

CHAPTER FOUR

Spontaneous Regression of Malignant Melanoma

Malignant melanoma is a tumor derived from melanin-producing cells or cells capable of producing melanin, i.e., melanocytes. Masson^{30, 31} has demonstrated that these primitive pigment cells are ectodermal in origin and arise embryologically from cells derived from the neural crest.

Malignant melanoma of the skin is a relatively uncommon tumor which usually arises from a pre-existing compound or junctional nevus. The malignant melanomas of the skin constitute approximately 1 to 2 per cent of all malignant tumors,^{9, 28, 37} and approximately 20 per cent of all malignant tumors of the skin.³⁷

The results of surgical treatment of malignant melanoma of the skin have been reported by numerous authors in recent years. Clifton, Knight, and Mathews¹⁰ in 1959 noted a five year survival rate of 29.0 per cent in 93 white patients treated prior to July 1, 1952. Daland¹² in the same year in a study of 170 private patients reported that 55.5 per cent of patients treated only by local excision were free of disease after five years, and 52.3 per cent of patients treated by local excision and regional node dissection were free of disease five years later. In this latter group the five year cure rate was 71 per cent when the nodes were microscopically negative for tumor cells and 26 per cent when the nodes were microscopically positive. Daland found a five year cure rate of 52.3 per cent when all cases were included which were treated for cure.

Pack³⁸ in 1959 reported a five year cure rate of 37.7 per cent for 138 cases treated at Memorial Cancer Hospital in New York from January 1, 1948, to January 1, 1951. Also in 1959 Gumpert and Meyer¹⁷ noted in 85 patients treated by excision of the primary tumor and re-

gional node dissection that the five year survival rate was 43 per cent when the lymph nodes were microscopically negative and 22 per cent when the nodes were microscopically positive. In 41 cases in which node dissection was not performed because of various reasons, Gumpert and Meyer found a five year survival rate of 27 per cent.

Block and Hartwell,⁴ in a 1961 report of 217 cases, noted a five year survival rate of approximately 50 per cent following "adequate" surgical treatment when regional lymph nodes were not involved and a five year survival rate approaching 25 per cent when metastatic involvement of regional nodes was treated by lymphadenectomy. Likewise in a study of 145 patients in 1961, Cade⁷ found a five year survival rate of 40.0 per cent and a five year disease-free rate of 24.8 per cent; in addition, in a study of 49 patients he found a 10 year survival rate of 22.4 per cent and a 10 year disease-free rate of 14.2 per cent. In the same year James,²² in an analysis of 130 cases from Ohio State University Hospital, noted an overall five year survival rate of 32.9 per cent and a 10 year survival rate of 19 per cent.

In 1962 Charalambidis and Patterson⁸ reported that, of 43 patients with melanoma of the skin treated by wide local excision and regional lymph node dissection before distant metastasis or histologic invasion of nodes was apparent, 74.8 per cent survived five years or more. Petersen, Bodenham, and Lloyd⁴⁰ in 1962 reported a five year cure rate of 51.6 per cent in a series of 93 patients, and Teimourian and McCune⁴⁵ in 1962 reported an overall five year survival rate of 50.4 per cent in a study of 115 patients.

Some of the cases of spontaneous regression of malignant melanoma have been reported incidental to the evaluation of a series of patients with malignant melanoma. Accordingly some estimate of the frequency of spontaneous regression of malignant melanoma may be obtained by calculating the incidence of spontaneous regression in these series. Thus, Daland and Holmes¹³ reported one case of spontaneous regression among 174 patients with malignant melanoma (incidence of 0.58 per cent); Pack³⁸ had one case of possible spontaneous regression in a series of 1190 cases (incidence of 0.08 per cent); Cade⁷ noted one case of spontaneous regression in 226 patients (incidence of 0.44 per cent); Vogler, Perdue, and Wilkins⁴⁷ found one case of spontaneous regression among 253 cases (incidence of 0.4 per cent); and Petersen, Bodenham, and Lloyd⁴⁰ reported two patients with spontaneous regression in a series of 621 patients with malignant melanoma (incidence of 0.32 per cent).

Seventeen cases of possible spontaneous regression of malignant melanoma of the skin and two cases of possible spontaneous regression of metastatic malignant melanoma of the choroid were collected.

**COLLECTED CASES OF SPONTANEOUS REGRESSION
OF MALIGNANT MELANOMA OF SKIN****I. F. S. Mathews (1915)³²**

A male, 45 years of age, was seen because of a pigmented nevus located over the middle of the scapula. The patient stated that the nevus had always been present but had shown a recent increase in size. On physical examination, in addition to the pigmented nevus, a fullness above the corresponding clavicle and a large mass of axillary nodes were noted. The axillary mass was about the size of a small fist and was freely movable, and some of the nodes were at least as large as hickory nuts.

The case was considered hopeless. However, the nevus was excised and the main mass of axillary nodes was removed through an axillary incision about 3 inches long. No operation was performed on the supraclavicular swelling and the operation on the axillary region was grossly incomplete.

The surgical specimens were examined by Dr. Francis Carter Wood, who made a diagnosis of primary melanoepithelioma with axillary metastases. On microscopic examination of the primary tumor a moderate number of pigment-bearing cells were noted to be scattered throughout the tumor (Fig. 1). Almost no pigment was present, however, in the tumor tissue removed from the axilla. The metastatic tumor cells were noted to be diffusely invading the surrounding connective tissue.

Because the axillary mass had developed to the size of a fist within a period of five weeks, rapid progression of the disease was expected after the operation. However, two years later the patient appeared well. *The supraclavicular swelling had disappeared and only a nodule the size of a hazelnut could be felt in the axilla.*

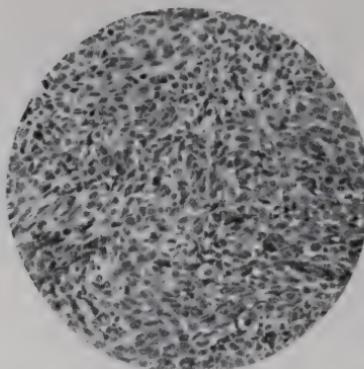


FIGURE 1. Case 1. Photomicrograph of a surgical specimen. (Mathews, F. S.: Ann. Surg., 62:114, 1915. Published by the J. B. Lippincott Co.)

2. *E. M. Daland and J. A. Holmes (1939);¹³ E. M. Daland (1958);¹¹ W. F. MacGillivray (1958)²⁷*

D. J., a 42 year old male, was admitted to the Worcester City Hospital on February 28, 1928, with a tumor of one year's duration at the base of the small toe of the right foot. This lesion was excised, and on microscopic examination a diagnosis of melanotic sarcoma was made (Figs. 2 and 3). The patient returned to the hospital on July 28, 1928, with a pigmented area around the scar of the incision. A tarsometatarsal amputation of the fourth and fifth toes of the right foot was performed at this time. A node in the right groin was also excised and was reported as metastatic melanosarcoma. The patient returned to the hospital on November 8, 1928, with a recurrence of the tumor in the amputation scar, and on November 11, 1928, the anterior part of the scar, including the area of discoloration, was excised. The patient was admitted to the hospital with erysipelas of the right buttock on December 9, 1928, and was again admitted to the hospital on January 11, 1929, with erysipelas of the right hip and thigh.

At the Pondville Hospital the patient was first seen on January 2, 1929. Physical examination at this time revealed an operative scar in the right groin and the presence of many dark nodules which appeared and felt like lead shots. They were distributed on the anterior surface of the thigh along the course of the sartorius muscle and were especially prominent over the femoral triangle. The foot showed the loss of the fourth and fifth digits and the metatarsus. An infected scar was indented and appeared to be surrounded by infiltrating tumor. Radiation treatment was not deemed advisable and the patient was discharged on January 7, 1929.

The patient was followed at periodic intervals in the clinics of both the Worcester City Hospital and the Pondville Hospital. The development and progression of metastatic disease throughout the skin of the thigh was observed during 1929. On November 20, 1930, the patient was readmitted to the Worcester City Hospital with multiple cystlike masses on the inner aspect of the thigh and palpable nodules in the foot, in the right groin, and above the right knee. The nodules were excised and identified histologically as melanosarcoma (Figs. 4 and 5).

The patient was again admitted to the Worcester City Hospital in November 1932 for a left inguinal herniorrhaphy. At this time a nodule was removed from the left groin which was identified microscopically as metastatic melanosarcoma (Figs. 6 and 7). Physical examination at this time revealed discrete, black-pigmented indurated areas scattered over the right thigh.

On February 23, 1933, it was noted that *many of the growths on the front of the right thigh had grown smaller and in some instances*
(Text continued on page 171.)

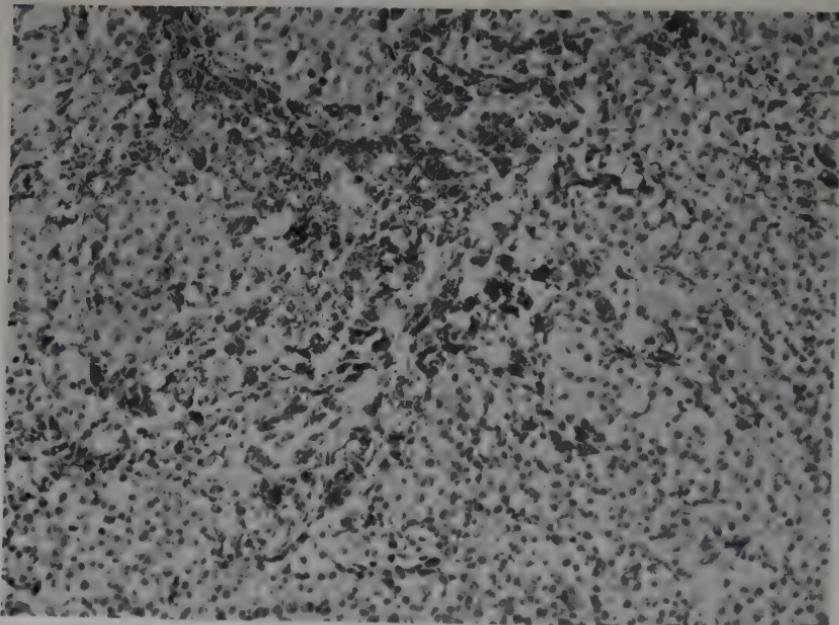


FIG. 2

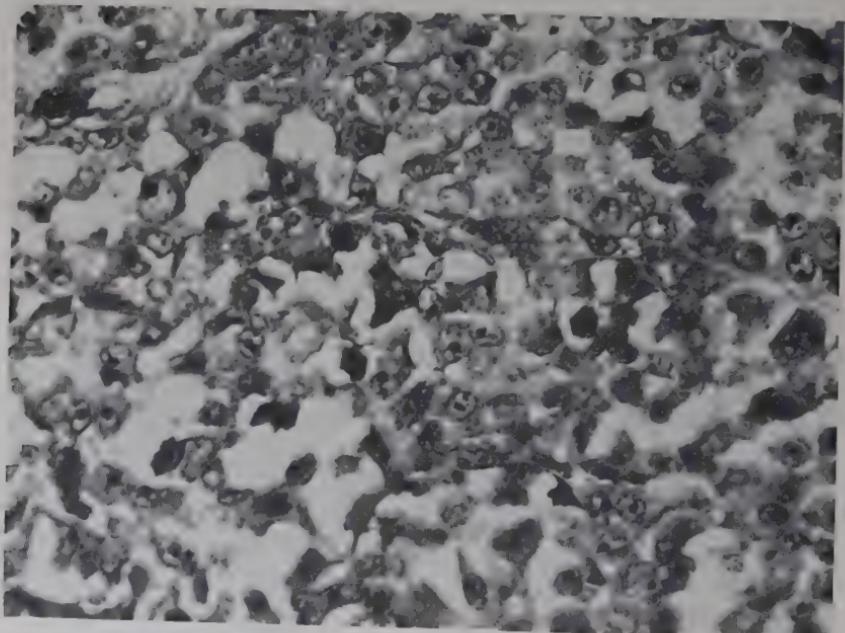


FIG. 3

FIGURES 2 and 3. Case 2. Photomicrographs of a tumor excised on February 28, 1928 (Fig. 2, 150 \times ; Fig. 3, 450 \times). (Courtesy of W. F. MacGillivray.)

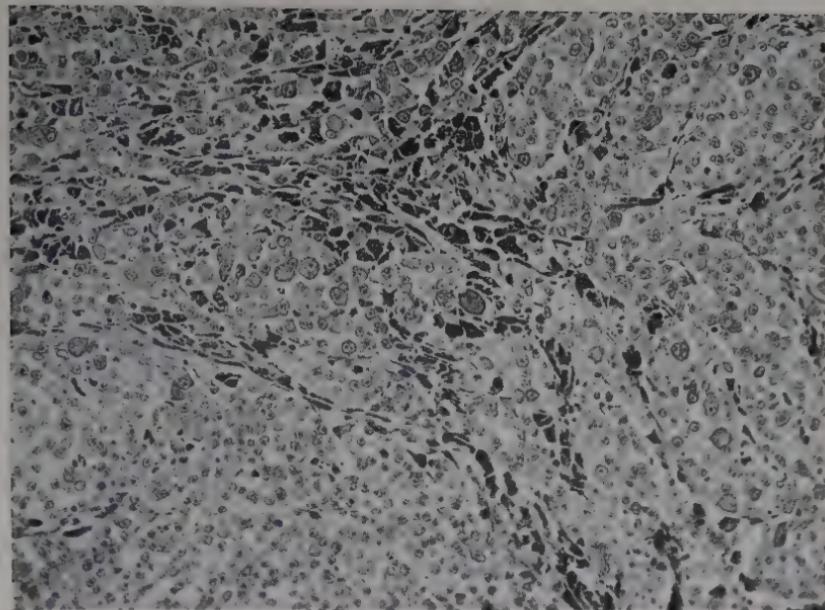


FIG. 4

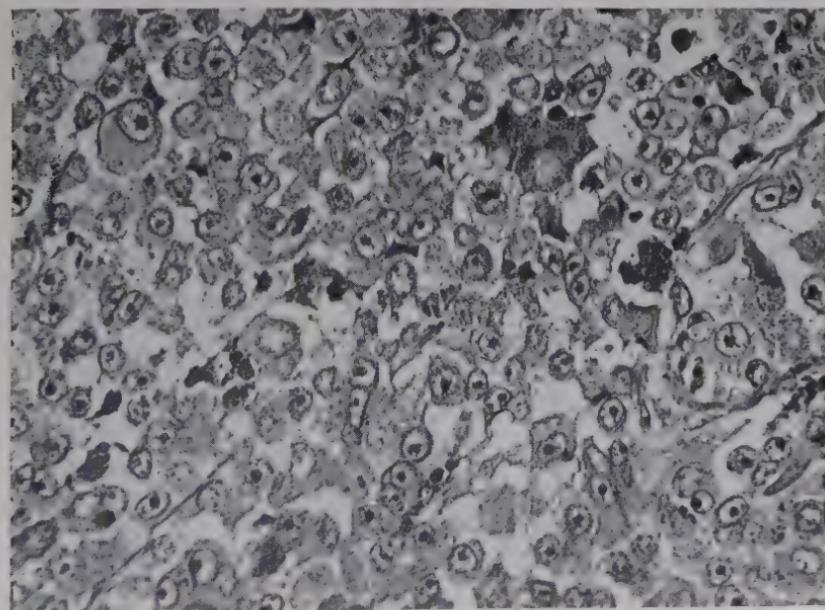


FIG. 5

FIGURES 4 and 5. *Case 2.* Photomicrographs of a nodule excised in November 1930 (Fig. 4, 150 \times ; Fig. 5, 450 \times). (Courtesy of W. F. MacGillivray.)

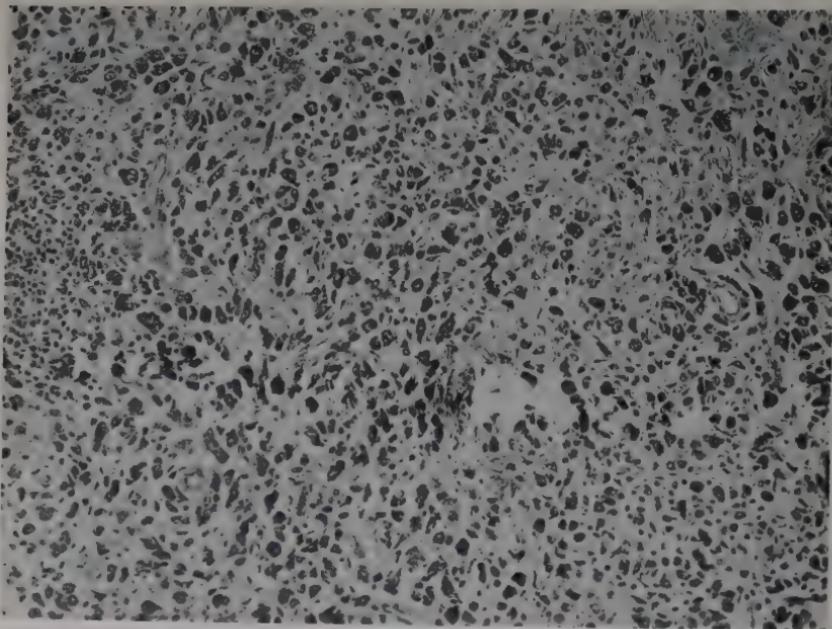


FIG. 6



FIG. 7

FIGURES 6 and 7. *Case 2.* Photomicrographs of a nodule excised from the left groin in November 1932 (Fig. 6, 150 \times ; Fig. 7, 450 \times). (Courtesy of W. F. MacGillivray.)

had almost disappeared. The patient was examined on December 7, 1933, by Dr. Daland, who noted that pigmented areas on the thigh still remained but that tumor nodules could no longer be palpated beneath the pigmented areas.

The patient was readmitted to the Worcester City Hospital in December 1934 with signs of a cerebrovascular accident. At this time a small tumor mass was palpable in the right groin and a large tumor mass was noted in the region of the right knee. The patient expired on February 4, 1935, presumably of cerebral metastases. No autopsy was performed.

Thus, this patient apparently had regression of some subcutaneous tumor nodules in 1933, although he subsequently died of cerebral metastases in 1935.

3. *G. T. Pack (1950);³⁵ G. K. Higgins and G. T. Pack (1951);¹⁹ G. T. Pack (1955)³⁴*

A. D., a 32 year old female, was first seen at the Memorial Cancer Center in New York on May 3, 1940. The patient had had a pigmented nevus in the skin over the right Achilles tendon all her life. Approximately one year previously she had been kicked in this area and after that the lesion increased in size, became elevated and crusted, and bled frequently.

The patient was admitted to the Memorial Cancer Hospital and a wide excision of the lesion and an application of a skin graft was performed on May 7, 1940. On microscopic examination the lesion was identified as malignant melanoma (Figs. 8 and 9).

On June 29, 1940, the patient was readmitted to the hospital for an elective groin dissection. Microscopic study of the lymph nodes did not reveal metastatic melanoma.

On September 14, 1942, multiple skin nodules were present in the midportion of the right lower leg, the pretibial region, the upper third of the anterior surface of the thigh, just below the tibial tubercle, on the lower aspect of the right tibia above the ankle, in the popliteal space, and on the lateral aspect of the thigh at the junction of the upper and middle thirds of the thigh. Three of the nodules were excised and on microscopic examination were found to contain metastatic melanoma (Figs. 10 and 11).

On subsequent examination at the Memorial Cancer Center it was noted that many of the other nodules had apparently disappeared. The only medical therapy the patient had received between visits was 14 injections of antirabies vaccine after a dog bite in September 1943.

On examination in July 1952 a freely movable nodule 0.6 cm. in size and attached to the overlying skin was noted over the right ulnar

(Text continued on page 175.)

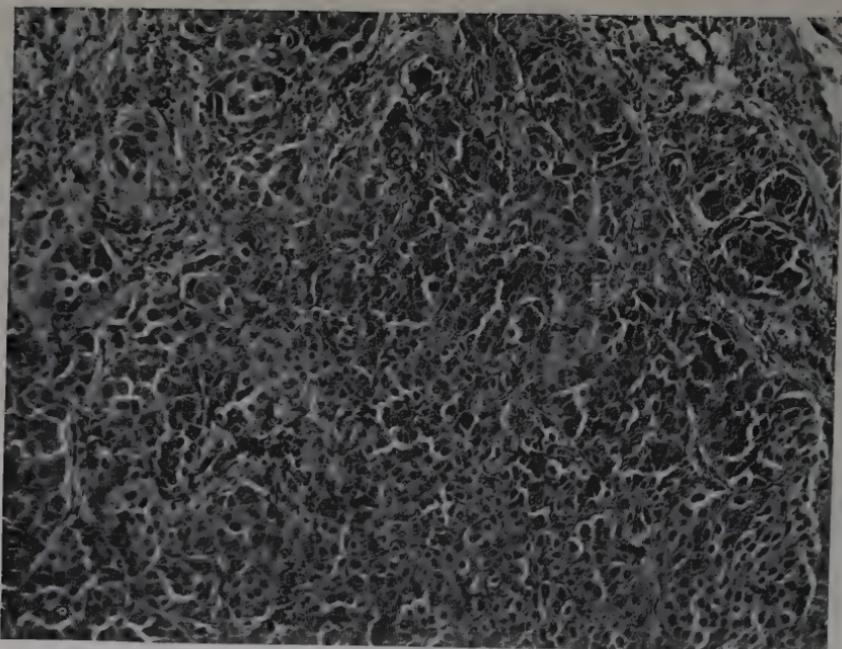


FIG. 8

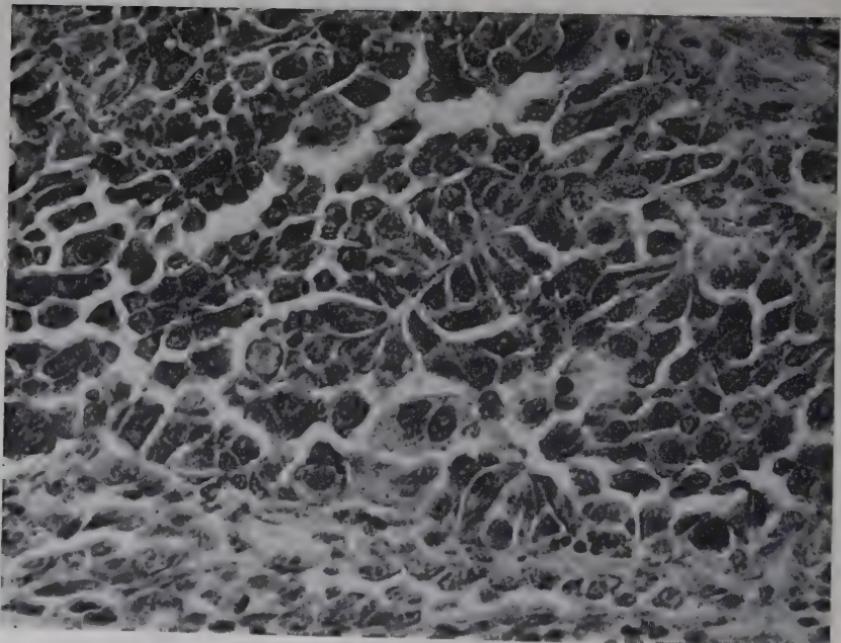


FIG. 9

FIGURES 8 and 9. *Case 3.* Photomicrographs of a tumor excised from the right foot on May 7, 1940 (Fig. 8, 150 \times ; Fig. 9, 450 \times). (Courtesy of G. T. Pack.)

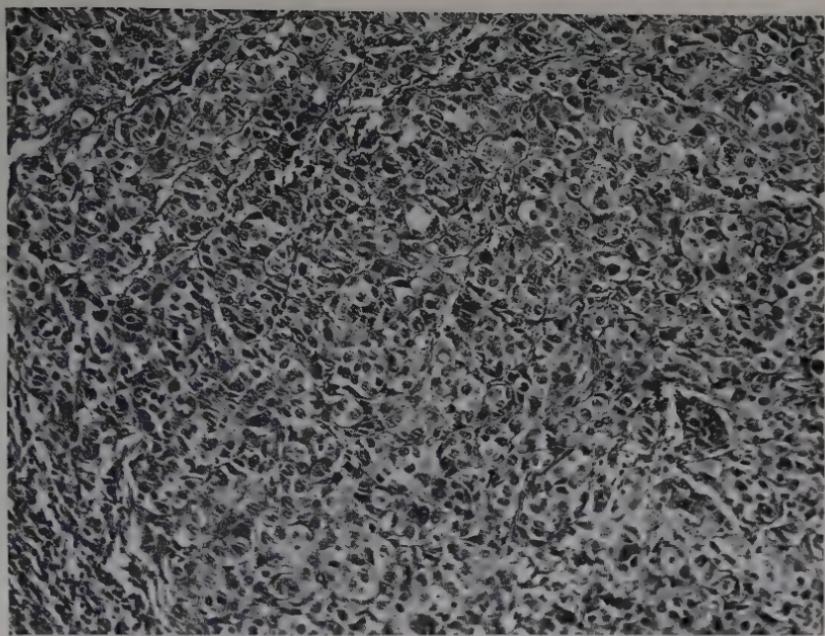


FIG. 10

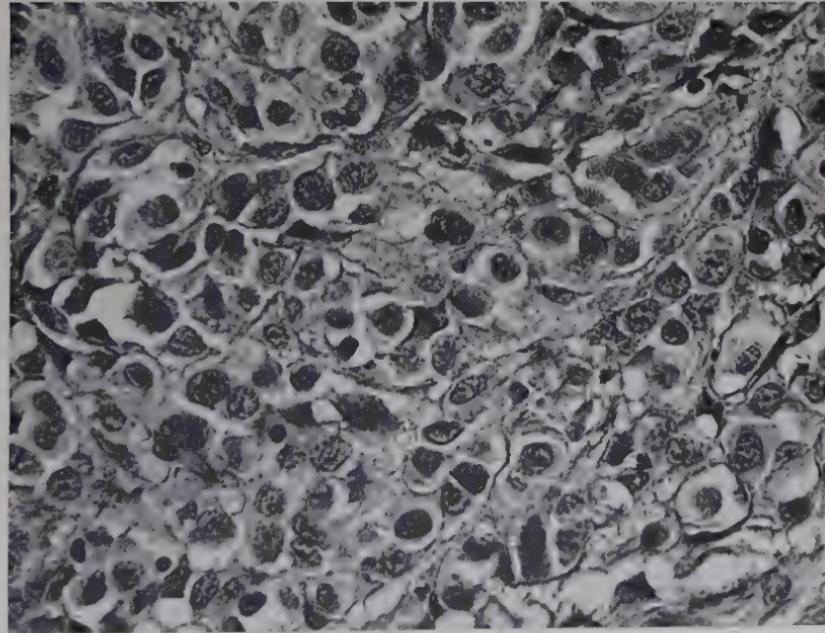


FIG. 11

FIGURES 10 and 11. *Case 3.* Photomicrographs of a skin nodule excised on September 14, 1942 (Fig. 10, 150 \times ; Fig. 11, 450 \times). (Courtesy of G. T. Pack.)

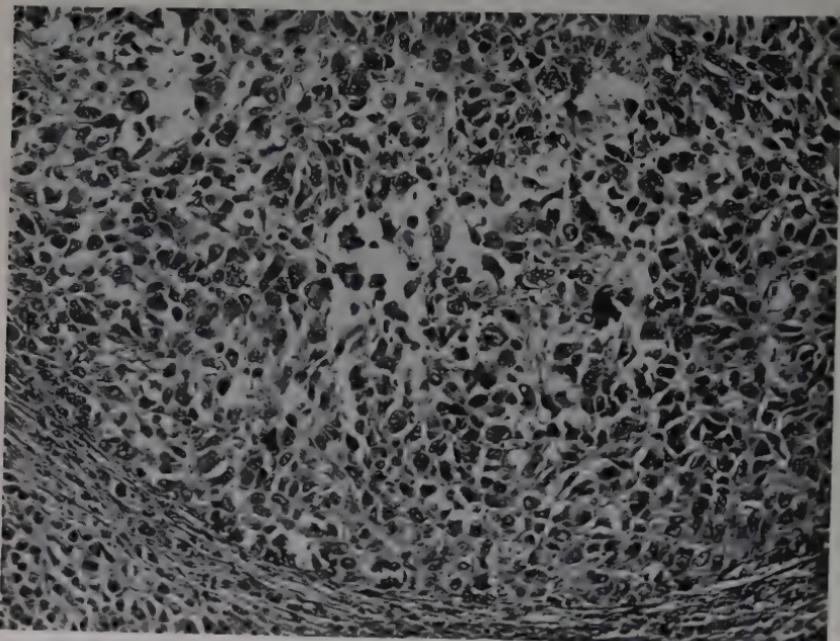


FIG. 12



FIG. 13

FIGURES 12 and 13. Case 3. Photomicrographs of a nodule excised in July 1952 (Fig. 12, 150 \times ; Fig. 13, 450 \times). (Courtesy of G. T. Pack.)

styloid. The nodule was excised and on microscopic examination was found to be metastatic melanoma (Figs. 12 and 13).

The patient was admitted to the James Ewing Hospital in New York on June 18, 1953, with generalized melanomatosis. She expired, and postmortem examination revealed metastatic melanoma involving the heart, urinary bladder, stomach, small intestine, trachea, breasts, etc.

Thus, the multiple subcutaneous metastases disappeared in 1943, although the patient subsequently died of generalized melanomatosis in 1953.

4. J. E. Levi and E. F. Lewison (1952)²⁴

M. T., a 43 year old white female dwarf, was seen in the outpatient department of the Johns Hopkins Hospital in March 1947 because of a large purple-black mass in the skin of the abdomen which had been present for approximately one month. The tumor measured 8 by 10 cm. and was first noted by the patient in January 1947.

The patient was mentally as well as physically retarded. She stated that a mole on her left leg had been burned off with acid in 1946. The patient also stated that she had never menstruated and had had multiple fractures at the ages of 31 and 37. She had been told that her bones were rarefied.

Physical examination revealed that the genitalia were infantile and the vagina was too small to permit examination. Neither the uterus nor the adnexa were palpable on rectal examination. In addition to the abdominal tumor there was a mass in the left axilla and another in the left buttock.

The lesion in the axilla was excised and on microscopic examination was found to be a malignant melanoma. In an attempt at estrogen replacement therapy the patient was started on 17-ethynodiol diacetate 0.15 mg. daily, which she took for about three months. The mass in the abdominal wall increased in size.

In October 1947, seven months later, the patient returned because the abdominal mass had grown still larger and appeared ready to ulcerate. She had not taken any medication for four months. In addition to the masses in the abdominal wall and the left buttock there were tumors in the left posterior chest wall, the right axilla, and the left inguinal region. On October 24, 1947, a palliative resection of the large mass on the abdominal wall was performed. Microscopic examination of the tumor revealed malignant melanoma.

The patient then disappeared and was not seen until August 1949. At this time she stated that she had never felt better. Physical examination revealed that the previously noted masses in the left buttock, posterior thoracic wall, and right axilla had disappeared. The mass in the left inguinal region measured slightly over 1 cm. in diameter.

In October 1949 the patient returned again for follow-up examination and was found to have glycosuria. A few months later she was readmitted to the hospital for regulation of her diabetes and an investigation of her endocrine status. Urine tests revealed a 4 plus sugar but no evidence of melanin. Follicle-stimulating hormone (FSH) studies showed positive results up to 192 mouse units per 24 hours but negative results at 384 units (6 to 52 mouse units per 24 hours is normal). A chest x-ray revealed no evidence of pulmonary metastases. On January 26, 1950, a biopsy was done on the left inguinal mass, and microscopic examination revealed only scarring and melanin pigment. The patient was discharged on February 5, 1950.

She was readmitted to the hospital on February 25, 1951, with a three month history of abdominal pain, anorexia, and intermittent vomiting. On physical examination the abdomen was noted to be distended. A urinary FSH test on April 21, 1951, gave negative results at 96 and 385 mouse units per 24 hours. The 24 hour urinary 17-ketosteroid assay was moderately depressed to 2.8 mg.

An exploratory celiotomy was performed on April 25, 1951. The entire left upper quadrant of the abdomen was occupied by a dark-colored tumor mass which involved the mesentery, the liver, and a major portion of both large and small bowels. There were also a number of enlarged lymph nodes, one of which contained black pigment. This node was removed and a liver biopsy was done. On microscopic examination of both lesions a diagnosis of malignant melanoma was made. At the time of celiotomy the pelvic organs were noted to be infantile. The patient left the hospital on May 4, 1951, and died at home on May 19, 1951. Permission for an autopsy was denied.

Thus, tumor masses in the left buttock, the posterior thoracic wall, and the right axilla disappeared sometime between October 24, 1947, and August 1949, although the patient subsequently died on May 19, 1951, of disseminated melanomatosis.

5. *W. C. Sumner (1953);⁴³ W. C. Sumner and A. G. Foraker (1960)⁴⁴*

R. R., a 30 year old white female, was first examined on February 14, 1949, because of a painless lump in the right breast which had been present approximately one year and which appeared to have increased rapidly in size and to have become slightly painful in the preceding five months. The patient had had a painless mass in the left inguinal region for three years, and five or six months previously she had noted a mass in the left arm near the shoulder. Also she had noticed several small tumors in her abdominal wall and her back in the previous three or four months. The patient was five and a half months pregnant at the time of the examination. She had had three uneventful pregnancies.

Physical examination revealed a firm, slightly tender, freely movable mass with irregular borders in the upper outer quadrant of the right breast. The mass measured 6 by 6 cm., felt somewhat cystic, and was not fixed to the skin or the underlying tissue. No lymphadenopathy was palpable in either the axilla or the supraclavicular regions. Three masses in the abdominal wall were similar to those felt in the breast. The abdominal masses were located in the midline above the umbilicus, over a lower costal cartilage on the left, and in the left lower quadrant. They varied from 1 to 2 cm. in diameter. On the left arm and shoulder and extending posteriorly there was an area of scaly lesions characteristic of a healing ringworm infection. On the anterior surface of the left arm there was a 2 by 3 cm. mass similar to that in the right breast. Subcutaneous tumors similar to those in the abdominal wall were scattered over the back. Another mass 4 by 5 cm. was noted in the left femoral region.

The patient was admitted to St. Luke's Hospital in Jacksonville, Florida, and on February 28, 1949, the tumors of the right breast, left arm, and left femoral region were excised. The lesions were grossly similar. Microscopic sections revealed metastatic malignant melanoma (Fig. 14).

The incisions healed per primam. A search for the primary tumor was made but none was found. However, just above the internal malleolus of the left leg, a depigmented area 1 by 1.5 cm. was found (Fig. 15). The patient stated that three and one-half years previously she had had a "black mole" which became infected and disappeared. She also stated that during a previous pregnancy a lump had appeared in the left groin but had not been treated.

It was felt that the patient was incurable and that no definitive treatment should be given. However, the larger tumors of the abdominal wall and back were excised under local anesthesia on March 28, 1949. The tumors were very friable and most of them were torn during excision, with the escape of a black fluid into the incision. It was consequently expected that the patient would have prompt local recurrence with fungating ulceration. When seen on April 4, 1949, however, all the incisions were well healed.

The patient had a normal delivery of a full-term normal male child on May 20, 1949, under the care of a local physician.

The patient was again seen on November 11, 1949, because of a 2 cm. mass beneath the scar in the left femoral region. Roentgen examination of the chest and eye-ground studies were negative for metastases. On December 6, 1949, a superficial femoral node dissection was performed. The lymph nodes removed in this dissection measured up to 0.5 cm. in diameter. Microscopic studies of these nodes revealed that many of the nodes were free of tumor cells. However, one node showed a small cluster of viable tumor cells which appeared to be in various stages of degeneration (Fig. 16).

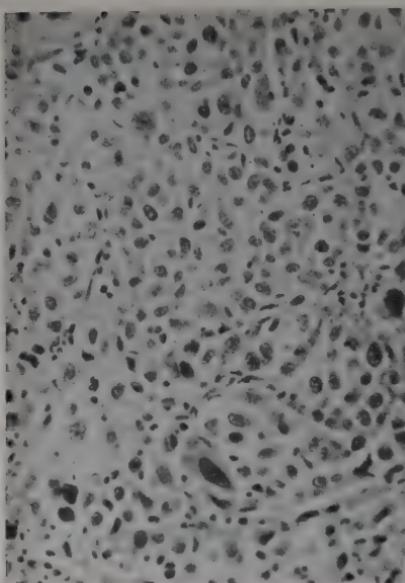


FIG. 14



FIG. 15

FIGURE 14. Case 5. Photomicrograph of a tumor excised on February 28, 1949.

FIGURE 15. Case 5. Photograph showing a depigmented area just above the internal malleolus of the left leg. (Figs. 14 and 15 from Sumner, W. C.: Cancer, 6:1040, 1953. Published by the J. B. Lippincott Co.)

The patient was without evidence of recurrence until July 3, 1950, when a mass approximately 2.5 cm. in diameter was noted in the right supraclavicular region. Again a roentgenogram of the chest and eye-ground studies revealed no evidence of metastases.

An attempt to remove the mass was made in the office on July 7, 1950. Most of the node was removed piecemeal, and it was believed that not all of the node was removed. Again it was expected that a fungating mass would develop. However, the incision healed.

On examination on December 13, 1952, no evidence of any tumor could be found. A roentgenogram of the chest showed no evidence of metastases and a urinalysis showed no melanin. It was noted that *in most of the areas where the patient had had malignant melanoma, the skin had become depigmented* (Fig. 17). Also, over an area on the inner surface of the right eyebrow, where the patient thought she had had a tumor which had never been excised, not only was the skin depigmented, but the eyebrow had no pigment.

The patient was last examined on February 4, 1953, four years after her first visit, and no changes from the findings of September 1952 were noted. The diagnosis of malignant melanoma was confirmed by several pathologists who reviewed the slides.

Related to the case of R. R. is that of J. H., a 28 year old male with microscopically proved metastatic malignant melanoma. He was seen on June 1, 1954, with recurrent tumors in the left parietal and left buttock regions and an enlargement of lymph nodes in the right axilla. This patient was given 250 cc. of the first patient's (R. R.) blood, which was of the same type and proved to be compatible by crossmatching. Six weeks later, on July 20, 1954, J. H. stated that he realized the "lumps" on his head and right thigh were disappearing. *Within six months all the lesions had disappeared or markedly regressed. Within another three weeks all of the lesions had disappeared.* Following the regression in the scalp, the overlying hair became white whereas all the rest of his hair remained black. The patient remained free of tumor until November 1955, when a small metastasis was noted in the proximal phalanx of the ring finger of the right hand. The finger was amputated, and on microscopic examination metastatic melanoma with much central necrosis and fibrosis was found.

Sera from both patients (R. R. and J. H.) were examined at the National Cancer Institute. No virus activity was found nor did the sera have any inhibitory effects on melanoma cultures.

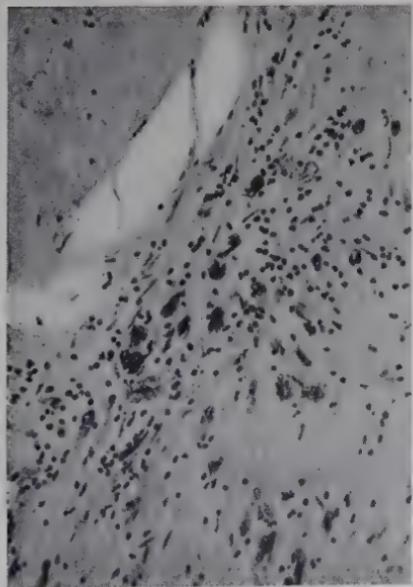


FIG. 16



FIG. 17

FIGURE 16. Case 5. Photomicrograph of the left femoral lymph node excised on December 6, 1949, showing a cluster of viable tumor cells in various stages of degeneration.

FIGURE 17. Case 5. Photograph showing an area of depigmentation. (Figs. 16 and 17 from Sumner, W. C.: Cancer, 6:1040, 1953. Published by the J. B. Lippincott Co.)

Another patient with far-advanced (almost terminal) melanoma with metastases to the brain, liver, and lungs received two pints of R. R.'s blood without any improvement.

6. E. P. Allen (1955)¹

A 38 year old married white female was first seen in May 1943. For several years she had had an elevated area about the size of a thumbnail and normal in color on the extensor surface of the right forearm. Part of this area became black possibly following a scratch with a pin about the middle of 1942. This area was excised by her doctor in July 1942, and the pathologist, Dr. J. O. Mercer, reported:

A circumscribed tumor composed of small naevoid cells with regular nuclei associated with a large quantity of melanotic pigment and surrounded by a zone of hyaline fibrous tissue. It is not invasive. This is a simple melanoma. There is no evidence of malignancy.

A black area appeared in the scar two months later and by May 1943 a tumor the size of a marble had developed. At this time a wide excision down to the deep fascia was performed. The pathologist reported:

A cellular tumor composed of actively mitotic oval cells and large collections of pigment mainly extracellular. The tumor had invaded the hyaline fibrous tissue and local fat. The appearances are quite unlike those previously reported on. It is malignant melanoma.

Because of the invasive characteristics of the tumor the patient was referred to the author for radiation treatment in May 1943. On examination at this time the patient appeared well with no evidence of residual tumor. An estimated tumor dosage of 4700 r was administered to the forearm over a period of 17 days through opposing 15 by 10 cm. fields. The patient was again examined on November 8, 1943, when she was 10 weeks pregnant. There was no evidence of recurrence at this time.

An examination in mid-March of 1944 (10½ months after the second excision), when the patient was seven months pregnant, revealed multiple bluish subcutaneous nodules up to the size of a marble on the left waistline, the right flank, and the right upper arm. To confirm the clinical diagnosis of metastatic tumor, a nodule in the right upper arm was excised on March 10, 1944. The assistant pathologist reported that the specimen was a lymph node which had been almost entirely replaced by tumor consisting of solid masses of darkly staining polyhedral cells. There was little pigment present. The tumor was thought to have become more cellular and less well differentiated.

By May 8, 1944, 14 days after the birth of a normal child, the patient had developed additional tumor masses in the right scapular and

inguinal areas. The patient was again examined on July 10, 1944. At this time it was found that *all the nodules had disappeared except a small nodule in the right groin.* The patient was known to be entirely well in June 1955 (12 years after the excision of the primary tumor and 11 years after the disappearance of the metastatic nodules).

The microscopic sections in this case were twice reviewed by Dr. J. O. Mercer. Late in 1944 he agreed with his assistant's opinion that the tumor in the lymph node was malignant melanoma, and in 1955 he stated:

The original report that the tumor was a pigmented nevus should certainly be qualified by a statement that, in the light of modern views on the histology of melanoma, it was clearly a malignant tumor when it was first removed.

7. H. W. Meyer (1955)³³

M. M., a 36 year old female, had a lesion of the left arm removed at the Lenox Hill Hospital in New York on November 14, 1934. On histologic examination a diagnosis of melanosarcoma was made (Fig. 18).

The patient was readmitted to the Lenox Hill Hospital in May 1935,

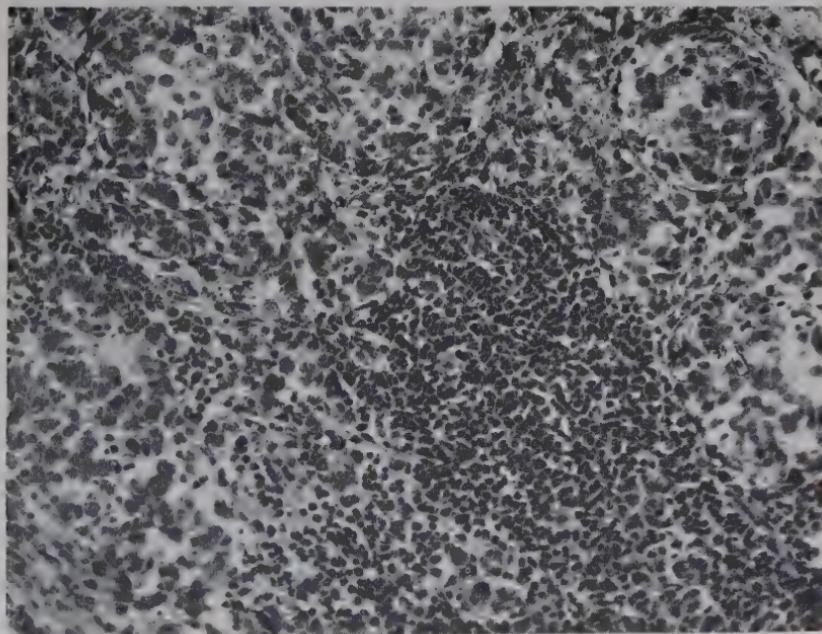


FIGURE 18. Case 7. Photomicrograph of a tumor of the left arm excised on November 14, 1934 (125 \times). (Courtesy of R. M. Paltauf.)



FIG. 19

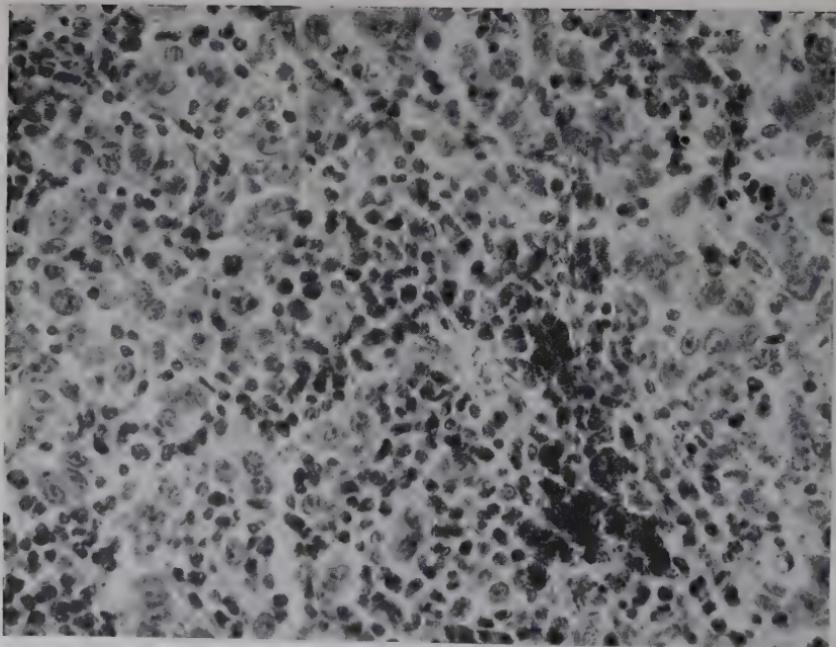


FIG. 20

FIGURES 19 and 20. *Case 7.* Photomicrographs of a left axillary mass partially excised on May 16, 1935 (Fig. 19, 125 \times ; Fig. 20, 450 \times). (Courtesy of R. M. Paltauf.)

and on May 16 a partial excision of a left axillary mass complicated by an abscess was performed by Dr. Muehleck. A considerable amount of tumor was left in the axilla. On histologic examination a diagnosis of malignant melanoma was made (Figs. 19 and 20).

Twenty years after the last operation the patient was known to be alive and well and *the axillary mass had completely disappeared.*

8. A. B. Vial and F. W. Coller (1955)⁴⁸

V. P., a 63 year old male, was first seen at the University of Michigan Hospital in October 1951. The patient had a history of having had an ulcerated brown lesion removed from the anterior aspect of the right thigh at the Harper Hospital in Detroit in March 1950. In December 1950 a mass in the right groin was excised at the same institution. The mass recurred and during April and May of 1951 it was irradiated. However, the tumor continued to grow unabated.

On October 10, 1951, a large mass (4 inches in diameter) of metastatic nodes was removed from the right groin. On microscopic examination, this tissue was found to be metastatic melanoblastoma (Figs. 21 and 22). (The tumor tissue which was removed at this operation was used as an antigen for the stimulation of antibodies in rabbits.) A large sloughing neoplastic ulcer resulted at the site of the excision in the groin. Many pigmented satellite skin nodules and a large liver were present.

On December 11, 1951, the antibodies tagged with 27 mc. of I¹³¹ were given the patient intravenously. On December 17, 1951, at least five parenchymal lung lesions characteristic of metastases were noted on a chest roentgenogram. On examination on January 3, 1952, a 40 per cent reduction in the size of the groin lesion was noted, and a chest roentgenogram on January 4, 1952, showed the presumptive pulmonary lesions to be less prominent. The patient was again given antibodies tagged with I¹³¹ on January 4, 1952.

A chest roentgenogram on January 18, 1952, demonstrated the continued regression of the presumptive metastases with a single residual lesion visible in the sixth left anterior interspace. On March 14, 1952, a chest roentgenogram showed the complete disappearance of the presumptive metastases.

On examination on May 20, 1952, no tumor was noted. However, a little pigment reappeared in several spots on the skin where tumor had been previously noted. Several of these areas were subjected to biopsy, and on microscopic examination it was reported, "Melanin pigment [noted] in phagocytes throughout the dermis in the specimen received. No nevus cells were identified other than these melanophores."

On February 24, 1954, a right inguinal recurrence 5 cm. in diameter

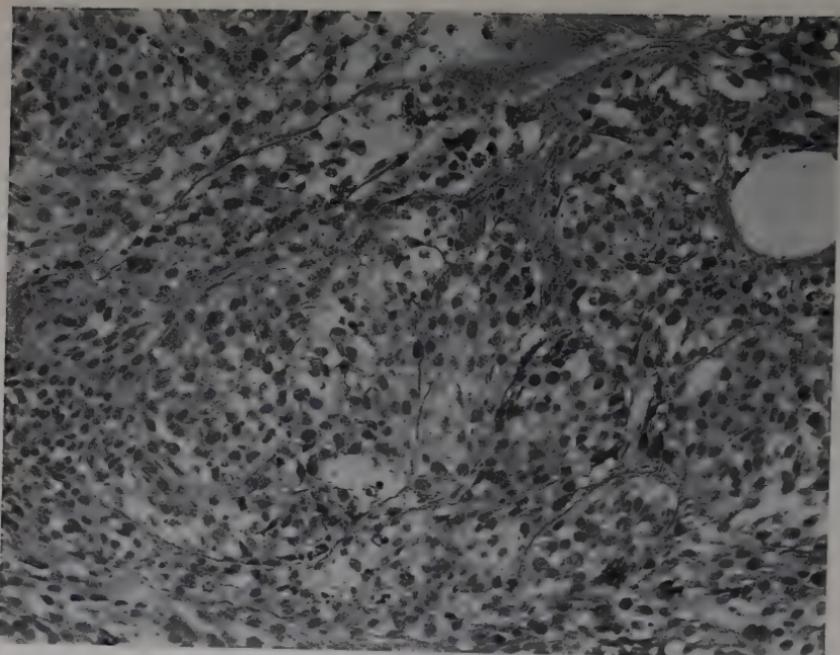


FIG. 21

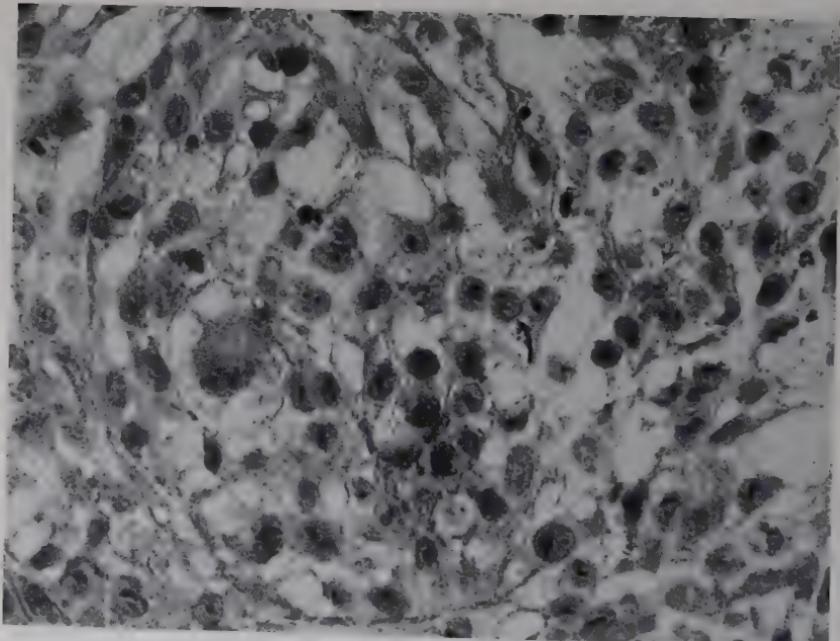


FIG. 22

FIGURES 21 and 22. *Case 8.* Photomicrographs of a tumor removed from the right groin on October 10, 1951 (Fig. 21, 125 \times ; Fig. 22, 450 \times). (Courtesy of A. B. Vial and F. W. Coller.)

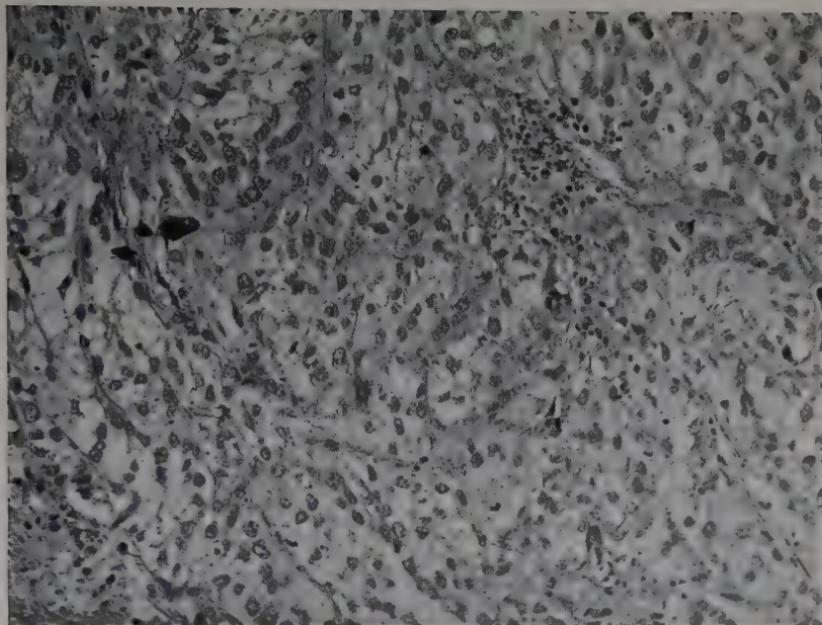


FIG. 23

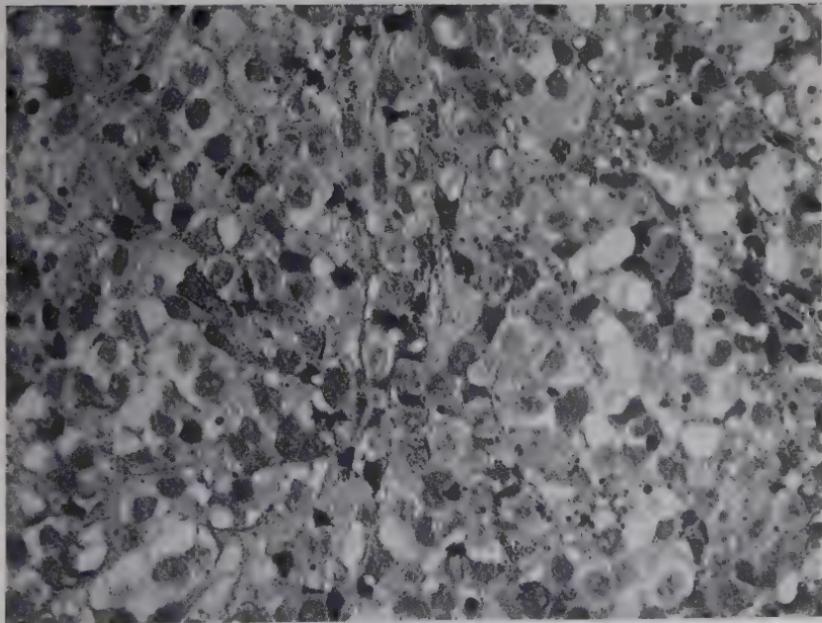


FIG. 24

FIGURES 23 and 24. *Case 8.* Photomicrographs of a tumor removed from the right inguinal region on February 24, 1954 (Fig. 23, 125 \times ; Fig. 24, 450 \times). (Courtesy of A. B. Vial and F. W. Coller.)

was excised and on histologic examination was reported to be metastatic malignant melanoblastoma with abundant pigment (Figs. 23 and 24).

The patient was last examined on October 31, 1955, at which time there were no clinical findings of malignant disease. A chest roentgenogram showed no evidence of pulmonary metastases.

9. W. Boyd (1957)⁵

A 33 year old woman then four months pregnant was seen by Dr. R. I. Harris of Toronto in 1942 because of a malignant melanoma of the thigh. This lesion had developed at the site of a pigmented mole which had been present since birth but which had begun to increase in size during the period of pregnancy. The tumor was excised and on microscopic examination the diagnosis of malignant melanoma was confirmed.

The patient delivered her baby and was next seen when the child was three months old. At this time she had an enormous mass of intensely pigmented glands in the groin and a large mass in her liver. The patient was emaciated and it appeared that the end was near.

However, three years later she was alive, active, and well. *The liver had decreased markedly in size and the mass in the groin was no larger than a hen's egg.* She had received no treatment.

In 1947 the tumor again became active and she died in the course of a few months.

10. W. Boyd (1957);⁵ M. B. Mackenzie (1958, 1963)²⁸

D. F., a 23 year old female, was seen on February 5, 1952, because of a small ulcerated lesion on the lateral aspect of the instep of her right foot which had been inflamed and tender for one week. The lesion had been present for many years and at first was circular and small. In 1949, after the patient had attempted to remove it herself, it started to enlarge and similar but smaller spots appeared around it.

On examination the main lesion was noted to be a slightly elevated brownish-black nodule with an ulcerated and inflamed center. It was surrounded by similar but smaller nodules. The skin area involved was approximately 4.5 cm. in diameter (Fig. 25).

The patient was admitted to the Reddy Memorial Hospital in Westmount (Montreal), Quebec, and on February 25, 1952, a radical excision of the tumor and its satellite secondaries with subsequent skin graft and radical ipsilateral groin dissection, was performed. The microscopic diagnosis was malignant melanoma of the skin of the foot with no metastases to the inguinal lymph nodes. The primary lesion was immediately subepithelial in location and showed considerable evidence

of anaplasia and very active growth (Figs. 26 and 27). There was evidence of early vascular invasion by the primary tumor, and evidence of secondary tumor in the wall of a peripheral vessel (presumably lymphatic) in the subcutaneous tissue of the skin removed from the foot. The secondary tumor was quite remote from the primary tumor.

The patient married in June 1952 and moved from Montreal. She was next seen in October 1952 (eight months after surgery). At this time she was pregnant, and a number of small lesions resembling freckles were noted in the skin graft. A few hemorrhagic-appearing spots were also noted on the inner aspect of the same foot. Two weeks later two additional small reddish spots were noted, one on the inner aspect of the right foot and the other on the skin graft.

In March 1953, 13 months after the operation and in the seventh month of the patient's first pregnancy, numerous reddish spots appeared on the lower leg, on the thigh, and adjacent to the scar in the groin (Fig. 28). These were presumed to be secondary tumor deposits. In May 1953, one day prior to the delivery of a normal baby, the patient's liver was palpable two to three finger-breadths below the costal margin; it was firm and irregular. In August 1953 the patient showed an increase in the number of lesions on the calf and thigh. However, the liver could no longer be felt.

The patient did not return for another check-up until May 1954. At that time she was in the fifth month of her second pregnancy and did not feel well. Her main complaint was marked swelling of the right leg. She stated that *the lesions on her leg had started to fade away after the second month of this pregnancy*. This was confirmed by comparison of the appearance of the leg with previous photographs.

The patient was admitted to the hospital for further investigation.



FIGURE 25. Case 10. Photograph of an ulcerated lesion on the lateral aspect of the right foot, February 5, 1952. (Courtesy of M. B. Mackenzie.)

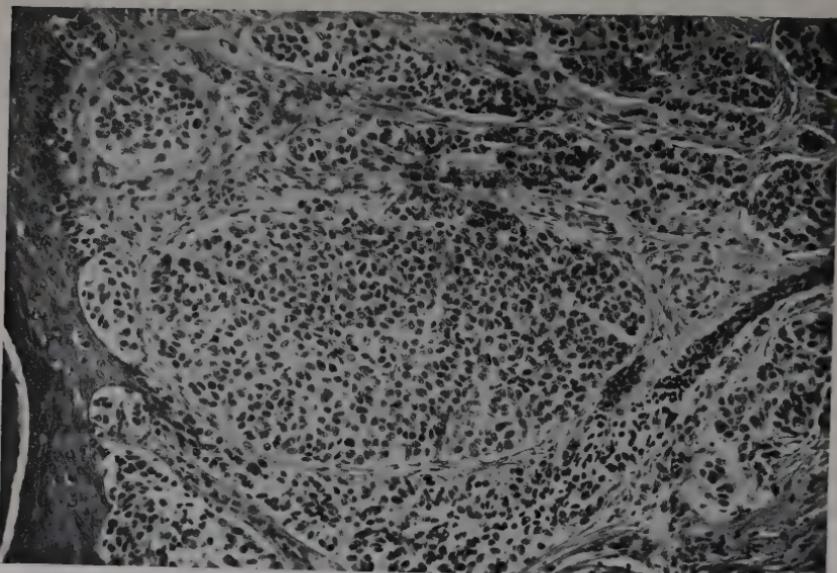


FIG. 26

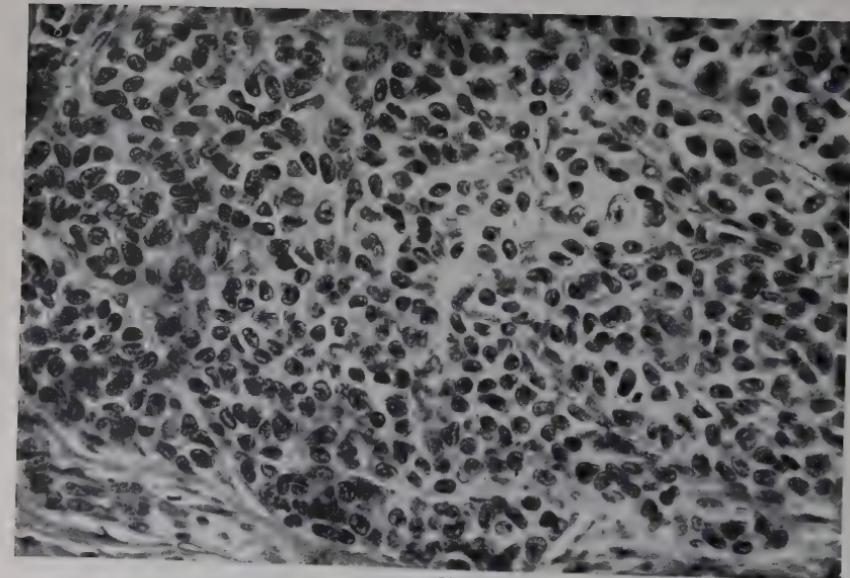


FIG. 27

FIGURES 26 and 27. Case 10. Photomicrographs of an ulcerated tumor of the right foot excised on February 25, 1952 (Fig. 26, 150 \times ; Fig. 27, 450 \times). (Courtesy of M. B. Mackenzie.)

and one of the fading lesions was removed for histologic examination on May 13, 1954. Microscopic study revealed nests of large cells with pale cytoplasm and relatively large nuclei which resembled nevus cells rather than those of malignant melanoma. Only a few of these contained small quantities of pigment. These cells were surrounded by granulomatous inflammatory tissue containing reticulum cells and lymphocytes. Immediately surrounding the inflamed areas were many melanophores containing brown granular pigment. Melanoblastic cells were few in number and were surrounded by a large zone of chronic granulomatous inflammation. A rare mitotic figure was seen among the melanoblasts; however, in general the melanoblasts showed no evidence of the anaplasia or pleomorphism seen in the primary lesion. Histologically the lesion was classed as a metastatic malignant melanoma, but the microscopic findings confirmed the clinical evidence of regression of the metastases (Figs. 29 and 30).

A year later, in November 1955, the patient was hospitalized for delivery of her third child. At this time another skin biopsy specimen was taken from one of the areas of previously heavy secondary involvement. The epidermis revealed no abnormal changes. The upper corium was very vascular and in several places revealed the presence of melanin which either was free among the collagen fibers or was contained within histocytes. The accumulations of melanin were always seen in the vicinity

(Text continued on page 193.)



FIGURE 28. Case 10. Photograph of the right thigh taken in March 1953 showing multiple secondary tumor deposits. (Courtesy of M. B. Mackenzie.)

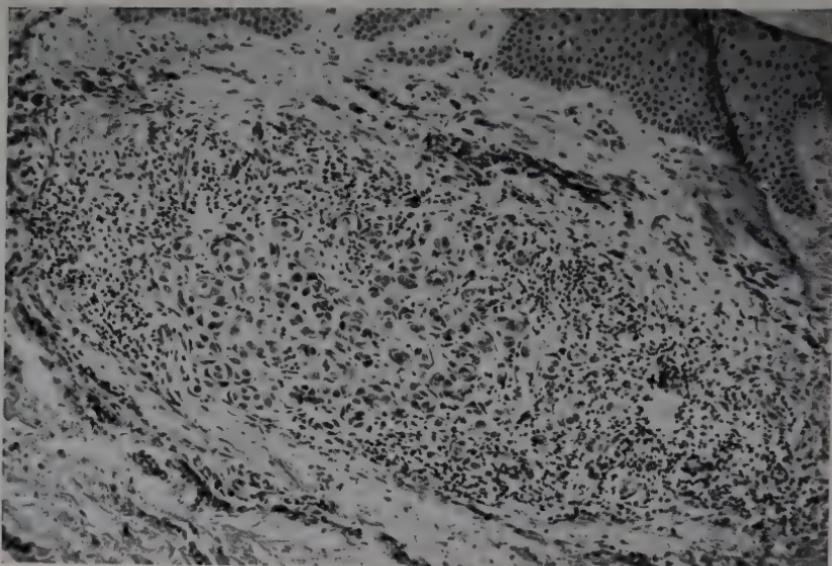


FIG. 29

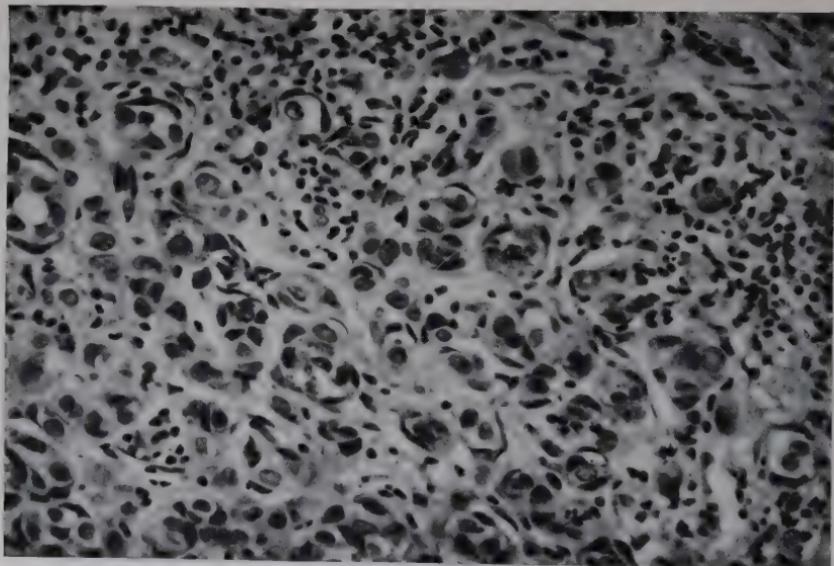


FIG. 30

FIGURES 29 and 30. *Case 10.* Photomicrographs of a regressing lesion excised on May 13, 1954 (Fig. 29, 150 \times ; Fig. 30, 450 \times). (Courtesy of M. B. Mackenzie.)

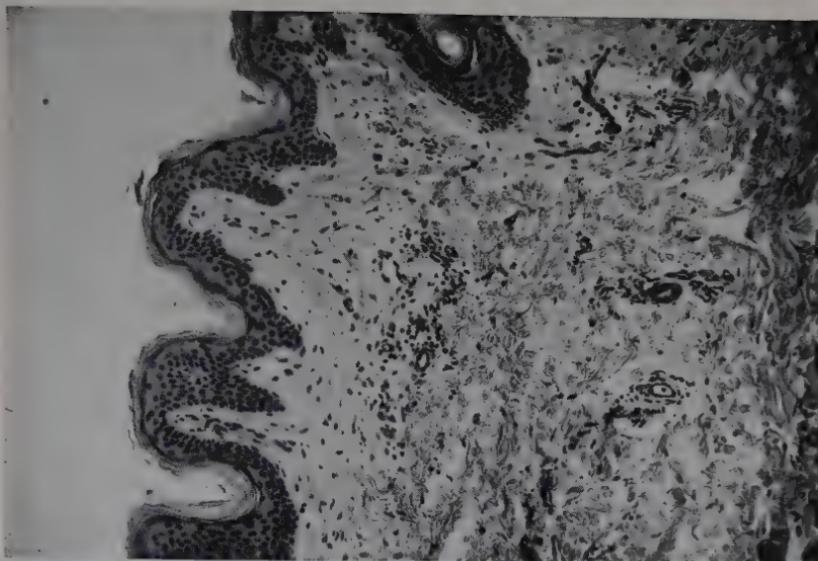


FIG. 31

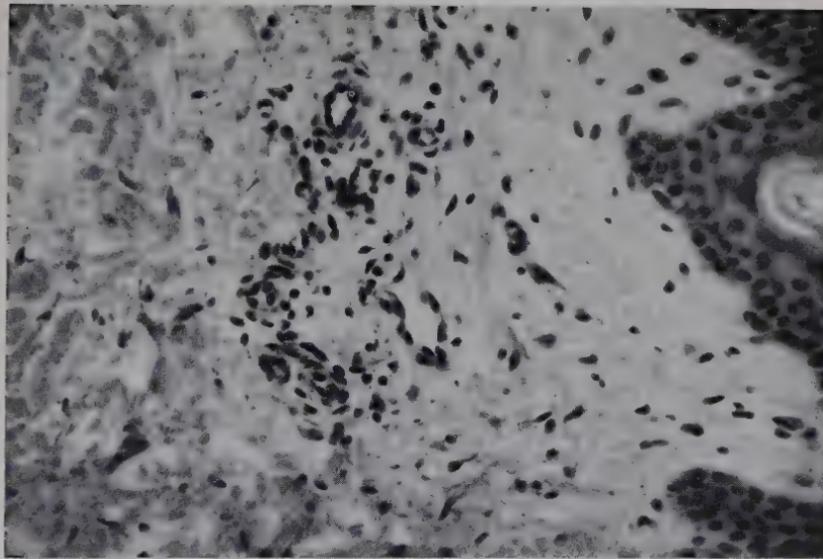


FIG. 32

FIGURES 31 and 32. *Case 10.* Photomicrographs of a lesion excised in November 1955 showing no nevus cells or melanoblasts (Fig. 31, 150 \times ; Fig. 32, 450 \times). (Courtesy of M. B. Mackenzie.)

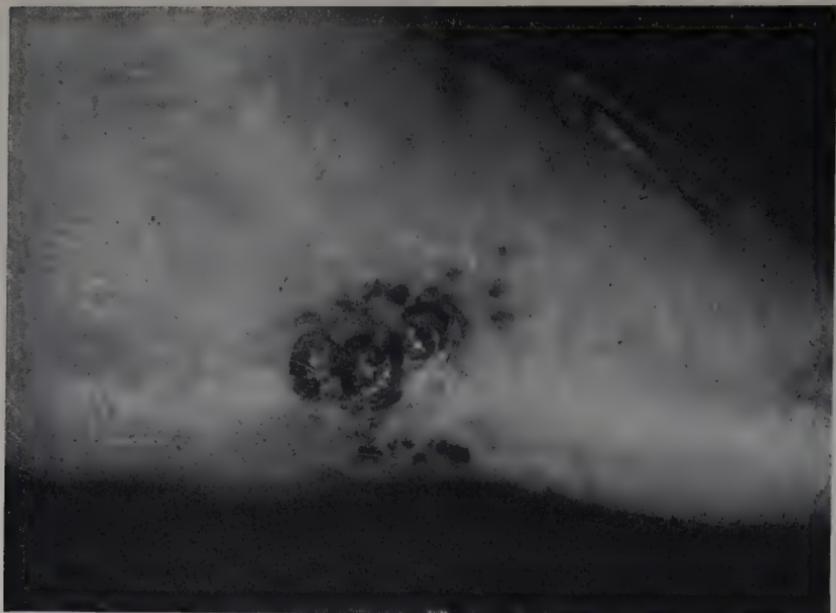


FIG. 33



FIG. 34

FIGURES 33 and 34. *Case 11.* Photographs taken in March 1949 showing a fungating papillary lesion in the midportion of the lateral aspect of the right foot. (Courtesy of W. R. Vogler.)

of small vessels. No cells resembling nevus cells or melanoblasts were noted (Figs. 31 and 32).

On examination almost seven years after the radical operation, the right leg was noted to be still swollen; however, *the liver was not palpable and the skin was clear with no residual trace of melanomata.* The patient was clinically well and the mother of four healthy children.

The patient developed a sudden recurrence of tumor and died with extensive involvement of the deep lymphatic tissues on April 26, 1962. Her terminal illness was almost explosive in the rapidity of its development.

11. W. R. Vogler, G. D. Perdue, and S. A. Wilkins, Jr. (1958)⁴⁷

M. C., a 52 year old white female, was first seen at the Emory University School of Medicine in Atlanta, Georgia, in March 1949. She gave a history of having had a "blood blister" on the lateral aspect of the right foot the preceding year. On physical examination a fungating papillary lesion was noted in the midportion of the lateral aspect of the right foot. The lower edge of the lesion encroached upon the plantar surface. Numerous pigmented nodules surrounded the lesion (Figs. 33 and 34). Three weeks later a right groin dissection was performed and metastatic melanoma was found in the lymph nodes.

(Text continued on page 197.)



FIGURE 35: Case 11. Photograph taken in March 1950 showing a metastatic nodule on the right side of the thigh, (Courtesy of W. R. Vogler.)

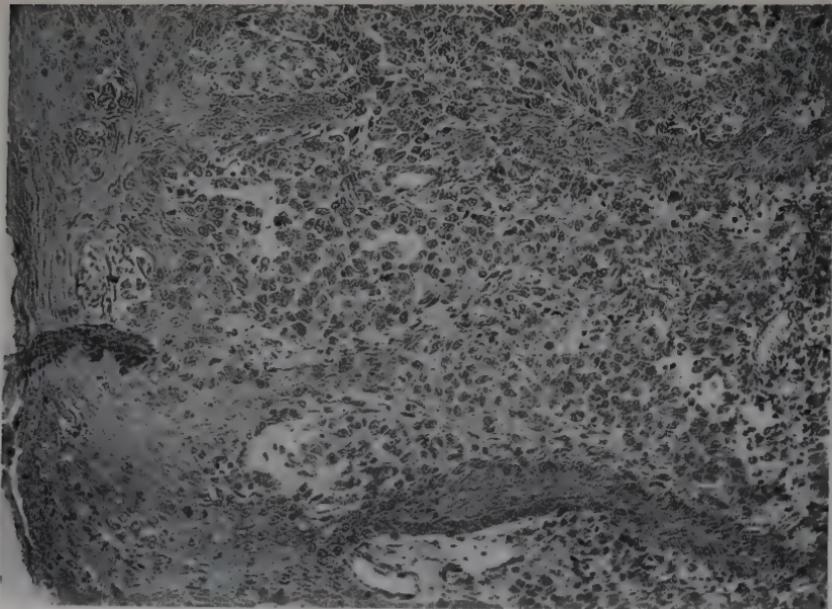


FIG. 36

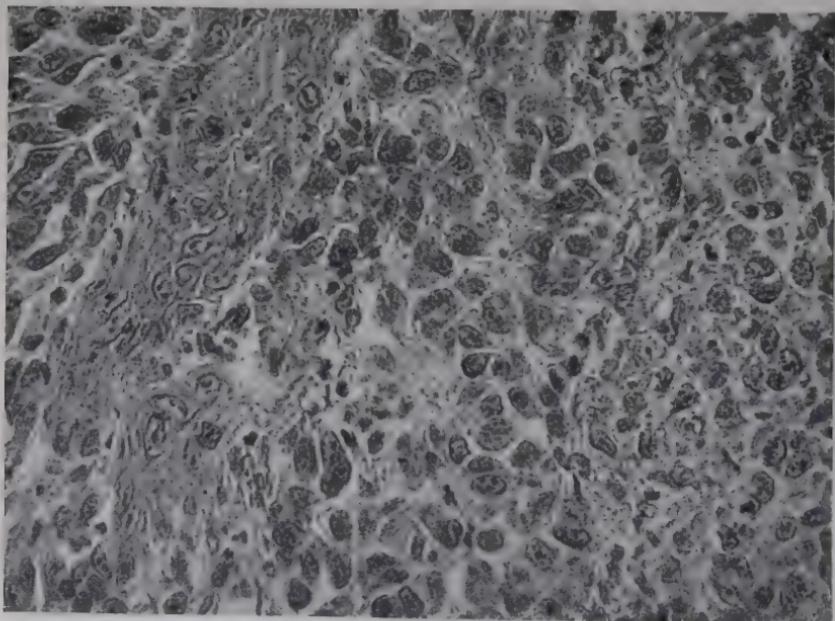


FIG. 37

FIGURES 36 and 37. Case 11. Photomicrographs of a nodule excised in March 1950 (Fig. 36, 150 \times ; Fig. 37, 450 \times). (Courtesy of W. R. Vogler.)

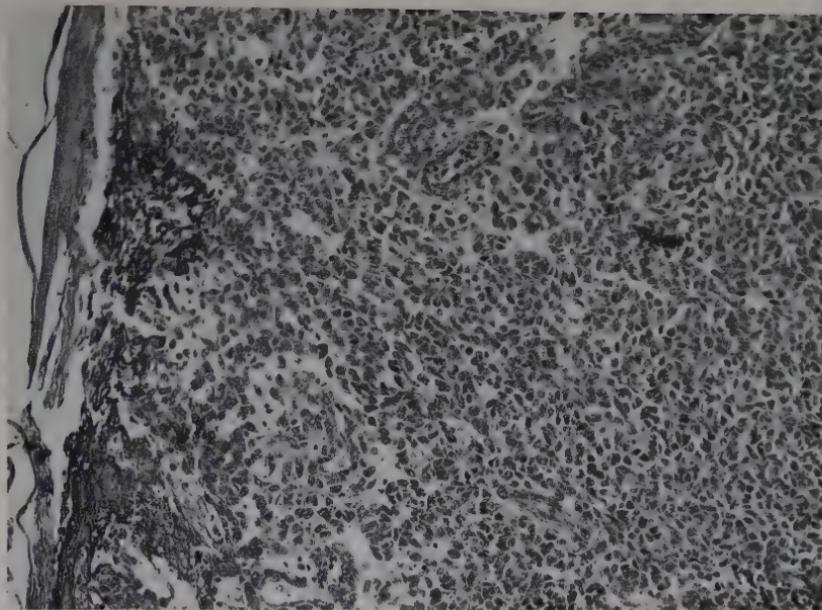


FIG. 38

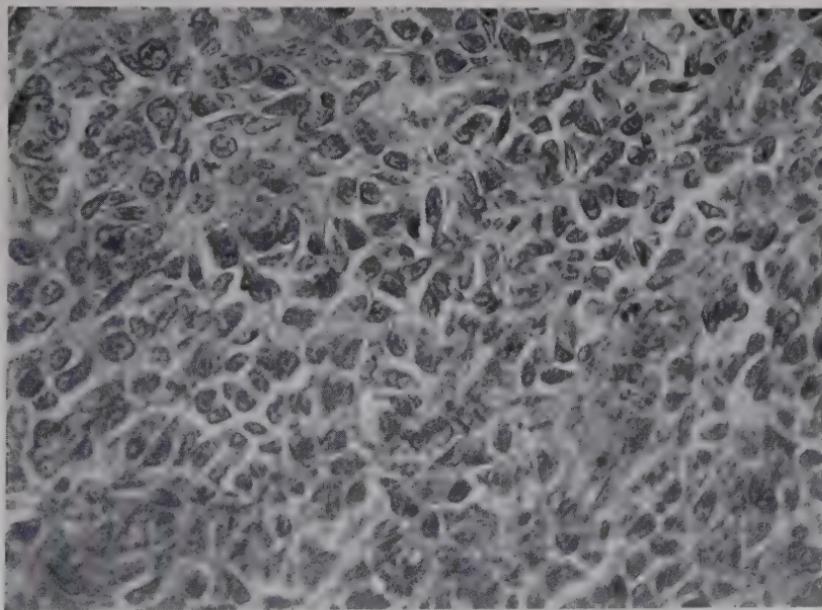


FIG. 39

FIGURES 38 and 39. *Case 11.* Photomicrographs of a lesion excised in October 1953 (Fig. 38, 150 \times ; Fig. 39, 450 \times). (Courtesy of W. R. Vogler.)

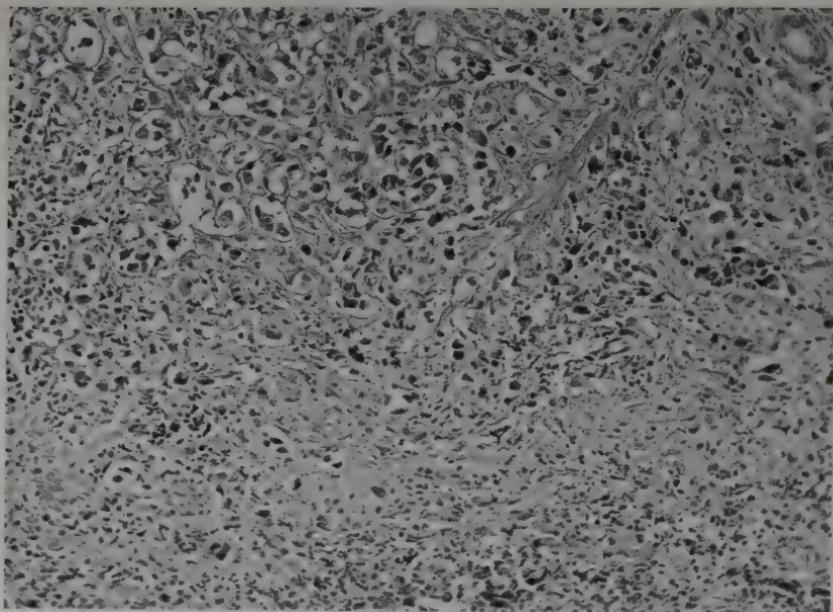


FIG. 40

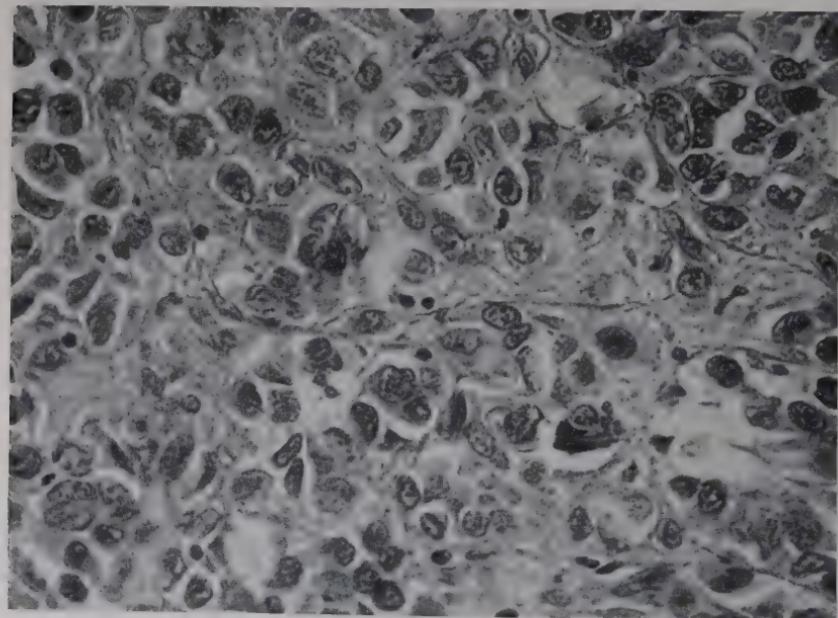


FIG. 41

FIGURES 40 and 41. *Case 11.* Photomicrographs of a nodule excised in March 1958 (Fig. 40, 150 \times ; Fig. 41, 450 \times). (Courtesy of W. R. Vogler.)

There was no clinical evidence of malignant disease until March 1950, when the patient returned with metastatic nodules on the right side of the thigh (Fig. 35). Excision biopsy of one of these nodules was performed and on microscopic examination metastatic melanoma was found (Figs. 36 and 37). A radical procedure was refused and accordingly she was treated by low-voltage x-ray, with the resultant regression of many of the nodules. Metastatic nodules continued to appear in the skin of the thigh and leg during the next year. The patient was not seen again until March 1953, when only one nodule was present, just above the knee in the lateral aspect of the right leg. In October 1953 another lesion developed just above the right external malleolus. Both of these lesions were excised and a diagnosis of metastatic melanoma was made on microscopic examination (Figs. 38 and 39).

No additional lesions were noted until June 1954, when numerous nodules were observed distributed over the right leg. One nodule was excised and on microscopic examination was found to be metastatic melanoma. Although 22 skin nodules which each received 2000 r regressed, it was observed that *some untreated ones also disappeared*. No new lesions were noted from July 1954 until March 1958, when the patient returned with a nodule over the right ankle. This lesion was examined and the diagnosis of metastatic melanoma was confirmed on microscopic examination (Figs. 40 and 41). The patient when last seen on July 24, 1958, was without evidence of recurrent cancer.

12. S. Cade (1961)⁷

A patient had a primary malignant melanoma removed from the front of the leg. Metastases then occurred in the inguinal lymph nodes and were excised. Subsequently an operation for intestinal obstruction revealed a solitary pigmented polypoid metastatic tumor in the small intestine, and the involved segment of small bowel was resected.

Following this operation a crop of subcutaneous metastases appeared near the scar from the excision of the primary growth, in the leg, and in the thigh. *These slowly regressed without treatment, leaving pale, thin scars.* The patient was alive and clinically free of disease four years later.

13. F. W. Ellis (1962)¹⁴

D. D., a 20 year old white male, was first found to have a malignant melanoma of the skin of the left posterior cervical region in June 1955. This was removed by a radical neck dissection and the diagnosis of malignant melanoma was confirmed by microscopic examination (Figs. 42 and 43).

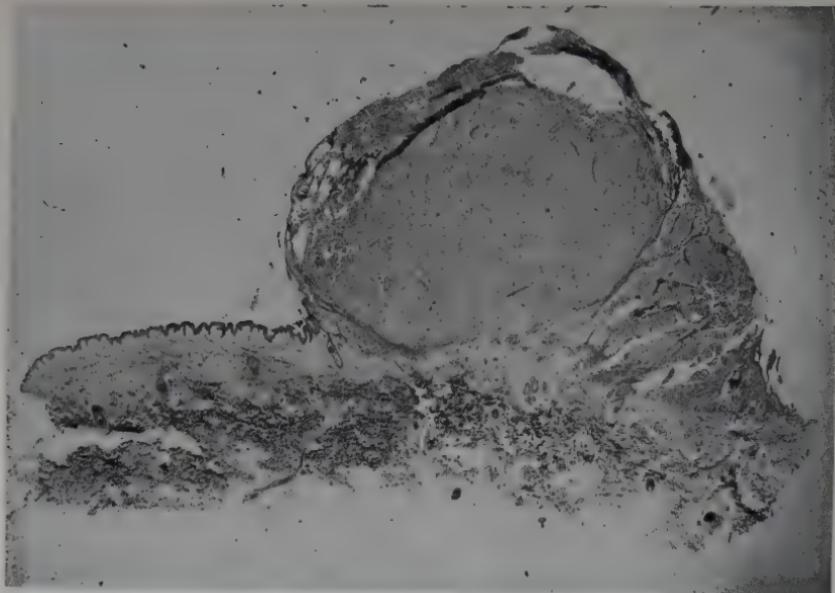


FIG. 42

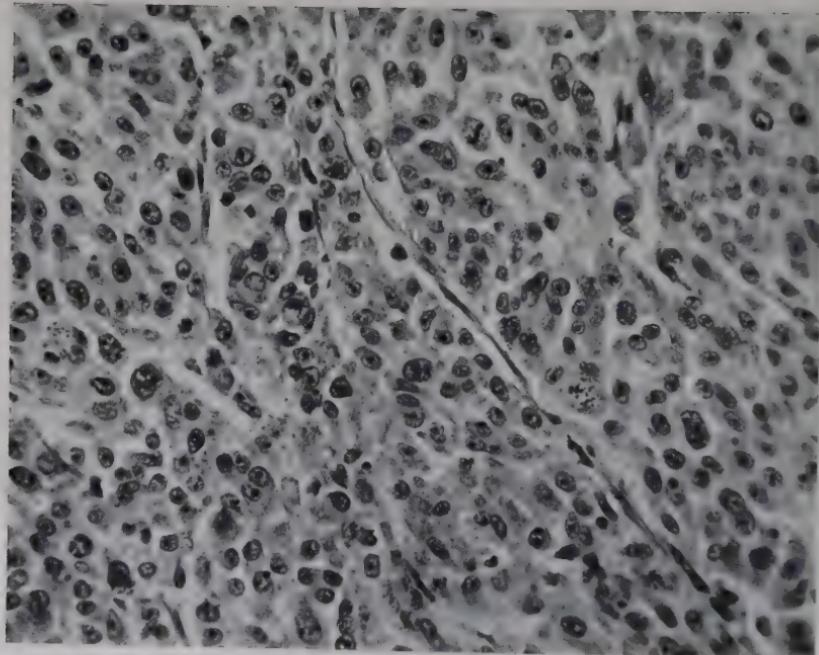


FIG. 43

FIGURES 42 and 43. *Case 13.* Photomicrographs of a tumor removed in June 1955 (Fig. 42, low power; Fig. 43, high power). (Courtesy of F. W. Ellis.)

He subsequently developed multiple recurrences, positive lymph nodes, and satellite lesions down the back. He underwent seven more surgical excisions and plastic repairs of the neck and of the parotid, supraclavicular, and occipital areas. The diagnosis of malignant melanoma was established on examination of many dozens of specimens (Fig. 44).

In November 1955 chest x-rays showed multiple spherical nodules which were interpreted as metastases (Figs. 45 and 46). By February 1956 the disease was thought to be out of control, and the last attempt at excision had to be abandoned because of tumor invading the ligamentum nuchae and posterior cervical spines. At this time, the patient had developed focal jacksonian epileptic seizures which were thought to be due to cerebral metastases. He was transferred to another hospital for preterminal care.

In July 1956 the patient was feeling entirely well and showed *striking bone-white depigmented areas in the scars at the site of the recurrent local melanomas and the satellite lesions of the upper back* (Figs. 47, 48, and 49). From this time on he had no further convulsive seizures and the pulmonary lesions disappeared (Fig. 50). The patient was known to be entirely well in November 1962.

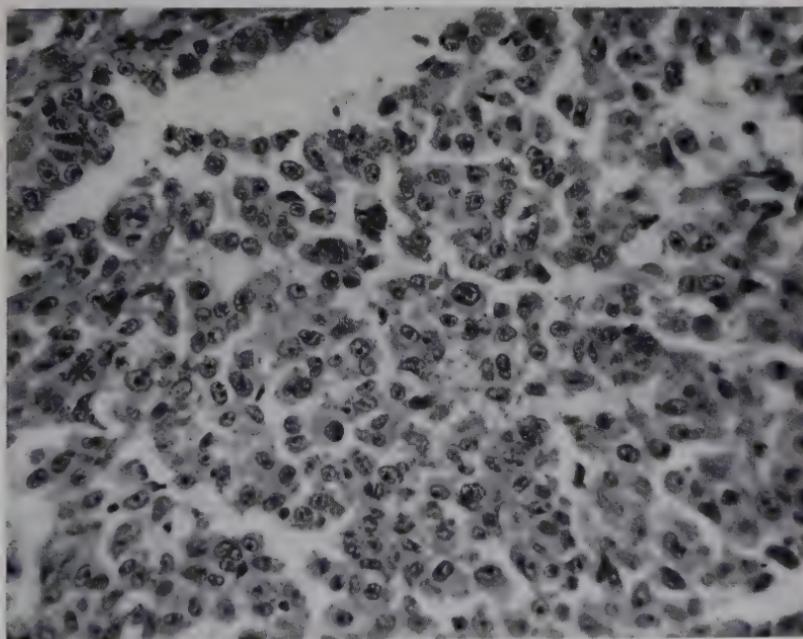


FIGURE 44. Case 13. Photomicrograph of a recurrent tumor. (Courtesy of F. W. Ellis.)



FIGURE 45. Case 13. Chest x-ray taken in November 1955 showing multiple spherical nodules. (Courtesy of F. W. Ellis.)

14. N. C. Petersen, D. C. Bodenham, and O. C. Lloyd (1962)⁴⁰

F. G., a 54 year old female, in 1952 noticed a black mark 1.6 cm. in diameter on the inner side of the left leg. In October 1953 the lesion began to ulcerate and in December 1953 a ring of satellites suddenly appeared.

On January 30, 1954, excision of the primary lesion and at least 12 satellites was performed. On histologic examination a diagnosis of malignant melanoma was made (Figs. 51 and 52). Histologic sections showed that the satellite lesions were derived by lymphatic spread in the papillary layer of the dermis. A skin graft was applied and a groin dissection was performed. There were four lymph nodes in the groin, none of which contained tumor cells.

On April 21, 1954, excision (with a 3 cm. margin) of three nodules in the posterior edge of the graft and one nodule 3 cm. behind this site was performed. Microscopic examination revealed that these lesions were lymphatic metastases (Figs. 53 and 54).



FIGURE 46. Case 13. Chest x-ray taken in November 1955 showing multiple spherical nodules. (Courtesy of F. W. Ellis.)

On May 28, 1954, an excision of skin from the thigh (40 by 21.5 cm.) containing about 30 similar metastases was performed. On June 18, 1954, a hindquarter amputation was performed because of 36 more nodules on the leg.

On July 9, 1954, four more lesions were noted in the pubic region. Further treatment was considered useless. The spots remained the same for 11 months and then gradually became smaller and disappeared within one month. Examination on September 26, 1961, revealed no evidence of recurrence.

15. N. C. Petersen, D. C. Bodenham, and O. C. Lloyd (1962)⁴⁰

M. H., a 38 year old female, noted that a congenital mole on the right side of the forehead began to grow and itch in April 1947.

On October 7, 1947, a fairly close excision of a dark, ulcerated melanoma (1.5 by 1.5 by 0.5 cm.) was performed. Microscopic examination revealed round and spindle cells spreading diffusely into the dermis and

(Text continued on page 207.)



FIG. 47



FIG. 48

FIGURES 47 and 48. *Case 13.* Photographs taken in July 1956 showing depigmented areas on the back in the scars at the site of the local recurrent melanomas. (Courtesy of F. W. Ellis.)

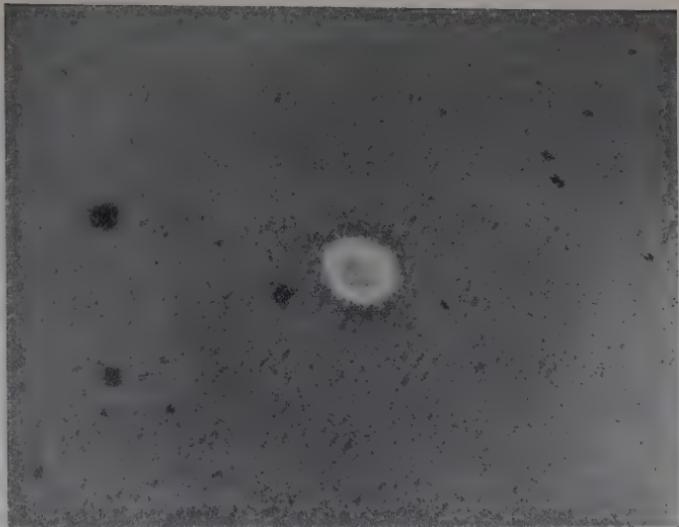


FIGURE 49. *Case 13.* Close-up photograph of depigmented satellite lesion. July 1956. (Courtesy of F. W. Ellis.)



FIGURE 50. *Case 13.* Chest x-ray showing no evidence of the previous nodules. (Courtesy of F. W. Ellis.)

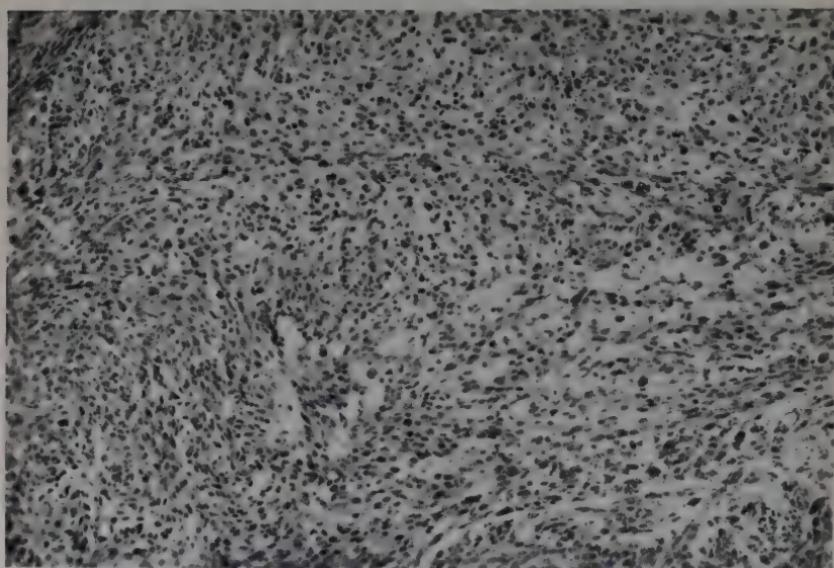


FIG. 51

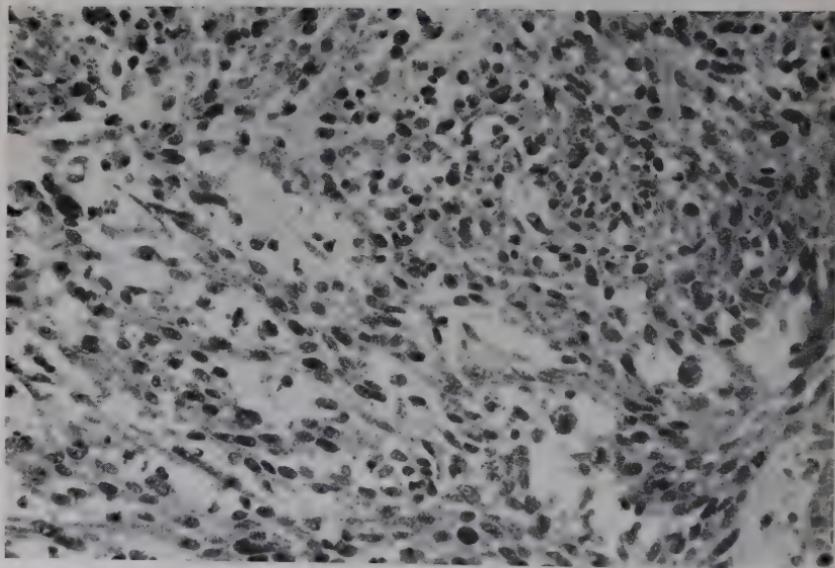


FIG. 52

FIGURES 51 and 52. *Case 14.* Photomicrographs of a primary tumor excised on January 30, 1954 (Fig. 51, 150 \times ; Fig. 52, 450 \times). (Courtesy of O. C. Lloyd.)

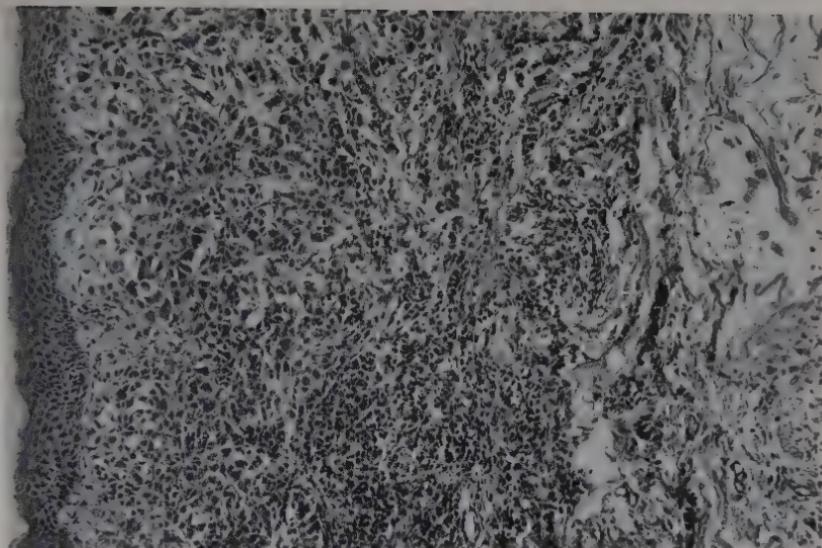


FIG. 53

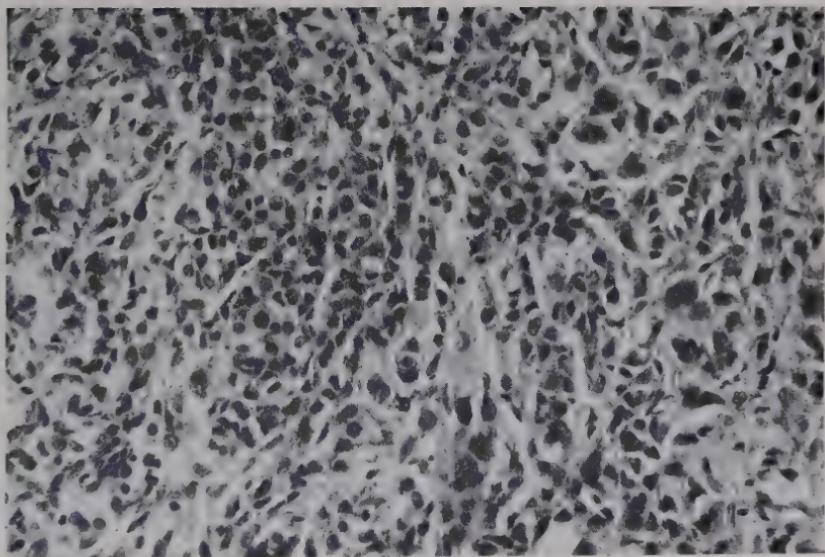


FIG. 54

FIGURES 53 and 54. *Case 14.* Photomicrographs of a nodule excised on April 21, 1954 (Fig. 53, 150 \times ; Fig. 54, 450 \times). (Courtesy of O. C. Lloyd.)

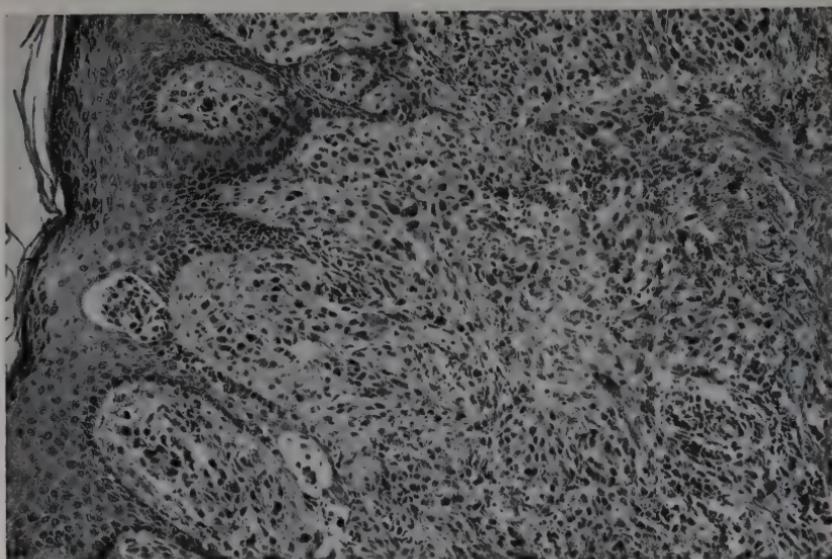


FIG. 55

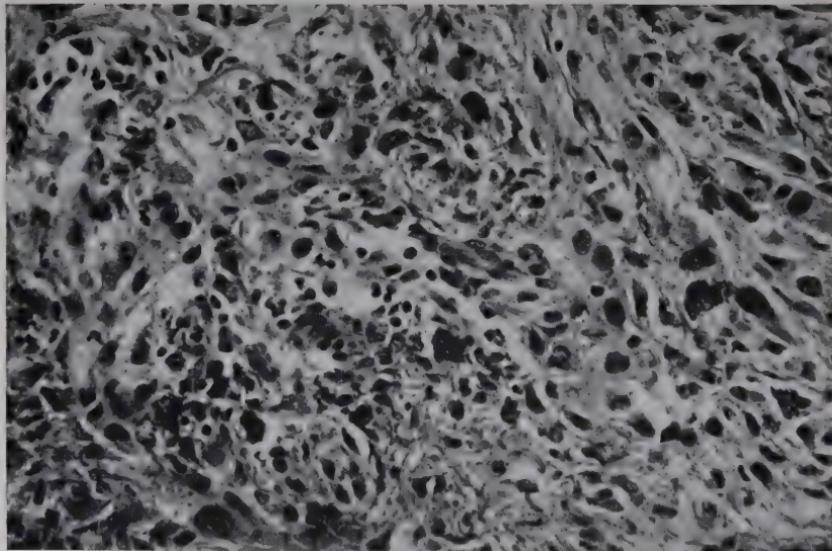


FIG. 56

FIGURES 55 and 56. *Case 15.* Photomicrographs of a primary tumor excised on October 7, 1947 (Fig. 55, 150 \times ; Fig. 56, 450 \times). (Courtesy of O. C. Lloyd.)

subcutis, with obvious invasion of the dermal lymphatics. A diagnosis of malignant melanoma was made (Figs. 55 and 56).

On November 7, 1947, re-excision of the area contiguous with the preauricular nodes, parotid gland, and upper cervical lymph nodes was performed. Metastases were found in the preauricular nodes.

On November 24, 1948, block dissection of the right side of the neck was performed. Extensive submaxillary and other metastases were found and removed, but some growth had to be left behind. From December 1947 to January 1948 radiation therapy was administered to the neck.

In January 1949 a mass was noted in the right supraclavicular region accompanied by pain in the arm. After a few months *the mass got smaller without treatment*. In June 1950 no mass could be felt, and on January 18, 1962, examination revealed no evidence of recurrence or metastasis.

16. H. W. Baker (1963)²

H. L., a 46 year old white male, was admitted to the hospital on March 12, 1956, because of a lump on the right ear. The patient had first noted a "dark spot" on the ear one year previously. Nine months before admission this spot had been "burned off" by a physician. A month later a nodule had appeared at the original site and had been enlarging slowly during the eight months prior to admission.

Physical examination revealed a firm, subcutaneous nodule measuring 8 mm. on the antitragus of the right ear. The nodule was nontender and bluish. There was a firm node measuring 1 cm. in the upper cervical region just beneath the lobe of the ear (Fig. 57). No suspicious nevi were noted. A chest roentgenogram was normal.

An incision biopsy of the tumor of the ear was performed and a histologic diagnosis of epidermoid carcinoma was made. On March 21, 1956, a subtotal resection of the ear was performed in continuity with a parotidectomy. A diagnosis of malignant melanoma of the ear with metastasis to one lymph node overlying the lower pole of the parotid gland was made (Figs. 58 and 59). The patient had an uneventful post-operative course. A plastic prosthesis was constructed for his ear, and he was discharged from the hospital on March 30, 1956.

There was no evidence of recurrent tumor until December 1956, when a subcutaneous nodule 5 mm. deep was noted just posterior to the angle of the mandible, and a poorly defined subcutaneous mass measuring 1 cm. was palpable at the posterior limits of the site of the neck dissection. Hospitalization was recommended but refused by the patient. By March 1957 the nodule behind the angle of the mandible had doubled in size and the posterior nodule was also larger.

The patient was next seen in June 1957, at which time a large tumor mass was fungating through the skin of the upper cervical region, extend-



FIGURE 57. *Case 16.* Photograph taken in March 1956 showing a tumor of the ear and a node in the upper cervical region just beneath the lobe of the ear. (Courtesy of H. W. Baker.)

ing up over the mastoid and onto the right cheek. The mass was fixed to deeper structures, bled easily, and much of it was black (Fig. 60). The patient was in considerable pain but refused hospitalization. He was given a prescription for pain medication.

The patient did not return for his scheduled follow-up examinations and was not seen again until 13 months later (July 15, 1958), when he appeared to be in good health. An examination revealed *marked scarring in the right upper cervical region at the site previously occupied by the fungating mass and an unusual loss of pigmentation of the skin in the scarred areas.* There were no palpable enlarged cervical nodes. A complete physical examination revealed *no evidence of tumor*, and a chest roentgenogram was normal.

The patient was closely questioned about his course during the preceding 13 months. He had received no medical advice or treatment to the area of the mass. He stated that there had been frequent hemorrhages from the tumor and that it gradually decreased in size until the area finally healed. He attributed this to prayer.

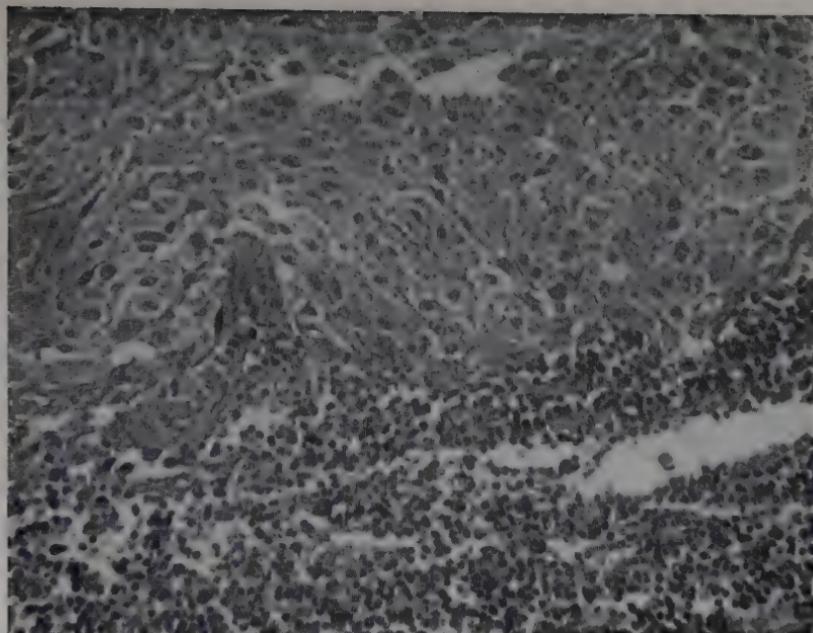


FIGURE 58. *Case 16.* Photomicrograph of a tumor excised on March 21, 1956 (115 \times). (Courtesy of H. W. Baker.)

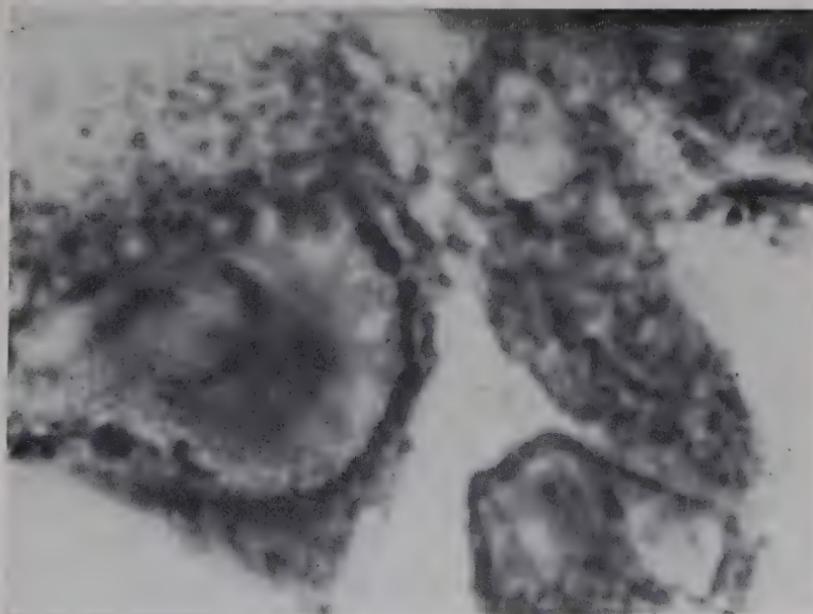


FIGURE 59. *Case 16.* Photomicrograph of a tumor excised on March 21, 1956 (1000 \times). Masson's silver stain reveals melanin granules. (Courtesy of H. W. Baker.)



FIGURE 60. *Case 16.* Photograph taken in June 1957 showing massive recurrence in the neck. (Courtesy of H. W. Baker.)



FIGURE 61. *Case 16.* Photograph taken in September 1962 showing no evidence of the tumor. (Courtesy of H. W. Baker.)

The patient was last examined on March 12, 1963, seven years after the operation and six years after the development of the massive tumor mass. There was no evidence of tumor (Fig. 61).

17. J. McCredie (1964)²⁶

A. R., a 32 year old male, had a mole on the dorsum of the left foot cauterized in May 1955. In July 1956 he noted a lump in his left groin. Excision of the mass was performed at the Toronto General Hospital by Dr. W. B. Bigelow on December 15, 1956. On microscopic examination a diagnosis of metastatic melanocarcinoma was made (Figs. 62 and 63).

Accordingly an extensive dissection of the left inguinal and femoral nodes was performed by Dr. Bigelow, also on December 15, 1956. Microscopic examination of these nodes did not reveal any evidence of malignant melanoma. The patient was discharged from the hospital on December 20, 1956, and subsequently received extensive cobalt therapy to the left inguinal region and left upper thigh anteriorly.

In October 1958 the patient reported that during the preceding two or three months he had noticed the development of 12 to 14 subcutaneous nodules mostly on the trunk, on the chest wall, in the left axilla, and in the right forearm. The patient stated that the nodules had begun as tiny pinpoints which gradually grew over a period of two or three weeks, in some instances to the size of a thumb. After another two weeks the lesions had become deeply pigmented and *then gradually disappeared*, always leaving a small pinpoint of nodularity in the subcutaneous tissues. Physical examination on October 17, 1958, revealed three subcutaneous nodules. One, approximately 1 cm. in diameter and definitely pigmented, was in the infraclavicular region on the right side, another was in the left axilla, and the third was in the right forearm. It was considered that these lesions might be regressing metastatic subcutaneous nodules.

On physical examination on October 24, 1958, it was noted that *the skin nodules present one week previously had disappeared except for a bluish nodule 0.5 cm. in diameter in the skin of the right forearm*. Since this nodule seemed to involve a vein it was suggested that the original nodules might have been thromboses in the veins rather than metastatic deposits. At the time of the examination on December 19, 1958, the patient reported that the skin nodules continued to appear and disappear. The lesion in the forearm at this time looked like a thrombosis except that it was painless and nontender.

On examination on March 16, 1959, the liver was not palpable and a chest x-ray was reported as normal. The patient was seen on June 4, 1959, because of nausea and vomiting. Physical examination did not reveal any enlargement of the liver; however, urine examination revealed the presence of melanin and this finding was confirmed on July 10, 1959.



FIG. 62

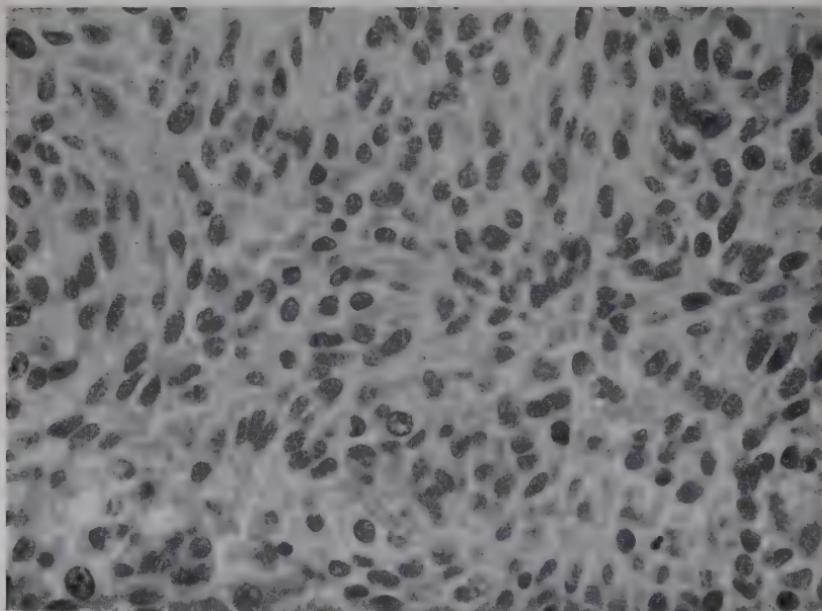


FIG. 63

FIGURES 62 and 63. *Case 17.* Photomicrographs of tissue removed on December 15, 1956, showing metastatic melanocarcinoma (Fig. 62, 150 \times ; Fig. 63, 450 \times). (Courtesy of W. Anderson.)

Physical examination on August 28, 1959, demonstrated that the liver edge was four finger-breadths below the right costal margin. From August 1959 until February 1960 the patient's weight fell from 141 pounds to 85 pounds. He was completely bedridden, unable to eat, and had intermittent high fever, marked weakness, sweating, and vomiting. He was admitted to Scarborough General Hospital for transfusions six to eight times between November 1959 and February 1960; he received 23 pints of blood during this period. On February 23, 1960, the patient was given blood transfusions at Scarborough General Hospital. Following the administration of the third pint of blood (blood group A, Rh negative), he developed some chest tightness and shortness of breath. Accordingly the transfusion was discontinued. A few days later the patient awoke feeling for the first time that he would get well. Approximately one week later his appetite improved and two weeks later he began to eat well. The nausea and vomiting gradually subsided.

The patient was admitted to the Princess Margaret Hospital for study on May 13, 1960. On physical examination the *liver edge was not palpable, the urine was negative for melanin, and it was felt that the patient had had an amazing remission of his melanocarcinoma*. He was discharged from the hospital on May 20, 1960.

By August 19, 1960, the patient's weight was restored to 144½ pounds and he felt well. There was clinical evidence of a minimal degree of gynecomastia bilaterally. Multiple physical and laboratory examinations in 1961, 1962, 1963, and 1964 showed no evidence of recurrent melanocarcinoma.

Plasma from this patient was given to another patient with lung metastases from melanocarcinoma, with no improvement. Also plasma from the first patient and from blood donors (of February 23, 1960) was injected subcutaneously into masses of melanocarcinoma on the second patient without any response. (It was not possible to trace one of the donors who gave blood to the patient on February 23, 1960.)

Metastatic Malignant Melanoma of Choroid

18. V. B. Levison (1955)²⁵

A male, aged 60, had his right eye excised at Moorfields Eye Hospital on February 21, 1951. On microscopic examination a diagnosis of malignant melanoma was made.

The patient was seen at Addenbrooke's Hospital on February 26, 1953. There was no clinical evidence of recurrence and the liver was not palpable. However, a chest x-ray showed multiple small opacities at

the base of the left lung, and examination of the urine revealed the presence of melanogens. Accordingly a diagnosis of presumptive pulmonary metastases was made. No treatment was given.

Re-examination on July 8 revealed *the disappearance of the presumptive pulmonary metastases and no melanogens in the urine*. After that examination, repeated clinical and radiologic examinations showed no evidence of recurrence, and melanogens were not present in the urine.

19. *N. Malleson (1955)*²⁹

A 22 year old white male South African was seen in November 1950 because of an enlarged supraclavicular lymph node. He had been seen by another physician 18 months previously because of this tumor mass. A chest x-ray at that time (April 1949) was normal.

On physical examination the supraclavicular node was found to be firm, smooth, egg-shaped, and mobile. A chest x-ray in November 1950 revealed gross enlargement of the right paratracheal group of lymph nodes. The patient's health was good.

The patient was admitted to the Hampstead General Hospital, and the supraclavicular tumor mass was removed. On microscopic examination the pathology department of the hospital made a diagnosis of metastatic malignant melanoma, with the choroid the probable site of the primary tumor. The pathology department at University College Hospital made a similar diagnosis.

A search for the primary tumor revealed only a small pigmented area touching the left optic disc at the 5 o'clock position. No treatment was given.

Serial chest x-rays showed *the paratracheal glands to be gradually decreasing in size, and by early 1952 his chest films were essentially normal*. The patient was known to be alive and well in September 1954.

OTHER BRIEFLY REPORTED CASES

Gould¹⁶ reported a case of spontaneous regression of a tumor which almost certainly was a malignant melanoma. However, the case has not been included in the collected series because the protocol did not indicate whether the diagnosis had been confirmed by microscopic examination.

The patient, H. S., a male, had a congenital mole excised from the front of his chest in October 1902 at the age of 37. A small healthy scar marked the site of the surgery. Tiny nodules soon appeared in and under the skin. The nodules were most numerous on the trunk but were scattered over almost the entire body except the lower limbs below the groin. On July 14, 1903, it was noted that no new nodules had appeared

and that all the old ones were flatter and smaller. On July 30, 1903, many of the nodules were found to have *disappeared completely*; others were present only as black stains which were visible but not palpable. On October 1, 1903, the patient was found to have gained weight, and only two palpable nodules were present over the whole surface of the body. In February 1904 two new nodules appeared near the right knee. In March 1904 the liver was noted to be enlarged and a new nodule was noted on the right side of the neck. The patient expired in September 1904 after he had been confined to his bed for only three or four days.

Handley¹⁸ stated that R. H. Jocelyn Swan noted in a patient under his care that macroscopic nodules of melanotic growth shrank and disappeared.

ANALYSIS OF COLLECTED CASES

In the collected series of 19 cases there were 8 males and 10 females; in one case report the patient's sex and age were not stated. The ages of the 10 female patients ranged from 20 to 63 years, with 7 of the patients in the fourth decade. The ages of the 8 male patients ranged from 22 to 60 years, with 4 of the patients in the fifth decade.

The primary tumor was excised or cauterized (cases 4 and 17) in all the collected cases except one (case 5) in which the primary tumor was never found and a second (case 19) in which the primary was thought to have been in the choroid. In eight patients (cases 2, 3, 5, 6, 10, 11, 12, and 14) regression of cutaneous metastatic lesions occurred. In six of these eight patients (cases 2, 5, 6, 10, 12, and 14) there was no treatment other than treatment of the primary tumor. One patient (case 3) received 14 antirabies vaccine injections because of a dog bite, and one patient (case 11) received irradiation to some cutaneous nodules; however, some cutaneous lesions which did not receive irradiation also regressed.

In six patients (cases 1, 4, 7, 9, 15, and 16) the residual primary tumor (case 16) or lymph node metastases (cases 1, 4, 7, 9, and 15) regressed. In four of these patients there was no treatment other than the initial treatment of the primary tumor. In case 4 a large abdominal wall tumor mass was excised, and in case 7 an abscess was present in the area of the axillary metastases which underwent regression.

In two patients (cases 18 and 19) presumptive pulmonary metastases regressed, and in two patients (cases 8 and 13) presumptive pulmonary metastases and cutaneous metastases regressed. One of these latter patients (case 13) received no treatment other than treatment of the primary tumor, and the other (case 8) was given antibodies tagged with I¹³¹. In one patient (case 17) subcutaneous nodules which possibly were metastatic lesions regressed, and later the presumptive liver metastases (the diagnosis was based on hepatic enlargement and the presence of

melanin in the urine) regressed following the administration of blood transfusions.

Five of the patients (cases 2, 3, 4, 9, and 10) were known to have subsequently died of disseminated melanomatosis.

POSSIBLE CAUSES OF SPONTANEOUS REGRESSION OF MALIGNANT MELANOMA

The possibility that some instances of spontaneous regression of malignant melanoma are related to hormonal influences must be strongly considered because of the evidence that hormones may influence the evolution of malignant melanoma. For example, Spencer⁴² has cited some observations which indicate that hormones greatly influence the evolution of malignant melanoma:

1. Malignant melanomas are uncommon before puberty.
2. Malignant melanomas have not been reported in castrated persons.
3. Periods of elevated hormone levels (adolescence and pregnancy) are accompanied by excitation of tumor growth.

Likewise, White⁴⁸ has noted that although the distribution of malignant melanoma is approximately equal in the two sexes there is (a) a statistically significant higher rate of survival in females and (b) a decrease in the five year survival rate in both sexes with advancing age, a decrease which is out of proportion to the decrease expected in life expectancy with aging in the general population. White⁴⁹ noted that in four patients the activation of metastatic melanoma occurred within six months of the cessation of the menses; these recurrences came 18, 14, 8, and 7 years after the excision of the primary tumor. Wright, Clark, and Milne⁵² also noted that the prognosis in females under 50 (pre-menopausal) is noticeably better than in females over 50 or in males of any age. (Eight of the 10 female patients with spontaneous regression of malignant melanoma in this collected series were under 50.)

Although the earlier report of Pack and Scharnagel³⁹ suggests that pregnancy adversely affects the prognosis of malignant melanoma, the later studies of George, Fortner, and Pack¹⁵ and White et al.⁵⁰ indicate that pregnancy has no discernible effect on five year survival. Also White et al.⁵⁰ point out that termination of the pregnancy is not effective in causing the regression of an established malignant melanoma.

The relationship of pregnancy and spontaneous regression of malignant melanoma may be evaluated in four patients of the collected series (cases 5, 6, 9, and 10) in whom both pregnancy and malignant melanoma were present. In three of these patients (cases 5, 6, and 9) metastases developed and grew during pregnancy and regressed following preg-

nancy. In case 6 the regression occurred two and a half months after delivery, and in cases 5 and 9 the regression was noted approximately three years after delivery. In case 10 metastases developed during the patient's first pregnancy, regressed during a second pregnancy, and did not reappear during a third pregnancy.

Because of the evidence that malignant melanoma may be a hormone-dependent tumor, various kinds of hormonal suppression or ablation have been tried in patients, usually with little or no effect. Thus Howes²⁰ noted no response to bilateral orchietomy and Huggins and Bergenstal,²¹ Barker et al.,³ and Pack and Scharnagel³⁹ noted no improvement following adrenalectomy. However, Wigby and Metz⁵¹ noted in one patient an almost complete disappearance of extensive generalized metastases (subcutaneous nodules and pulmonary metastases) following the heavy irradiation of the pituitary gland. Wigby and Metz also treated four more patients with extensive regional glandular involvement by pituitary irradiation without any significant response. Similarly Shimkin et al.⁴¹ noted no improvement following either irradiation of the pituitary or surgical hypophysectomy. Pack and Scharnagel³⁹ point out that although pigmented neval and melanoma cells are apparently extraordinarily sensitive to hormonal stimulation, presumably of pituitary, adrenal, and ovarian origin, the process apparently is not reversible since ovarian castration, testosterone, pituitary irradiation, and other hormone-depressant measures have been ineffective in treatment. Likewise, Cade⁶ states that neither castration, adrenalectomy, hypophysectomy, nor hormonal administration is effective in altering the course of metastatic malignant melanoma. (It is interesting to note that in one patient in the collected series, case 4, a diagnosis of ovarian agenesis was made on the basis of clinical and operative findings.)

The possibility that an immune mechanism may have been responsible for the spontaneous regression in some of the collected cases of malignant melanoma must also be considered. In one patient (case 3) subcutaneous metastases regressed after the administration of 14 anti-rabies vaccine injections for a dog bite; in another patient (case 8) the regression of pulmonary and subcutaneous metastases occurred following the administration of antibodies tagged with I¹³¹, and in a third patient (case 17) a dramatic regression of presumptive liver metastases occurred following a blood transfusion. In addition, blood from a patient who had a spontaneous regression (case 5) was transfused into a patient with metastatic melanoma, and this patient's metastases disappeared.

Similarly, Teimourian and McCune⁴⁵ have reported the case of a 29 year old male who developed pulmonary metastases (confirmed by biopsy) eight months after the excision of a malignant melanoma of the shoulder and an axillary dissection in continuity. This patient was transfused with the blood of a female patient who had survived for 10 years without recurrence after the removal of a malignant melanoma of the

back and bilateral axillary metastases. During the four months following the transfusion the pulmonary metastases gradually diminished in size and almost disappeared. Brain metastases with hemiplegia then appeared. Following another transfusion, however, the patient again improved until he was able to work. He died approximately one year later and at autopsy the lung metastases were found to be only small areas of necrosis.

Although various attempts to duplicate these results in other patients were ineffective in each instance, one must still maintain a strong suspicion that an immune reaction may have occurred which caused the regression in some of these cases.

In one patient (case 7) the destruction of axillary metastases by an abscess may have been responsible for the disappearance of the tumor.

References

1. Allen, E. P.: Malignant melanoma, spontaneous regression after pregnancy. *Brit. Med. J.*, 2:1067, 1955.
2. Baker, H. W.: Personal communication.
3. Barker, W. F., Yuhl, E. T., Beal, J. M., Jr., Hill, M. R., Jr., and Goodwin, W. E.: Bilateral adrenalectomy in the treatment of advanced neoplastic disease. *Western J. Surg.*, 61:491, 1953.
4. Block, G. E., and Hartwell, S. W., Jr.: Malignant melanoma: A study of 217 cases. *Ann. Surg. (suppl.)*, 154:88, 1961.
5. Boyd, W.: Spontaneous regression of cancer. *J. Canad. Assn. Radiol.*, 8:45, 1957.
6. Cade, S.: Malignant melanoma. *Brit. Med. J.*, 1:119, 1957.
7. Cade, S.: Malignant melanoma. *Ann. Roy. Coll. Surg. Eng.*, 28:331, 1961.
8. Charalambidis, P. H., and Patterson, W. B.: A clinical study of 250 patients with malignant melanoma. *Surg. Gynec. Obstet.*, 115:333, 1962.
9. Clark, R. L., Jr., and Macdonald, E. J.: The natural history of melanoma in man. In Gordon, M. (ed.): *Pigment Cell Growth*. New York, Academic Press, 1953, pp. 139-148.
10. Clifton, R. B., Knight, C. D., and Mathews, W. R.: Malignant melanoma: An analysis of 135 cases. *Amer. Surg.*, 25:189, 1959.
11. Daland, E. M.: Personal communication.
12. Daland, E. M.: Malignant melanoma (personal experience with 170 cases). *New Eng. J. Med.*, 260:453, 1959.
13. Daland, E. M., and Holmes, J. A.: Malignant melanomas. *New Eng. J. Med.*, 220:651, 1939.
14. Ellis, F. W.: Personal communication.
15. George, P. A., Fortner, J. G., and Pack, G. T.: Melanoma with pregnancy (a report of 115 cases). *Cancer*, 13:854, 1960.
16. Gould, P.: Cited by Handley, W. S.: The pathology of melanotic growths in relation to their operative treatment. *Lancet*, 1:927, 1907.
17. Gumpert, S. L., and Meyer, H. W.: Treatment of 126 cases of malignant melanoma (long term results). *Ann. Surg.*, 150:989, 1959.
18. Handley, W. S.: The pathology of melanotic growths in relation to their operative treatment. *Lancet*, 1:927, 1907.
19. Higgins, G. K., and Pack, G. T.: Virus therapy in the treatment of tumors. *Bull. Hosp. Joint Dis.*, 12:379, 1951.

20. Howes, W. E.: Removal of testes in treatment of melanoma. *J.A.M.A.*, *123*: 304, 1943.
21. Huggins, C., and Bergenstal, D. M.: Inhibition of human mammary and prostatic cancers by adrenalectomy. *Cancer Res.*, *12*:184, 1952.
22. James, A. G.: Malignant melanoma. *J.A.M.A.*, *176*:5, 1961.
23. Krementz, E. T.: End results in skin cancer. *In Proceedings of the Fourth National Cancer Conference*. Philadelphia, J. B. Lippincott Co., 1960, pp. 629-635.
24. Levi, J. E., and Lewison, E. F.: Malignant melanoma in a patient with ovarian agenesis. Case report of prolonged survival. *J. Clin. Endocrin.*, *12*:901, 1952.
25. Levison, V. B.: Spontaneous regression of a malignant melanoma. *Brit. Med. J.*, *1*:458, 1955.
26. McCredie, J.: Personal communication.
27. MacGillivray, W. F.: Personal communication.
28. Mackenzie, M. B.: Personal communications.
29. Malleson, N.: Spontaneous regression of malignant melanoma. *Brit. Med. J.*, *1*:668, 1955.
30. Masson, P.: Les nævi pigmentaires; tumeurs nerveuses. *Ann. Anat. Path. (Paris)*, *3*:417, 657, 1926.
31. Masson, P.: My conception of cellular nevi. *Cancer*, *3*:9, 1951.
32. Mathews, F. S.: Melanosarcoma of shoulder and nodes about shoulder: Well after incomplete operation. *Ann. Surg.*, *62*:114, 1915.
33. Meyer, H. W.: Personal communication.
34. Pack, G. T.: Personal communication.
35. Pack, G. T.: Note on the experimental use of rabies vaccine for melanomatosis. *Arch. Derm. Syph. (Chicago)*, *62*:694, 1950.
36. Pack, G. T.: End results in the treatment of malignant melanoma (a later report). *Surgery*, *46*:447, 1959.
37. Pack, G. T., and Livingston, E. M.: The treatment of pigmented nevi and melanomas. *In Pack, G. T., and Livingston, E. M. (eds.): The Treatment of Cancer and Allied Diseases*. New York, Hoeber Medical Division, Harper & Row, Publishers, 1940, Vol. III, pp. 2071-2094.
38. Pack, G. T., and Miller, T. R.: Metastatic melanoma with indeterminate primary site (report of two instances of long term survival). *J.A.M.A.*, *176*:55, 1961.
39. Pack, G. T., and Scharnagel, I. M.: The prognosis for malignant melanoma in the pregnant woman. *Cancer*, *4*:324, 1951.
40. Petersen, N. C., Bodenham, D. C., and Lloyd, O. C.: Malignant melanomas of the skin. *Brit. J. Plast. Surg.*, *15*:49, 97, 1962.
41. Shimkin, M. B., Boldrey, E. B., Kelly, K. H., Bierman, H. R., Ortega, P., and Naffziger, H. C.: Effects of surgical hypophysectomy in a man with malignant melanoma. *J. Clin. Endocrin.*, *12*:439, 1952.
42. Spencer, R. P.: Malignant melanoma (medical progress). *New Eng. J. Med.*, *253*:18, 1955.
43. Sumner, W. C.: Spontaneous regression of melanoma (report of a case). *Cancer*, *6*:1040, 1953.
44. Sumner, W. C., and Foraker, A. G.: Spontaneous regression of human melanoma; clinical and experimental studies. *Cancer*, *13*:79, 1960.
45. Teimourian, B., and McCune, W. S.: Surgical management of malignant melanoma. *Amer. Surg.*, *29*:515, 1963.
46. Vial, A. B., and Coller, F. W.: Personal communication.
47. Vogler, W. R., Perdue, G. D., and Wilkins, S. A., Jr.: A clinical evaluation of malignant melanoma. *Surg. Gynec. Obstet.*, *106*:586, 1958.

48. White, L. P.: Studies on melanoma. II. Sex and survival in human melanoma. *New Eng. J. Med.*, **260**:789, 1959.
49. White, L. P.: The role of natural resistance in the prognosis of human melanoma. *Ann. N. Y. Acad. Sci.*, **100**:115, 1963.
50. White, L. P., Linden, G., Breslow, L., and Harzfeld, L.: Studies on melanoma: The effect of pregnancy on survival in human melanoma. *J.A.M.A.*, **177**:235, 1961.
51. Wigby, P. E., and Metz, M. H.: Striking regression of generalized subcutaneous and visceral metastases of malignant melanoma (melanoblastoma) following intensive high voltage roentgen irradiation of the pituitary gland. *Amer. J. Roentgen.*, **41**:415, 1939.
52. Wright, R. B., Clark, D. H., and Milne, J. A.: Malignant cutaneous melanoma: A review. *Brit. J. Surg.*, **40**:360, 1953.