapy in patients with carcinoma of the breast with positive lymph nodes, a more efficient treatment regimen can be planned and instituted. There is a well known inaccuracy of the clinical evaluation of regional lymph nodes. Approximately one-third of patients who clinically are considered to have uninvolved nodes by palpation will have, in reality, metastatic disease by histological examination. Such patients would be, thereby, inadequately treated and this is stressed in many publications by advocates of routine prophylactic dissections. Their data indicate that patient survival rates are greater in those patients with microscopic tumor in lymph nodes than in those patients who have their regional lymph nodes dissected only after they become clinically palpable. The evidence supports the thesis that if the surgeon carefully considers the histologic type of the tumor, mitotic activity, and depth of invasion, he can reasonably select patients for elective lymph node dissection. Melanoma arising in a Hutchinson's melanotic freckle gives rise to nodal metastases only in tumors with advanced mitotic activity, and shows invasion of the reticular zone of the dermis or the subcutaneous fat. Lymph node involvement can be correlated with tumors of advanced mitotic activity, showing invasion to the papillary-reticular derma interface and beyond. Wanebo's[40] data predicts that 7% of patients with Level III primaries will have positive nodes, and this increases to 25% and 75% respectively for Levels IV and V. If such patients are treated by surgery alone, only 27% of the patients with positive nodes will survive for five years, as compared to 82% for patients with pathologically proven negative nodes. These statistics are of great prognostic significance to the patient and should clearly stimulate the clinician to consider adjuvant chemotherapy or immunotherapy. The surgeon might also consider direct measurement of tumor thickness in parafin section as described by Breslow.[1] Utilizing these criteria Hanson and McCarten[8] found that elective lymph node dissection doubled the rate of survival for patients with lesions greater than 1.5 mm in thickness but had no effect on those with thinner lesions. Patients with lesions less than 0.76 mm in thickness all survived whether or not lymph nodes were resected. Sugarbaker and McBride[36] have recently reported on 418 patients with primary melanoma of the trunk. Their retrospective calculation indicated that 184 regional lymph node dissections would have been required for probable salvage of 13 patients if surgical treatment for clinical disease had been used routinely. This 10% figure could most probably have been improved upon if either direct measurement of the primary, or of the level of invasion of the primary, were taken into account by the surgeon prior to elective lymph node dissection.

Regional lymph node dissection, in general, is associated with a morbidity of approximately 5%. Radical groin dissection, however, produces a 30–40% severe complication rate if the extended dissection is done routinely. If the superficial inguinal lymph nodes are negative for tumor, the deep inguinal lymph nodes will only rarely be positive. Approximately 10–15% of patients with grossly positive superficial inguinal lymph nodes will be found to have simultaneous melanoma in the high iliac and para-aortic chain of nodes. It is very doubtful that removal of iliac nodes or para-aortic nodes will prolong the survival of such patients. For all practical purposes, the surgeon should confine himself to superficial groin dissection for lower extremity lesions. Patients with melanoma involving mucous membranes and subungal regions should be strongly considered for elective regional lymph node dissections.

The role of surgery in the management of selected disseminated tumor involving distant lymph nodes, distant cutaneous lesions, and visceral organs continues to be modified as advances are made in chemotherapy and immunotherapy. Morton et al.[21] have recently reported the evaluation of results of surgical treatment in 60 patients with multiple pulmonary metastases. The authors report that approximately 60% of patients will survive five years after operation if aggressive surgical resection is completed in those patients who demonstrate a tumor doubling time greater than 40 days for a metastatic lesion. These data were applicable even in patients requiring bilateral thoracotomy. Our own experience would support this approach. Our posture has been to observe the tumor doubling time for one month, then to place patients with a tumor doubling time of greater than 30 days on combination chemotherapy, and if additional lesions do not develop during the next 60 days, to

follow this by resection of the metastatic pulmonary lesions. Chemotherapy is continued for 24 months.

Patients, who by CT scans have demonstrable solitary brain lesions that are surgically resectable should be considered for operation. Many such patients will experience a prolonged disease-free interval if lesions are surgically removed and if this procedure is followed by postoperative whole head irradiation and prolonged chemotherapy or immunotherapy are given. Removal of single or multiple small bowel metastases is indicated in patients who do not demonstrate other distant or visceral involvement. Not only are the intestinal obstruction, blood loss and pain relieved but also, if followed by aggressive adjuvant therapy, significant palliation may be realized. At present there are no data supporting the usefulness of "debulking" procedures, or of hemipelvectomy, or of fore-quarter amputation for management of disseminated metastatic melanoma.

The Question of Spontaneous Regression

Melanoma has been described as one of the more immunogenetic spontaneous malignancies in man. An interesting and, as yet unexplained, observation is that primary tumors have been reported to have a regression rate of 7–10%, while it is extremely unusual for a metastatic lesion to completely regress. The usual pattern observed is a "halo" of depigmentation around the mole followed by complete disappearance with replacement by a shallow scar. The phenomenon was originally described by Sutton[37] as leukoderma acquisitum centriugum. The histopathological changes in the "halo" or Sutton's nevus consist of a band of small lymphocytes invading the entire area around the nevus extending between nevus cells. The nevus cells may be destroyed, pigment released and carried away by macrophages so that the benign pigmented lesion may disappear completely. As noted above a malignant lesion may likewise disappear. The clinician will usually observe a completely depigmented scar of incomplete changes ranging from an inflammatory melanotic or amelanotic nodule, to a halo lesion, to tiny deposits of pigment in a surviving scar or, indeed, it may be faced with a metastatic lesion and no demonstrable primary growth. Under the latter circumstances the physician must make a complete search for the primary growth, so that the regressing or regressed site can be completely removed and any residual tumor extirpated. Nodular melanoma almost never undergoes spontaneous regression. The non-malignant portion of a Hutchinson's melanotic freckle commonly regresses; however, the clinically malignant and invasive areas do so less commonly. Superficial spreading melanomas are the usual histogenetic types of melanoma that undergo partial or complete regression. The prognosis of patients cannot be predicted by a primary lesion either undergoing, or not undergoing, spontaneous regression.

Hormonal Responsiveness of Melanoma

Clinical observations of exacerbation of melanoma during pregnancy and other high estrogen states have been made repeatedly. Sadoff et al.[25] have recently submitted evidence suggesting that melanoma may be an estrogen dependent tumor. The authors present several case reports showing activation of the disease following estrogen administration. They advanced their argument by including epidemilogical studies showing peak instances of melanoma in females in the third and fifth decades—periods representing high estrogen activity. Preliminary data is presented showing response of human melanoma to anti-estrogenic hormones. These phase one studies were generated following rodent experiments depicting an anti-melanoma activity of anti-estrogen compounds. George et al.[4] compare their series of 115 patients with coincidental pregnancies and melanoma to 330 patient controls. Such a study has obvious limitations; however, an increased instance of lymph node metastases in the study group was documented at the time that patients were able to receive therapy. Shiu et al.[29] have examined the influence of pregnancy on the prognosis of cutaneous melanoma in 250 cases. Even though they observed no statistical difference in the survival rate at five years for stage I melanomas, patients with stage II disease had significantly lower survival rates. Their study group had a 29% five year survival rate for pregnant patients as compared with 55% for nulliparious patients. Oral contraceptives have undergone similar scrutiny and case reports of these agents stimulating a change in appearance of pigmented lesions have been multiple. More complete studies of serum, skin, and tumor hormonal levels will obviously be required before more definitive answers will be forthcoming. Additionally, studies including both estrogen and progesterone receptor sites in melanoma tumor cells will be necessary before this question can be resolved.

Chemotherapy

The role of chemotherapy in the management of malignant disorders has progressed from utilization in terminal patients, with little practical possibility of demonstrating any beneficial effect, to utilization as an adjuvant to curative or near curative type surgery. Often chemotherapeutic drugs have a very high degree of specificity for the particular malignant cell type.

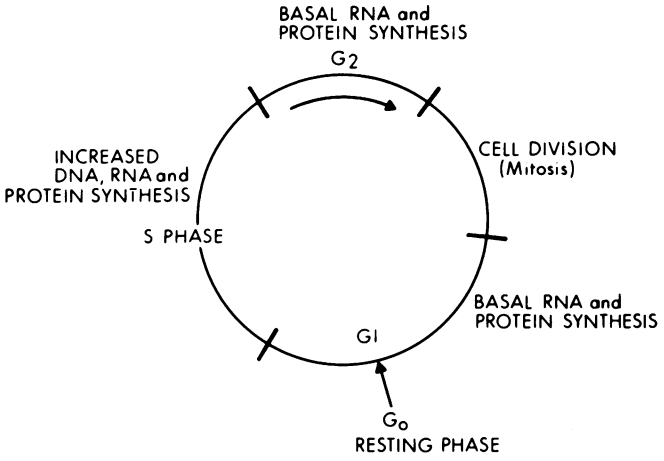

FIG. 9. The cell cycle.

Such examples would include Methotrexate for choriocarcinoma and streptozotocin for insulinoma. During the past three decades, much information has been gained concerning the cell cycle. As can be seen in Figure 9, following mitosis the cell advances from the G_0 resting phase to the G1 phase where basal RNA and protein synthesis takes place. During the S phase, increased RNA, DNA and protein synthesis is realized. The cell then enters the G2 phase where again basal RNA and protein synthesis predominate. The modern surgical oncologist is knowledgable of the metabolic processes taking place during the different phases of the cell cycle and plans a multiple drug program. Experience has taught us that multiple drugs are almost always more efficient than a single drug for the management of cancerous disorders. Additionally, a pulse-type program allows a greater dosage of drug to be delivered to the patient, thus rendering a more efficient anticancer effect. During the rest periods the patient is allowed to recover from the side effects deleterious to the GI tract, bone marrow, mucous membranes, and immunosuppressive effect. A drug regimen is selected based predominately on proven effectiveness against the tumor cell type being treated. Selection criteria should also include drugs that have little overlapping side effects and preferably those that will work at different phases of the cell cycle. The oncologist will consider agents that interfere with transition from the G1 phase to the S phase. This drug will be used in combination with a drug interferring with cell mitosis and perhaps a third drug acting predominately to prevent progression from the S phase to the G2 phase.

Many studies have been completed and reported concerning the therapeutic effect of various drug combinations for metastatic melanoma. In 1970, Moon[20] reported a 45% regression rate in 20 patients evaluated, utilizing a combination of BCNU and Vincristine sulfate. Imidazole carboxamide (DTIC) has been the most extensively studied single agent for metastatic melanoma. Approximately one-third of the patients so treated will realize either objective tumor regression or stabilization of the metastatic lesion for periods of a few weeks to several months. There has been considerable interest in the effectiveness of the nitrosoureas because of the high propensity of melanoma to metastasize to the central nervous system. Approximately 20% of the patients treated with either BCNU or CCNU will realize some therapeutic benefit. The greatest clinical experience has been realized for a combination drug regimen including DTIC, BCNU and Vincristine. Thirty to 40% of patients thus treated will realize meaningful clinical palliation. For the most part, responses have occurred in metastatic lesions involving skin, lymph nodes, and soft tissue. Responses in metastatic lesions involving the brain, lung, and liver are, for the most part, of relatively short duration and inconsistant to achieve. A more meaningful role for chemotherapeutic regimens will perhaps rest in their utilization as an adjuvant for control of subclinical disease. Numerous ongoing studies include different combinations of drugs being administered in a control fashion to patients with a relatively high likelihood for recurrence. Such patients would include those operated for mucous membrane melanoma, Level IV and Level V primary lesions, and patients with disease not evident beyond regional lymph node metastases.

The exact role of limb perfusion, as adjuvant or for management of recurrent disease remains unanswered. Shingleton, et al.[27] have recently reported a 28% five year survival rate in 43 patients treated by L-Phenylalanine mustard infusion for the management of recurrent melanoma of the extremity. Similar statistics have been reported by Stehlin[33] and Krementz.[9] McBride, et al.[15] have extended this form of therapy to include prophylactic isolated perfusion as a primary therapy for invasive melanoma of the limbs. When used in this fashion during the years of 1960 to 1970, the authors report on 202 patients with a two, five and 10 year determinant survival rate of 98%, 86%, and 83% respectively. In those patients, 2% developed local recurrences, 3% developed intransigent metastases, 18% developed positive regional lymph nodes and 6% developed disseminated disease as their first evidence of recurrence. Such improved statistics clearly merit further study utilizing this treatment approach as well as evaluation of more efficient single drug-multiple drug regimens.

Immunotherapy

Evidence collected during the past three decades has made it increasingly apparent that the host immune response plays an important role in the defense mech-

anism against the malignant process. The fact that infants born with immune deficiency have an extraordinarily high instance of spontaneous malignancy coupled with an 80 fold increase instance of malignancy in the immunosuppressed renal transplant patient, emphasizes the potential importance of immune responsiveness in the tumor-host relationship. Tumor allografts have been reported in the renal allograft recipient, whereas such an observation would be extremely rare in the immunocompetent host. Many spontaneous human neoplasms have been demonstrated to have tumor specific or tumor associated antigens and both humoral and cellular immune responses to these antigens have been clearly documented. The unpredictable clincial course of melanoma includes a significant rate of spontaneous remission, a frequency of many years from removal of the primary to appearance of metastatic lesions, and a rapidly advancing primary lesion with widespread metastases and death within weeks. This variable host response indicates that there must be host factors affecting the survival and growth of tumor cells.

Stuhlmiller and Seigler[35] have isolated at least two separate tumor antigen extracts from the membrane of melanoma cells by pronase digestion. These antigens are clearly separate from blood group antigens, fetal antigens, and HLA alloantigens. From their data one concludes that melanoma cells rapidly release large amounts of tumor associated antigen and that the release and regeneration time *in vivo* is approximately four hours. Shui et al.[28] have documented a humoral immune response to autologous melanoma cells quite separate from a humoral response to allogeneic melanoma cells. Such data indicate that melanoma expresses both autologous and cross-reacting tumor antigen specificities. Such data may prove extremely important when the clinician begins to develop effective specific immunotherapeutic techniques for clinical trial. Gupta and Morton[6] have been able to elute specific anti-tumor antibodies from human melanoma tissues. Their results support the hypothesis that anti-tumor antibodies are bound to melanoma cells *in vivo*.

When the clinician considers immunotherapy he must consider the host-immune responsiveness, the immunogenicity of the tumor cell type, and the possible presence of inhibiting or blocking substances in the serum of the tumor bearing patient. Immunotherapy may be administered as a) non-specific, active immunotherapy, b) specific, active immunotherapy and, c) passive immunotherapy.

Non-specific, Active Immunotherapy

Following Coley's original attempts, little was accomplished until the past decade. Bacilli Calmette-Guerin, Corynebacterium parvum and vaccinia have recently been employed as immunological adjuvants. Minden et al.[30] have demonstrated shared antigens between BCG and neoplastic cells. Varashie and Shawer[39] have observed a specific immunity against S91 melanoma in Balb-c mice pretreated with BCG. Morton's group[21] has reported a recurrence rate in stage II melanoma of approximately 70% in control patients as compared to 35–40% in patients hyperimmunized with BCG following primary excision and regional lymphadenectomy. These authors emphasize that intralesional BCG is the most effective therapy, and that only rare responses are observed with subcutaneous and visceral metastases. The two year survival rates reported for stage II melanoma patients surviving after regional lymphadenectomy alone or lymphadenectomy with postoperative BCG hyperimmunization are approximately 40% and 80% respectively. Similar results have been reported by Gutterman et al.[7]

Specific, Active Immunotherapy

Simmons[30] demonstrated both a protective affect against tumor take as well as tumor regression in rodents hyperimmunized with neuraminidase treated autologous tumor cells. Our group has utilized x-irradiated, neuraminidase treated melanoma cells plus BCG for its adjuvant effect in the management of 240 patients with melanoma. The survival rates at 24 months in this patient population is 87%. The efficiency of hyperimmunization with x-irradiated, neuraminidase treated melanoma cells plus BCG for the production of specific cytotoxic antibody to melanoma tumor cells was studied in this patient population. Stage I patients were uniform in their ability to develop specific anti-melanoma antibody in their serum while only 70% of stage II patients operated on for cure developed anti-tumor antibody. Stage II patients not surgically rendered free of gross disease were only 40% efficient in developing circulating antibody and stage III patients had demonstrable antibody in only 10% of 30 such cases evaluated. At the present time we are immunizing patients with Clark's III, IV, and V primary lesions, all stage IA patients and Stage II patients surgically rendered free of gross disease. The patients are followed for tumor specific cytotoxic antibody in an effort to gain an understanding of the importance of humoral immunity in the host-tumor relationship. Control patients not booster immunized with no cytotoxic antibody are included in the study protocol. Such experiments, in the future, may resolve many of the questions concerning the efficiency of specific active immunotherapy.

Passive Immunotherapy

Adoptive transfer of specifically immune lymphocytes to tumor-bearing rodent hosts has been partially

successful in experiments conducted by Rapp[23] and Treves.[38] We have utilized this technique in 174 patients with metastatic melanoma. The patients were placed on a blood cell separator and approximately 5×10^9 of their lymphocytes were obtained and layered on monolayers of melanoma cells maintained in tissue culture. These "sensitized" autologous lymphocytes were returned to the patients in an effort to passively convey specific cell-mediated immunity to melanoma. In the 174 stage II and III patients studied, the one, two and three year survival rates observed were 87%, 62%, and 57% respectively. Shin et al.[26] have recently reported long-term suppression of a transplanted solid tumor in a synegenic rodent model achieved by administration of cytotoxic antibody specific for the tumor cell type. Only anecdotal experience has been realized with this modality in man. Lawrence[12] has reported that transfer factor is capable of transferring immunity to skin allografts and certain fungal diseases. Preliminary clinical trials utilizing transfer factor in cancer patients has not been used extensively and no effectiveness has been documented. Pilch[22] has documented that immune RNA extracted from lymphoid tissues of a zenogeneic host following immunization with a specific tumor type could induce immunity in synegenic rodent tumor recipients. At the present time, clinical trials utilizing synegenic RNA for the induction of tumor immunity in man are being evaluated.

Numerous clinical trials are underway to evaluate the combined efficiency of alternating chemotherapy and immunotherapy in an effort to evaluate beneficial synergistic effect as compared to either treatment regimen alone. Ghose[5] has reported a rather dramatic remission with chlorambucil conjugated to specific goat anti-human melanoma antibody, Gutterman et al.[7] have shown an augmented response in metastatic melanoma lesions regional to BCG in patients infused with DTIC.

Immunodiagnosis

The clinician and pathologist together can usually establish the diagnosis of melanoma. The site of the lesion coupled with its histological characteristics and the presence of melanin within the tumor cells usually renders the diagnosis relatively easy to make. Amelanotic lesions may be much more difficult to diagnose. In many cases, the clinician is able to find the primary lesion and submits an amelanotic lesion to the pathologist. In such instances the pathologist usually renders an interpretation of "undifferentiated carcinoma" or "undifferentiated carcinoma consistent with" a number of primary lesions. A DOPA stain or electron microscopy for melanosomes may be very helpful in distinguishing the diagnosis of melanoma; however, both of these techniques have their shortcomings and are time consuming and not readily available. Immunological diagnosis has great potential because of its specificity and sensitivity. The abundant evidence documenting melanoma specific antigens on the surface of tumor cells allows specific antibody identification. We have reported the production and characterization of a specific chimpanzee anti-human melanoma antibody.[34] Our results utilizing this antibody have indicated that immunodiganosis of melanoma is quite specific, inexpensive and a simple technique for establishment of the diagnosis. We have utilized both complement dependent cytotoxicity of the tumor cells and immunofluorescence of tissue slices. Both techniques are simple, rapid and could easily become routine procedures in most clinical pathology laboratories. Another promising use for the chimpanzee anti-melanoma antiserum is in a radioimmunoassay. Such assays are capable of detecting nanogram quantities of antigen and are being used clinically for detection of such substances as renin, gastrin, insulin and a variety of other hormones. We have much evidence to suggest that melanoma cells shed their tumor specific membrane antigens into the blood and that these may later appear in the urine. Because these antigens are found in the body fluids, it may be possible to develop a radioimmunoassay for the detection of these antigens. Such an assay could be used to monitor clinically tumor-free patients for detection of very early recurrences. This would allow the clinician to institute surgery, chemotherapy, or immunotherapy at such a time that cure might still be possible before the tumor burden is great and the prognosis is grave.

Summary

Melanoma represents a malignant transformation of the melanocyte. While a variety of environmental or genetic factors may be important in its development, the biological course remains quite unpredictable. Melanoma with adjacent intraepidermal component of Hutchinson's melanotic freckle type is late to invade and can usually be managed locally and has an excellent prognosis. Superficial spreading melanoma is more pagetoid and circumscribed than Hutchinson's freckle. It may invade the dermis and subcutaneous tissue but usually does so late in its course. Melanoma without adjacent intraepidermal component is usually referred to as nodular melanoma and has no preliminary spreading pigmentation and the growth is usually dome shaped. This lesion characteristically invades the dermis and subcutaneous tissue. The clinical course of a melanoma can be predicted by the mitotic activity of the primary, by tumor thickness and depth of invasion.

A careful history plus physical examination, blood chemistries and stereoscopic chest x-ray should be obtained on all suspected patients. When indicated by clinical symptomatology or signs, or chemical abberations, liver/spleen scan, bone scan and brain scan may be helpful for staging the disease. If abdominal symptomatology suggesting blood loss and intermittent obstruction is present, a primary tube, small bowel x-ray study should be accomplished. Pulmonary tomograms are absolute prerequisites prior to thoracotomy. A reasonable treatment approach can be proposed if one considers the combined clinical reports of experienced medical centers. If the primary lesion involves only the epidermis and superficial papillary dermis, surgical excision with an adequate margin is all that is required.

Experience has taught us that if the primary melanoma involves the papillary-reticular dermal interface and deeper structures, or if the mitotic activity of the primary is great and the tumor thickness is 1.5 mm. or greater, the patient has a high probability of developing recurrent and metastatic disease. A proposed treatment approach for such patients is suggested: (A) Head and Neck Lesions. Surgical excision of the primary and regional node dissection followed by immunotherapy if the lymph nodes are negative. Immunotherapy or combination chemotherapy for 12–18 months should be advised if the lymph nodes are positive. (B) Extremity Lesions. Excision of the primary and regional node dissection followed by immunotherapy if the nodes are negative. Immunotherapy, systemic combination chemotherapy or lower limb perfusion should be entertained if the nodes are positive. (C) Truncal Lesions. Surgical excision of the primary and regional node dissection only if the regional nodes are palpable and felt to be clinically involved. Adjuvant immunotherapy for the node negative patient and immunotherapy or combination chemotherapy for the node positive patient for a period of 12–18 months is indicated. (D) Mucous Membrane Melanoma and Subungal Lesions. Excision of the primary for mucous membrane lesions and amputation and regional node dissection for subungal lesions. Immunotherapy or chemotherapy should be instituted and continued for 12–18 months. (E) Recurrent Local Disease. Wide surgical excision and split thickness skin grafting followed by immunotherapy or combination chemotherapy or alternating chemo/immunotherapy. (F) Recurrent Lymph Node Disease. Surgical removal of the involved lymph nodes, if possible, followed by pulse type combination chemotherapy for at least 24 months. (G) Small Bowel Disease. Documentation of the metastases by primary tube small bowel x-ray followed by resection of involved bowel and combination chemotherapy for at least 24 months. (H) Brain Metastases. Documentation that the brain metastases are single by CT scan. If indeed the metastasis is solitary and can be safely removed surgically, this should be accomplished and the surgical procedure followed by whole head irradiation and either immunotherapy or combination chemotherapy for 12–18 months. (I) Pulmonary Metastases. If the clinician can document that a solitary pulmonary metastasis has a doubling time of greater than 30 days, the patient should be placed on combination chemotherapy for an additional 60 days and if by pulmonary tomography no other lesions are demonstrable, wedge resection of the metastasis followed by combination chemotherapy for a period of at least 24 months is indicated.

Patients with disseminated disease should be considered for pulse type combination chemotherapy for palliation if the clinical situation suggests that the quality of life can be improved. Neurosurgical procedures for pain relief should always be considered if a patient survival time of 60 days or greater can be predicted.

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