MALIGNANT MELANOMA*

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THE MOST COMMON LESION of the skin is the pigmented nevus or mole. There are few human beings who do not have one or more of these growths. All such lesions are not primarily or secondarily malignant, as the average practitioner of medicine believes. If this were true, the entire world would soon be completely depopulated.

Of all malignant tumors, the malignant melanoma (melanotic sarcoma, melanotic carcinoma or malignant pigmented mole) is without doubt the most misunderstood and mismanaged, as evidenced by the high incidence of recurrence following local surgical treatment. Pack and associates[1] reported recurrence following operation elsewhere in 64 per cent of 552 cases of malignant melanoma and Adair[2] reported this incidence to be 61 per cent in 400 cases. Of the 67 cases encountered at the Ochsner Clinic during a period of seven and three quarters years, 54 (80.5 per cent) had recurrences following removal of the primary lesion elsewhere. This high incidence of recurrence emphasizes the necessity for a more thorough understanding of the clinical manifestations, pathologic behavior and surgical principles involved in the treatment of malignant melanomas.

Malignant melanoma of the skin is a rare lesion as compared with other cutaneous malignancies. Zeisler[3] found only 1.4 per cent of 500 cases of malignant growths of the skin to be melanomas. At the Memorial Hospital in New York during a period of 29 years there were only 862 cases[1] and only 67 cases have been encountered at the Ochsner Clinic over a period of seven and three quarters years.

Even though these growths are comparatively rare, they are associated with such a high mortality and morbidity that they deserve serious consideration. According to Spitz[4] the average five-year survival for adults of all ages with malignant melanoma is only 9.7 per cent. Zeisler[3] reported no cures or five-year survivals of patients with malignant melanomas. Even with adequate surgical treatment the prognosis is not considerably improved. Pack and associates[1] stated that with adequate surgical treatment only 38.4 per cent survive three years, and 17.7 per cent of those with localized melanoma live five years.

The anatomic sites most frequently involved with malignant melanomas in order of frequency are the lower extremity, head and neck, trunk, upper extremity and eye. The location of the 862 cases of malignant melanomas reported by Pack and associates,[1] in order of frequency, are shown in Figure 1. As can be seen in Table I, the anatomic distribution of the lesions in the 67 cases from the Ochsner Clinic is similar to that reported by Pack and associates.[1] From an analysis of this distribution, one can predict with a certain degree of accuracy that pigmented lesions (moles) of the lower extremity, head and neck, trunk and upper extremity can be considered malignant or border line. On the other hand, those occurring in the eye, soles of feet, palms of the hands, scrotum, vulva, or beneath the finger and toenails should be considered, from a prophylactic standpoint, as malignant from the beginning.

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The pathology of these lesions is variable. In most of them the pigmentation ranges from light brown to black. They have been classified by Allen[5] into the following groups: (1) junctional nevus (dermo-epidermal nevus), (2) intradermal nevus (common mole or neuronevus), (3) blue nevus (Jadassohn-Tieche nevus), (4) compound nevus and (5) juvenile nevus. For an excellent review of the origin, histopathology classification and general discussion of the subject of melanomas the reader is referred to Allen's paper.[5]

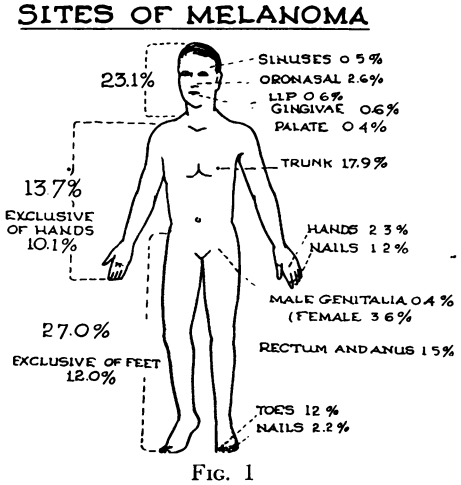

FIG. 1

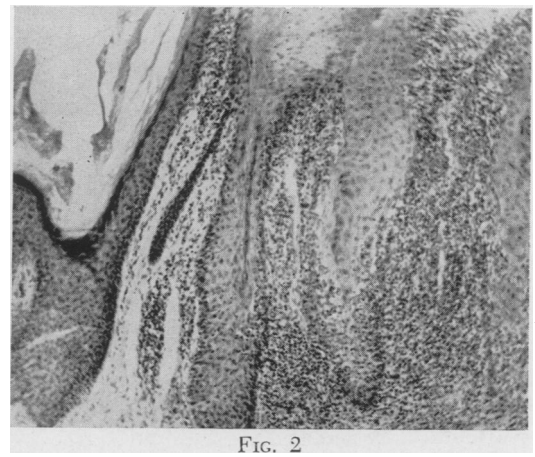

FIG. 2

FIG. 1.—Drawing showing the anatomic sites of occurrence of malignant melanomas in 862 cases reported by Pack and associates.[1]

FIG. 2.—Photomicrograph of a benign verucca. Note elongation of rete pegs.

TABLE I.—*Anatomic Distribution of Malignant Melanoma in 67 Cases at the Ochsner Clinic*

Site	%
Lower extremity	25.0
Head and neck	22.5
Trunk	22.5
Upper extremity	13.5
Rectum	3.0
Nose	1.5
Mouth	1.5
Undetermined	10.5
Total	100.0

There are two schools of thought as to the origin of these lesions. One[5] believes that they are of neurogenic origin and the other[6] that they originate in the epidermis. Allen[5] believes that most if not all arise in the germinal epithelium, whereas "the neuralists," as Allen[5] calls them, think that they arise from the terminal nerve twigs of the epidermis.

There is some controversy regarding the histopathology of these lesions. This will not be discussed here and only some of the typical histologic pictures encountered will be described. Figure 2 demonstrates the peculiar elongation of the rete pegs with cellular infiltration of the derma between the rete pegs—the typical histology of a benign verucca. Figure 3A is a photomicrograph of a typical benign dermo-epidermal type of nevus. The cellular nest in the epidermis and cellular infiltration of involvement of the derma are clearly and characteristically shown. Figure 4 is a photomicrograph of a typical blue nevus, which is benign; clearly shown are the cellular reaction and pigment which are confined to the chromatophores; the black spots in the dermo-epidermal structures represent the pigment. These photomicrographs

are from patients who had pigmented nevi, epidermal in origin, without clinical evidence of malignancy. They are dermo-epidermal in location, have the same pattern as malignant melanomas, and the cellular characteristics (large, oval or round nucleus and large nucleolus) are completely absent. This may be compared with Figure 5, which is a photomicrograph of a typical malignant melanoma of the dermo-epidermal type. The characteristic malignancy of the cellular components is seen in a higher

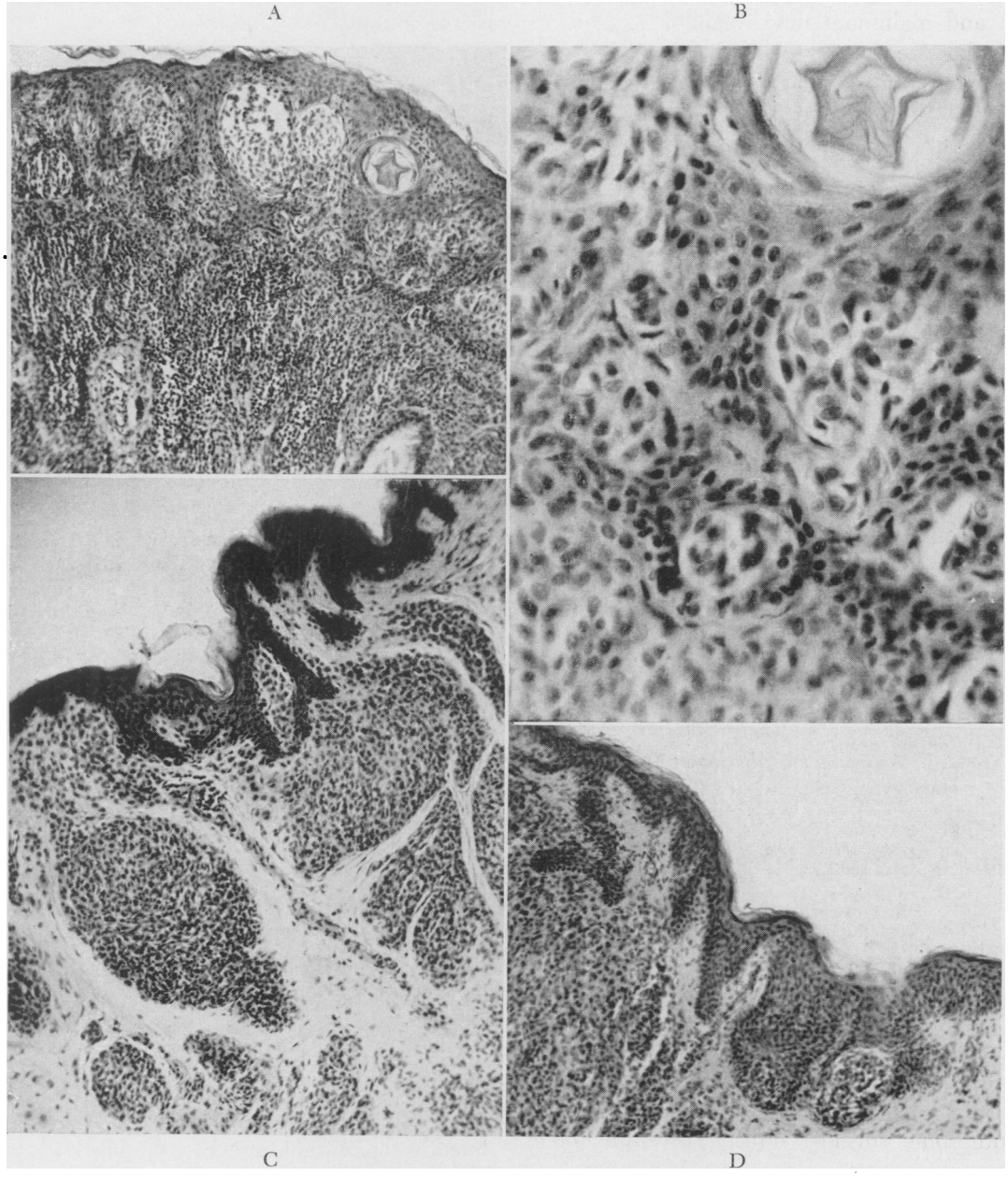

FIG. 3.—(A) Photomicrograph of a benign dermo-epidermal nevus; (B) higher magnification of 3A showing normal cellular constituents; (C, D) photomicrographs of benign nevi, which are frequently mistaken for malignant melanomas.

magnification of the same lesion in Figure 6. The cells are large, round or polygonal with round nuclei and large nucleoli. They have completely lost the cohesive relationship to the other cells; pigmentation is coarse and variable.

The histologic difference between benign and malignant nevi depends entirely upon the size, shape of the cell and size of the nucleus and nucleolus. The cellular pattern and the histologic characteristics are relationship and is accompanied by numerous cell mitoses. The histology is then typical of a malignant melanoma.

The histologic cellular picture varies greatly even in the same tumor. At times the picture is that of carcinoma, at others sarcoma. For this reason, the terms, *melanotic carcinoma* and *melanotic sarcoma*, have crept into the nomenclature. However, these terms have been largely replaced by the term, *malignant melanoma*.

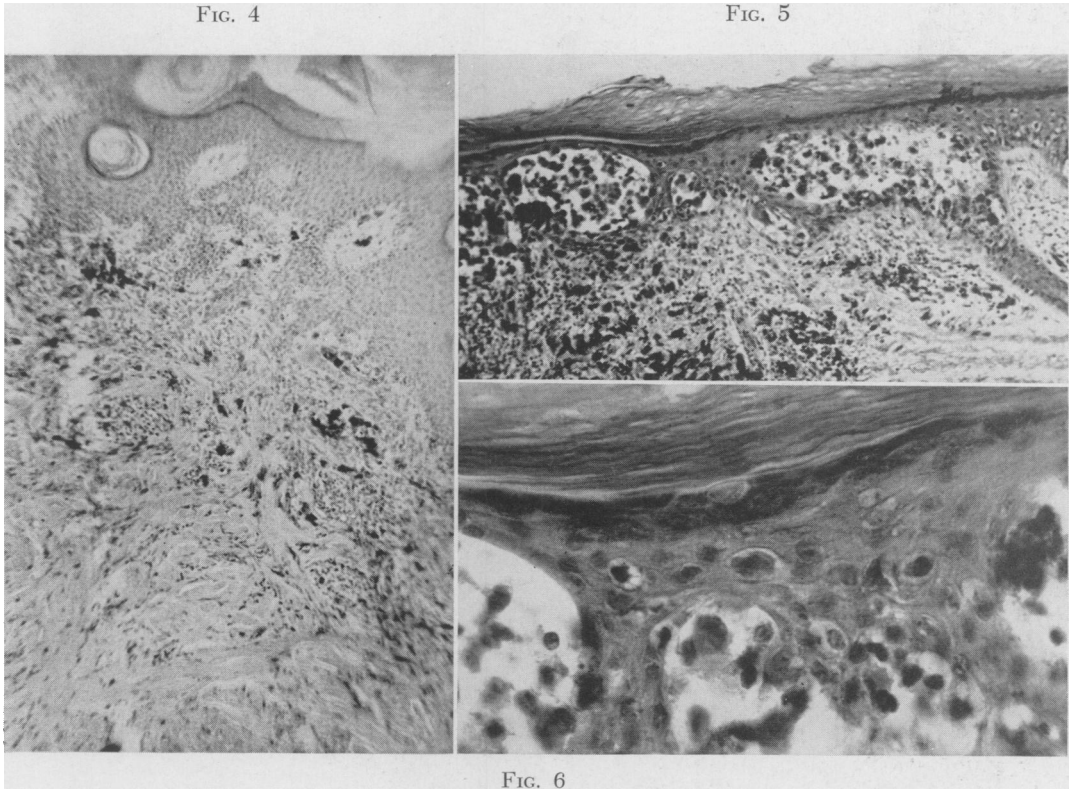

FIG. 4.—Photomicrograph of a blue nevus (Jadassohn-Tieche type) that is benign. The lesion is frequently mistaken clinically and microscopically for a malignant melanoma.
FIG. 5.—Photomicrograph of a malignant melanoma arising in a dermo-epidermal nevus.
FIG. 6.—High power of the same lesion as Figure 5 showing the characteristics of the malignant melanotic cell in epidermis.

present in the benign nevi and may remain dormant for months or years; yet trauma or meddlesome surgical interference for unknown reasons stimulates the cells to growth at varying speeds of unrestrained activity which is refractory to normal intercellular Regardless of the type of cell, the histology is that of a malignant tumor.

It is interesting that the melanotic mole occurring before puberty has the histologic picture of malignancy; yet clinically it is benign. According to Spitz,[1] the juvenile

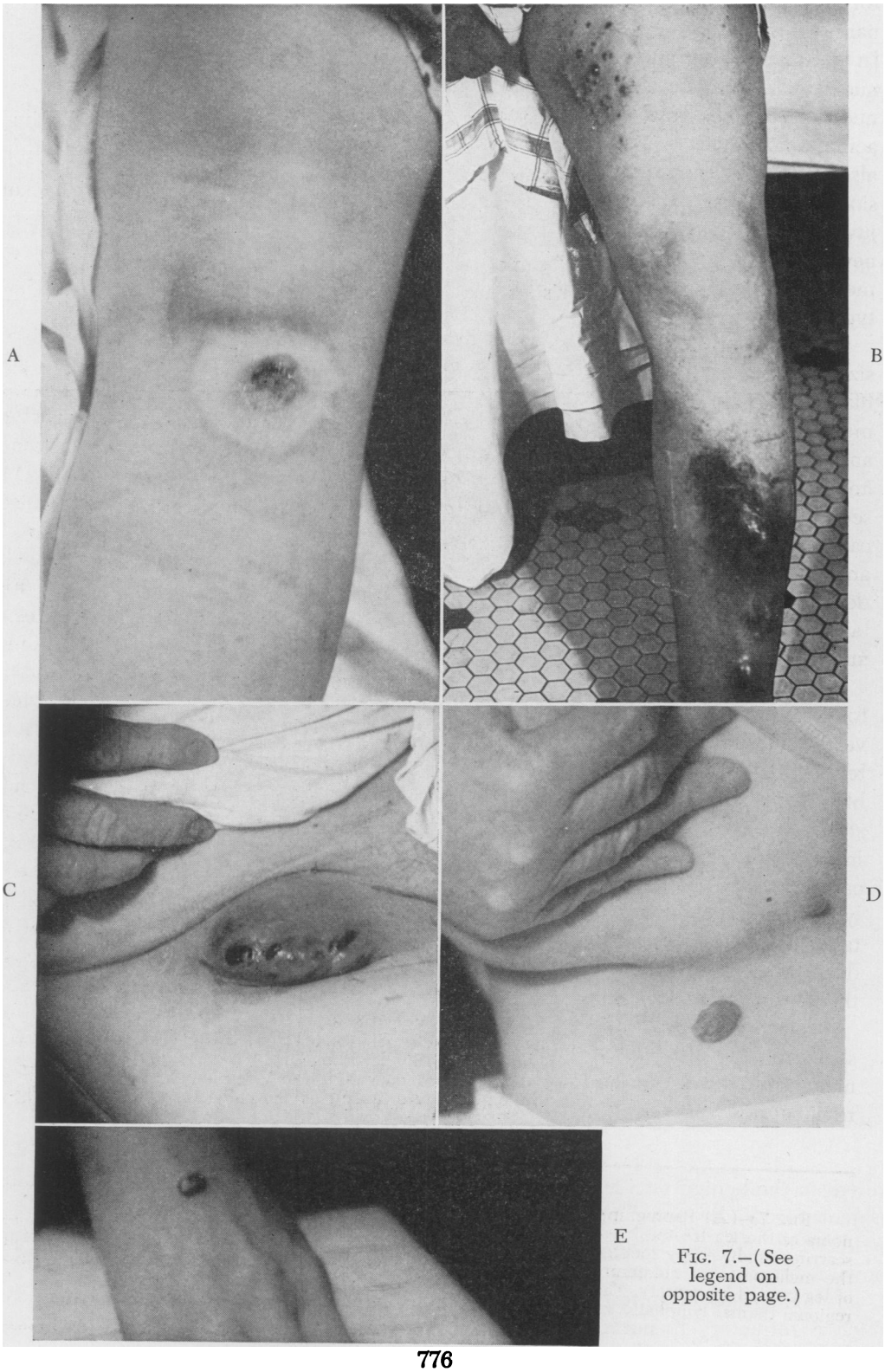

FIG. 7.—(See legend on opposite page.)

form of melanoma seems to be nonmalignant; yet the histology is that of malignancy. In the juvenile melanoma are large multinucleated or uninucleated giant cells whose nuclei are large and contain prominent acidophilic nucleoli. Mitotic figures are also frequently found in these peculiar lesions. Spitz[4] states that after puberty these juvenile melanomas seem to take on renewed growth and reveal all the local and metastasizing characteristics of the adult type.

That the malignant melanoma metastasizes by both the lymphatic stream and the blood stream is well known. Those that metastasize by the lymphatics have local and regional dermal and epidermal spread and regional lymph node involvement. They seem to remain localized lymphatically and can be completely eradicated both locally and regionally without assurance of freedom from recurrence but with the expectancy of a somewhat prolonged comfortable and active survival.

When the histologic study reveals mitosis of malignant cells around the blood vessels and large vascular sinuses, there is a tendency for the cells to break into the blood vessels, resulting in widespread metastasis by way of the blood stream primarily in the lungs and liver. In the majority of cases extension occurs both by way of the lymphatics and blood vessels. This may take place early and result in widespread deposits of the malignant cells. The lesion then becomes immedicable.

The more highly anaplastic the cellular structure, the greater the degree of malignancy and the earlier the metastasis, both regional and general. It is in this type that the pigment is scarce or completely absent. This is also true of metastatic nodules. They may be barely pigmented or the pigment may be completely absent.

The difference between benign and malignant pigmented nevi (melanoma) is one of degree in celluar activity as revealed histologically. When the benign melanoma is of the dermo-epidermal type, there are cells in both the epidermis and dermis that are foreign to the other normal cellular constituents and are frequently called malignant because of the presence of pigmented cells. However, the cells are small and reveal normal intracellular anatomy and relationship with adhesive characteristics which differentiate them from the true malignant melanoma (Figs. 3A, C, D).

In the malignant form the cellular distribution is similar but the cells are more embryonal, and contain a large nucleus and prominent acidophilic nucleoli. If Figures 3A and B are compared with Figures 5 and 6, it will be noted that both are dermo-epidermal in origin and Figures 3B and 6 have a somewhat similar pattern but the cells are entirely different. Both reveal higher magnification detailing the individual cellular characteristics. In Figure 3A the cells appear normal, with a small nucleus and nucleolus, differing from those in Figure 6, which shows not only the large cells and great nucleus but also definite and prominent nucleoli. Some giant cells and mitotic figures are present. From this discussion it is evident how closely the benign melanoma resembles the malignant one histologically.

Transformation of these lesions from benignancy to malignancy is evidenced clinically by a change in color, increase in size,

FIG. 7.—(A) Photograph of a malignant melanoma of the leg treated by roentgen ray. Note the scarring produced by roentgen therapy; activity of the melanoma has not improved. (B) Melanoma of leg treated by cautery. There is local recurrence, regional dermal lymphatic spread and involvement of lymph nodes. (C) Metastatic melanoma of femoral and inguinal nodes with ulceration. Primary lesion is situated on lower extremity. (D) Malignant melanoma in upper right quadrant of abdomen. No axillary nodes palpable. (E) Blue nevus (Jadassohn-Tieche type) of right hand.

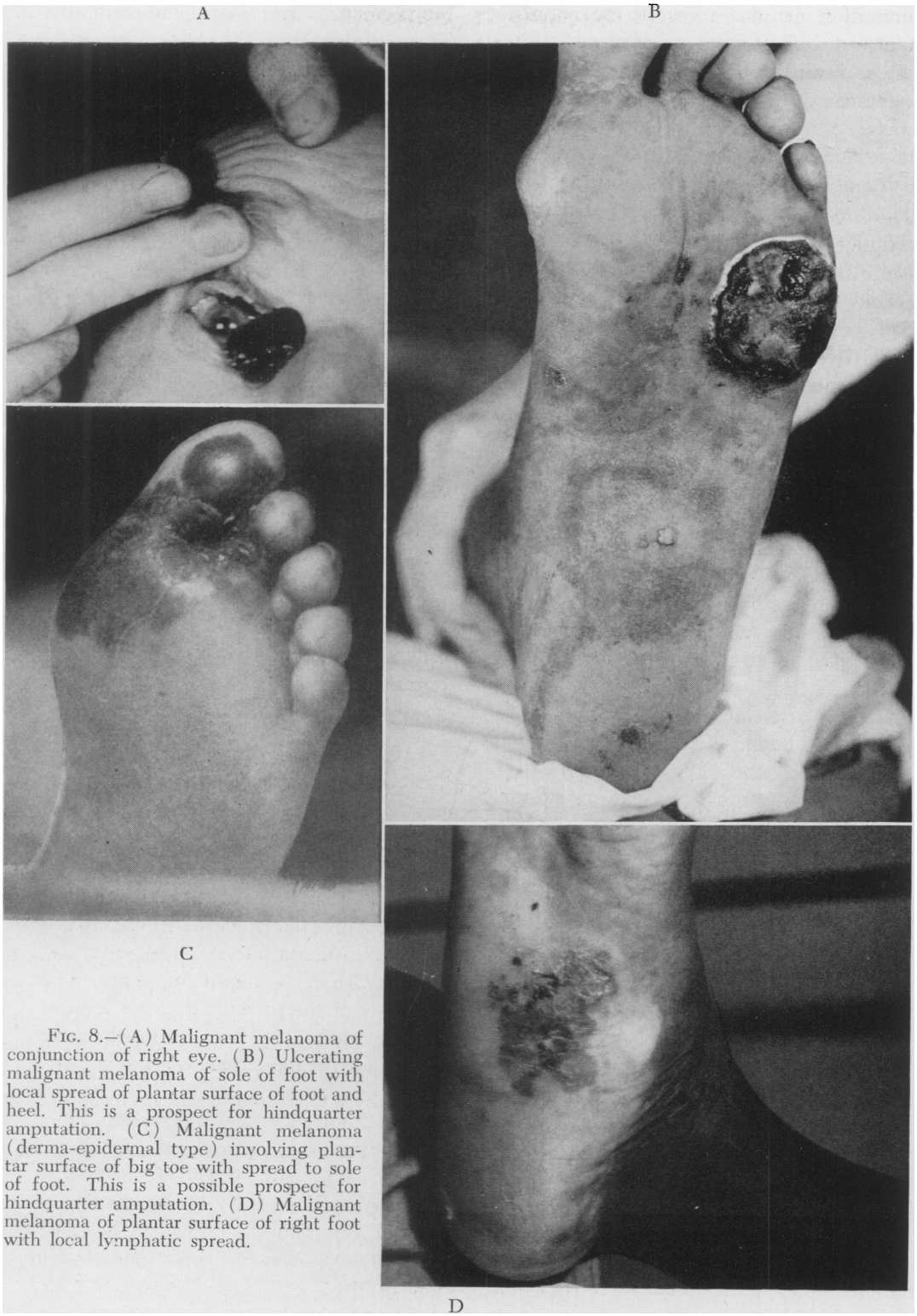

FIG. 8.—(A) Malignant melanoma of conjunction of right eye. (B) Ulcerating malignant melanoma of sole of foot with local spread of plantar surface of foot and heel. This is a prospect for hindquarter amputation. (C) Malignant melanoma (derma-epidermal type) involving plantar surface of big toe with spread to sole of foot. This is a possible prospect for hindquarter amputation. (D) Malignant melanoma of plantar surface of right foot with local lymphatic spread.

inflammation or ulceration of the lesion. Any change whatsoever that can be detected clinically in a previously quiescent pigmented mole should be considered malignant. All pigmented moles located in areas that are subject to trauma should be considered malignant at the outset.

The juvenile melanoma has the clinical appearance of active growth, that is, increase in size and elevation of the involved epidermis, and should be considered a potentially malignant lesion (it is histologically). After puberty it frequently assumes all the characteristics of the adult type, that is, rapid growth with local, regional and general metastatic spread.

The clinical signs of definite malignant changes, which are secondary, are well shown in Figures 7 and 8. The lesions in all these are either recurrent, ulcerated or metastatic. Most of these patients had had ill-advised surgical or other treatment. Such changes are commonly observed when patients with malignant melanomas are first seen. Ulceration in the malignant melanoma is common, especially when located in areas subjected to constant trauma and irritation. The majority of patients seen at the Memorial Hospital and at our Clinic presented clinical manifestations of local recurrence and distant metastasis. One of our patients had a metastatic nodule in the abdominal wall 20 years following removal of his eye elsewhere; no other metastatic deposits could be found at the time. Another patient had a melanoma removed from the shin of the right leg by cauterization 12 years before we saw him; at the time of his visit to the Clinic there was evidence of local recurrence. Therefore, in a high percentage of cases the presenting clinical manifestations are those of complicating metastasis with or without local recurrence. For this reason, all pigmented lesions should be considered as potentially malignant melanomas. The common mole, if it reveals activity of growth, should be considered as an early malignant lesion and treated accordingly. However, the common pigmented nevus in itself seldom becomes malignant.

It is the duty of the physician to differentiate between the benign lesion and the one that may become active or is active at the time the patient is first seen. This must be done to prevent the high percentage of meddlesome surgical interference that is responsible for the development of complicating metastases. The malignant melanoma is easily differentiated clinically from the benign nevi, so mistakes should be reduced to a minimum, thus preventing local and distant metastasis.

Much has been written about the treatment of malignant melanomas but it is generally agreed that a radical surgical procedure is necessary to eradicate the disease. The method of treatment will depend upon the underlying pathologic condition, that is, whether or not lymphatic spread, lymph node stations to which they metastasize, or early erosion of blood vessel walls and formation of intravascular malignant cell thrombosis are present. Performance of surgical procedures based upon such considerations will result in complete eradication of the disease at the first operation.

We believe that prophylactic coagulation by means of the cautery as treatment for a melanoma which appears clinically benign all too often precipitates a comparatively benign lesion into a full blown malignant one with early metastasis. From 60 to 65 per cent of the patients that we see give a history of having had a "black mole" burned off with the actual cautery or electric needle. Some patients state that a melanotic mole was destroyed months or years before they presented themselves with local or general spread of the disease. A typical case is that of a young woman admitted to Foundation Hospital in profound coma, who expired a few hours later and in whom autopsy revealed a large malignant melanoma of the brain. A history obtained

from her husband disclosed that she had had a black mole removed from her back one year before with the actual cautery. *It might be pointed out here that the use of the actual cautery, electric needle (coagulation), radium or roentgen ray in the treatment of melanotic moles of the dermo-epidermal type is to be condemned.* Moreover, biopsy of part of a lesion for histologic examination should never be done. Amadon[7] has shown that the use of coagulation by the actual cautery or electric needle produces gasses within the field of the melanoma with dispersion of live melanotic cells a good distance from the primary lesion. These cells, in a different environment, soon begin to grow actively, with either local recurrence or regional node involvement, or both. All 27 patients treated by coagulation of the primary growth, reported by Amadon,[7] had a recurrence at the primary site with regional and general metastasis.

All juvenile melanomas should be removed before puberty, since as previously stated, these growths take on renewed activity after puberty. In one of our adult patients with diffuse metastasis we were successful in reverting her to a juvenile status by irradiation of the pituitary, but this had no effect on regional and general spread of the disease, as the patient died within three months.

All melanotic moles on the palm of the hands, soles of the feet, scrotum or vulva, beneath the finger and toenails and the eye should be considered as malignant and should be removed with a wide segment of the integument and underlying fascia. Moreover, all melanotic moles which are subject to constant trauma by clothing should be removed in the same way.

Malignant melanomas of the body, hand, arms, head and neck, scrotum, vulva, legs and feet with no regional lymph node involvement should be treated by wide excision of the primary growth with fascia and lymph node dissection.[1, 8, 9] This treatment was recommended as early as 1907 by Handly[10] and in 1908 by Pringle.[8] They showed that since the deep dermal lymphatics are involved, a wide section of the epidermal structures including the fascia should be removed along with the regional lymph node. For lesions near the regional lymph nodes Pringle[8] in 1908 recommended removal of the primary growth, skin fascia and lymph glands in continuity. His advice is good today, because we advocate, as others, complete removal of the primary lesion and glands in continuity. For subungal melanomas, amputation of the finger or toe with regional dissection is recommended. For local recurrence or a widespread local lesion with metastatic regional node involvement of the upper or lower extremity, amputation with regional node dissection or forequarter and hindquarter ablation of the extremity is indicated.[1, 11, 12] In patients with malignant lesions on the scrotum, wide excision and regional node (bilateral inguinal and iliac) dissection should be done. Patients with malignant melanomas on the vulva should have vulvectomy and bilateral inguinal and iliac node dissection. For melanomas of the eye eventration of the involved eye is recommended by all ophthalmologists.

CONCLUSIONS

1. All melanotic moles of the dermo-epidermal and junctional types should be removed before puberty. All melanotic moles of this type in the adult (benign) which might be irritated by the clothing, or are situated on the palms of the hands, soles of feet, scrotum or vulva, or beneath the finger or toenails should be removed under general anesthesia.

2. Biopsy should never be done on patients with these benign lesions.

3. For malignant melanomas as radical a procedure as the patient's condition will permit is indicated. There should be no

hesitancy in performing forequarter or hindquarter amputations on patients with malignant melanoma located on or in the extremities.

4. *A local anesthetic should never be used for local excision.*

5. *The cautery, coagulation with the electric needle, radium and roentgen ray have no place in the treatment of these lesions.*

6. *Meddlesome surgical interference converts a benign into a malignant melanoma and is responsible for 75 per cent of the local recurrences.*

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DISCUSSION.—DR. JAMES M. MASON III, Birmingham, Ala.: It has been my good fortune to hear many of Dr. Gage's papers, and I have learned to appreciate the valuable points about surgery which he discusses from time to time.

In considering lymph node dissection in the treatment of any type of malignancy I have found Dr. Grantley Taylor's book on lymph node metastases to be of invaluable help. (Lymph Node Metastases; Grantley W. Taylor and Ira T. Nathanson, Oxford University Press, New York City, 1942.)

DR. R. LEE CLARK, Houston: Dr. Gage's paper points to the fundamental problem in the care of the patient with malignant melanoma. Early and adequate treatment is the only possible way to hope to combat this disease. It is not amenable to roentgen ray therapy. The principles for treating melanoma surgically are those for treating any malignant disease. The area of local disease must be excised along with the regional area of spread and the intervening lymphatics. This is the so-called "en bloc" resection, or in-continuity removal, and calls for the removal of the zone of lymphatic spread of the disease. Because melanoma may appear on any portion of the body, it is not always possible to do this; and in the case of a melanoma in the center of the back, removal of the glands in both axillae would have to be considered. When melanoma occurs on the extreme ends of the limbs, such as the heel, it is not possible to do an in-continuity dissection. If it is found that the regional lymphatics are involved, amputation of the limb must be considered.

Even with such radical measures, the survival rate is less than 20 per cent. Malignant melanoma is particularly difficult because it also spreads by blood stream, and even though the principles maintained by Halstead for removal of carcinoma of the breast and of Miles for carcinoma of the rectum are carried out—to wit, the excision of the local lesion with its zone of lymphatic spread, one all too often meets with failure because of visceral metastasis by the blood stream.

DR. WILLIAM S. MCCUNE, Washington, D. C.: Dr. Gage has covered this subject so thoroughly that it is difficult to add to his discussion. However, we have been interested in malignant mela-