

ENHANCEMENT OF NATURAL RESISTANCE TO
MALIGNANT MELANOMA WITH SPECIAL REFERENCE TO
THE BENEFICIAL EFFECTS OF CONCURRENT INFECTIONS
AND BACTERIAL TOXIN THERAPY



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MONOGRAPH #9

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1225 PARK AVENUE NEW YORK, N.Y. 10028

NEW YORK, 1969

INDEX

	page
INTRODUCTION	1
BACTERIAL INFECTION FEVER OR INFLAMMATION, SERIES A, 22 CASES	
Brief Abstracts	11
Detailed Histories	17
CONCURRENT PREGNANCY	37
TOXIN TREATED CASES, SERIES B, OPERABLE: 14 CASES	
Brief Abstracts	40
Detailed Histories	44
TOXIN TREATED CASES, SERIES C, INOPERABLE: 14 CASES	
Brief Abstracts	52
Detailed Histories	57
Conclusions	73
VACCINE VIRUS TREATED CASES (INOPERABLE)	74
RABIES VIRUS TREATED CASES	78
SUMMARY AND CONCLUSIONS	79
BIBLIOGRAPHY	80

INTRODUCTION

Few serious attempts have been made to stimulate or enhance the natural resistance of patients with malignant melanoma or other types of neoplasms. These include the following: induced bacterial infections (20, 21), injections of bacterial toxins (22, 28, 30, 39, 42, 45, 50, 51, 65, 69, 76, 80-84, 91, 92), rabies vaccine (34, 87), BCG (8, 85), yeast extracts (64, 65), tagged antibodies (103), vaccinia virus (6, 13, 73), tumor extracts (94, 95) or transplants of tumor tissue (96) or tumor and leukocytes (79).

The largest number of patients received injections of mixed bacterial toxins (*Streptococcus pyogenes* and *Serratia marcescens*) or developed a concurrent bacterial infection. A total of 222 determinate cases of cancer in which infection developed spontaneously or by inoculation have been abstracted in detail and analyzed. Cases which did not have microscopic confirmation of diagnosis or which were not followed for at least five years were excluded. Of these 222 infection cases 143 were traced from 5 to 54 years after onset; 24 of them later died of their neoplasm.

A total of 1065 determinate cases of cancer treated by bacterial toxin therapy have also been abstracted and analyzed. Of these 479 were followed from 5 to 70 years after onset of the neoplasm, but 103 died of their original cancers more than five years after onset, and 46 of them subsequently developed an entirely different type of neoplasm from 6 to 59 years after the first. Twenty-six of these second primaries proved fatal. Three patients subsequently developed fatal acute myelogenous leukemia 23 to 25 years after onset of their original cancers. (All three had been given irradiation, two for their first and one for his second primary cancer.) At least 51 patients are known to have died of cardiovascular disease. A considerable number are alive and well at the present time. This group of patients appears to be the largest series ever followed for such long periods.

In the majority of patients the condition was inoperable when infection developed or toxins were begun. It is therefore significant that 622 of these 1287 patients were traced 5 to 70 years after onset. The highest percentage of successes in the toxin treated cases occurred in the sarcomas of soft tissues and malignant lymphomas, especially reticulum cell sarcoma of bone. The slower growing, more differentiated lesions were not as easily controlled. However, some remarkable results have been obtained in treating inoperable or metastatic carcinomas of the breast, colon, uterus, ovary, head and neck, testicular cancer, malignant melanoma and neuroblastoma. In addition to complete or partial regression of such neoplasms, reduction or disappearance of lymphedema, ascites or pleural effusion were observed in certain cases. Remarkable regeneration of bone destroyed by osteolytic bone tumors or bone metastases has also been observed in a high percentage of cases that were operable when toxins were begun. In such cases toxin therapy was usually given as an adjuvant to surgery or radiation. Such treatment appeared to be especially effective if begun prior to, or immediately after surgery, or prior to and during radiation.

Spontaneous Regression:

In the course of these studies on host resistance in cancer we have analyzed the cases of "spontaneous regression." It was found that in all types of cancer the majority of such cases had a concurrent bacterial infection, a febrile or inflammatory episode or an incomplete surgical procedure. (20, 30, 36, 39-42, 77, 81, 82, 83, 92, 93). Often the reporting physician neglected to mention that such complications as fever or infection had occurred, since they were usually not considered relevant to the regression, because until recently little was known about the various defensive forces which may thus be activated. Most modern

surgeons seem unaware of the possible benefit which may occur when cancer patients develop an acute bacterial infection, especially streptococcal or staphylococcal. However, a number of older surgeons were well aware of this fact, i.e., Bolognino (10), Bruns (11), Da Costa (30), Grey Turner (42), Wyeth (80-83). For example, Da Costa stated: "Occasionally . . . suppuration cures a sarcoma . . . more cases of sarcoma are cured after operation if the wound suppurates than if it remains aseptic, and it has been proposed to deliberately inject the wound with pus germs to lessen the danger of recurrence. . . . After removing a sarcoma from any region the patient should be given injections of Coley toxins." (30)

Stimulation of Host Resistance by Streptococci, other Bacteria or Toxins:

Until recently physicians using toxin therapy were unaware of the fact that streptococci and their toxins are able to stimulate a host response to substances or tissues which do not normally elicit such a response in an animal or patient. For example, Glynn and Holborrow found that four strains of streptococci (three Group A and one group C) and a strain of *Staphylococcus aureus*, when grown on agar media, gave rise to agar antibodies in antisera prepared against them. (44) Burky found that by combining staphylococcus with lens substance, rabbits were sensitized to lens and developed high precipitin titres for lens tissue. (14)

In order to stimulate this response the organisms do not need to be alive, but the bacteria or their toxins must come into significant contact with the target tissue. These findings suggest why better results seem to have occurred in toxin treated patients or animals when at least some of the injections were made in or near the tumors, or where infections developed locally. In administering bacterial toxins now and in the future it may be more effective to begin with local injections.

In this connection it is of interest to note that the majority of so-called spontaneous regressions of cancer occurred in patients who developed streptococcal or staphylococcal infections, rather than nonpyogenic infections such as malaria, syphilis or typhoid fever. (10, 11, 20, 21, 30, 34, 39-42, 75, 77, 80-83, 84, 92, 93)

In recent years Havas has studied the effects of living hemolytic streptococci on ascites tumor cells (Sarcoma 37 and Krebs-2 Carcinoma). Three of eight strains of *Streptococcus pyogenes* were highly effective against the tumor cells, resulting in reduction of takes as well as reduction of tumor size. *Streptococcus lutea* and *fecalis* and *Serratia marcescens* were only partially effective in damaging tumor cells *in vitro*. The striking cytological changes produced by living streptococci were recorded by Havas with phase photomicroscopy. (52)

Christensen has studied the growth of Brown Pearce carcinoma in rabbits treated with living or killed streptococci. He found that none of the rabbits receiving injections of living streptococci developed metastases, while metastases occurred in 50% of the untreated controls. Heat-killed cultures were not effective. (17)

A group of Japanese investigators began working with streptococcal toxins about 1955 and they appear to have produced a more effective preparation than others available at the present time. In a recent review Okamoto, et al, summarized most of the data obtained in their laboratories with hemolytic streptococcal toxins in experimental tumors. (84a). They have achieved two distinct improvements in preparing their extracts: a) when suspended in Bernheimer's basal medium, in contrast to streptococci suspended in simple media such as phosphate buffered saline, the tumor destructive properties in hemolytic streptococci were found to be resistant to heating at 45°C. for 30 minutes. This is of obvious importance since heat sterilization has been used in making these

extracts for therapeutic use. b) preincubation of live cocci suspended in Bernheimer's basal medium containing penicillin yields a potent anticancer preparation which is 20 times more effective than live cocci suspended in NaCl without penicillin in inhibiting the growth of Ehrlich ascites carcinoma in mice. (84a). Their preliminary clinical trials appear promising. Unfortunately, they were not aware, apparently, of the end results which have been achieved with Coley toxins, judging from the comments they made on this subject. This may be attributed to the fact that so little has been published in the last dozen years.

The Role of Inflammation in Resistance to Cancer

Allen and Spitz discussed the variations in the reactive inflammatory barrier around malignant melanoma: "Rarely is an activated junctional nevus free from a zone of inflammatory cells which are usually lymphocytes along with some histiocytes and eosinophilic leukocytes — disposed in the upper cutis so as to resemble somewhat the inflammatory pattern of lichen planus. Although this reaction is the usual feature beneath the activated junctional nevi, the juvenile melanomas and the superficial melanocarcinomas, it is often inconspicuous or absent in the advancing margins of the more deeply infiltrating melanocarcinomas, as if the defensive barrier of the inflammatory cells had been broken through. (2) If the report that ACTH and cortisone may produce junctional nevi is substantiated, an important lead may be forthcoming. Inasmuch as the level of ACTH increases in pregnancy, the possibility of its action in the production of junctional nevi, which in some cases go on to melanocarcinomas, must be carefully considered." (2)

Since the inflammatory reaction appears to be of special significance in controlling the malignancy of melanoma, it is not surprising that erysipelas seems to have produced the most dramatic regressions, not only of this tumor but of other types of neoplasms, for this infection is accompanied by more intense inflammation than others. (41)

Of further interest in this connection is the fact that toxin therapy caused local erythema around the melanoma lesions, as well as markedly increased local heat over the skin of subcutaneous lesions (to 106°F.) when the body temperature was several degrees lower. Another symptom suggesting an induced inflammatory reaction in the tumor sites was the "red flare" observed in some cases following a toxin injection (Series C, Case 12). In others transient pain was noted in the tumor sites following toxin injections. Such reactions were not evident in terminal patients, possibly because the extent of the disease had rendered them anergic.

Lohmann studied the effect of inflammatory exudates in neoplastic cells. (61) She found that rat sarcoma cells were destroyed *in vitro* within 10 to 14 hours after being placed in the inflammatory exudate. She concluded that at all costs we must preserve the inflammatory capacity of the body in order to prevent or control cancer. (61) In addition to the direct cytologic effects acute inflammation may produce in malignant tumors, it is now recognized that the histamine liberated at sites of acute inflammation activates the reticuloendothelial system. The latter also plays a role in natural resistance to cancer. (7, 86)

Martin's finding regarding the deleterious effects of cortisone in the possible benefits of combination therapies is of great importance. Kelly has reviewed the experimental and clinical evidence which clearly indicates that corticosteroids usually accelerate the growth and dissemination of malignant tumors. We have personal knowledge of six patients in which this occurred. This is not surprising since acute inflammation appears to be an effective defense malignancy, as many of the physicians and surgeons in the 19th century recognized. (81)

It would seem therefore that we should avoid administering any anti-inflammatory drugs such as the corticosteroids, phenylbutazone or the salicylates

to patients known to have had cancer or to those under treatment for malignancy, since latent disease may thus be reactivated or disseminated.

The Role of Lymphoid Tissues in Host Resistance to Cancer:

The availability or integrity of lymphoid tissues appears to be important for adequate resistance to malignant tumors. Recent studies have been made of the relative incidence of cancer or leukemia in patients who have had appendectomies or tonsillectomies. For example, McVay studied 914 cases coming to autopsy in three institutions and concluded that the colon, and to a lesser degree, the lung, breast, cervix, stomach and pancreas, may be organs on which the appendix may confer some degree of protection. (47) Independently, Bierman has confirmed McVay's findings in a study of 1287 consecutive postmortem records and in 122 living patients with lymphomas and leukemias. These data suggest a systemic and local protective effect is produced by the appendix. (6a) Bierman noted that the amount of lymphoid tissue in the appendix is incredibly small compared to similar lymphoid deposits. Consequently the quality of the appendix and its constituents is probably more important than the quantity. The progressive fibrous obliteration of lymphoid follicles of the appendix occurs with aging (50% of all persons over 50 years). When it occurs prior to 30 years of age it may represent a pathologic phenomenon.

Murphy and his associates at Rockefeller Institute were among the first to emphasize the importance of lymphoid tissues in resistance to cancer. Their studies are reviewed in a monograph. (78) In this connection it is of interest to note that bacterial toxin therapy usually produces leukocytosis in cancer patients and often produces lymphoid hyperplasia in the regional nodes if injected intradermally, intramuscularly or intratumorally. Possibly toxin therapy may make the nodes more effective "strainers" for tumor cells.

Many excellent reviews on the clinical behavior and management of malignant melanoma have appeared in the last two decades, to which the reader is referred for discussion of the epidemiology, pathology, incidence, factors affecting prognosis, treatment and end results obtained with conventional forms of therapy for this neoplasm. (2, 9, 15, 38, 47, 48, 57, 59, 62, 88, 89, 90, 104) A number of these authors question the wisdom of performing "prophylactic" node dissections. For example, Catlin stated in 1954: "We found no evidence in our material to support the theory that radical operation made in all cases will produce better results." (15)

Block and Hartwell stated in 1951: "We found no evidence in our experience that, in the absence of clinically positive nodes, a prophylactic node dissection is better or worse than local excision alone . . . and we disagree with the dogma of Pack, that the elective or prophylactic lymphadenectomy must be done routinely to adequately treat malignant melanoma." (9) These authors cited several others who had reached similar conclusions, including Lund and Ihren who believe that therapeutic lymph node dissection is of no use, and that prophylactic node dissection is of value in only a small number of cases. (62) Kragh and Erich reported a five-year survival rate of close to 50% in a large series of primary malignant melanoma of the head and neck where prophylactic node dissection was rarely done. (57)

Lewis has recently reported on possible immunological factors in human malignant melanoma in Uganda, Africa. He stated that the natural history of this neoplasm in Uganda suggests there may be a host response which modifies the behavior of the tumor. (60a) "The most important finding was that patients who had a cytotoxic serum all fell into the group of patients who displayed host resistance clinically, whereas the serum of patients in whom the disease had advanced without resistance was not cytotoxic." (60a) In a personal communication he commented on the fact that nearly all their melanoma patients arrive in an advanced state having walked on the lesion sometimes for months or even

years as a result of which most of them have some degree of infection. (82)

Fortner, et al, recently noted that there appears to be a basis for strong suspicion that an interaction between the cancer cell and the host improves surgical rates. (58) It would appear that the administration of certain bacterial toxins, yeast extracts and BCG, or the development of a bacterial infection may significantly increase this interaction, unless prior therapy, or advanced age has inactivated the lymphoid tissues.

The Role of Fascia in Resistance to Metastases:

Olsen recently reported that in 112 patients with malignant melanomas located in the extremities, excluding the hands and feet, and in the abdominal wall, but without clinical signs of metastases, metastases to the regional lymph nodes developed more frequently in those patients in whom the underlying fascia had been removed, as compared with patients in whom it had been left intact (45% and 8-14% respectively).

As to how this may occur, Olsen believed that intact fascia acts as a barrier of some kind and should be left intact at operation. (86a)

The Role of Fever in Host Resistance to Cancer:

The apparently beneficial effects of certain infections or of bacterial products in cancer patients may be due in part to the fever they elicit, for tumor cells are much more thermolabile than normal cells. (91, 92) Recently Crile has shown that heating to 44°C. of S 91 melanoma or Sarcoma 180 destroyed a high proportion of the tumors without damage to the feet of the animals in which they were implanted. Heat and radiation were synergistic or at least additive in their effects on tumors when given within a few hours of each other. (29)

Analysis of the end results in the toxin treated cases, according to the amount of febrile reaction elicited, showed that the percentage of permanent successes was significantly higher in patients with reactions averaging 102°-104°F. and that this was especially evident in the inoperable cases. (91, Monograph #3, Fig. 4)

Streptococcal Enzymes:

The role of streptococcal enzymes must also be considered in the response of cancer patients to concurrent streptococcal infections or to certain bacterial toxin preparations, for both apparently stimulate the production of fibrinolysin. Extensive studies by Clifton and Grossi have shown that administration of human fibrinolysin to rabbits diminishes the mortality and is highly effective in preventing metastases by inoculation of V₂ Carcinoma or Brown-Pearce carcinoma (18, 47) O'Meara and Thornes have also studied the role of fibrinolysin as it relates to the rate and invasiveness of tumor growth. (86a)

Vaccinia Virus:

Burdick and Hawk in this country have used injections of vaccinia virus in a few advanced cases of malignant melanoma. (12, 53) In a personal communication, Burdick stated that in patients who progressed most favorably the vaccinia injections elicited a generalized hyperergic reaction. (82)

At least three physicians in Sydney, Australia have been using inoculations of pox virus in the treatment of advanced, multiple metastatic malignant melanomas. Belisario and Milton reported that except on rare occasions these inoculations did not produce generalized remission of the disease, either with or without the adjuncts they used. They added that it had not been effective in any of the metastatic lesions except those in the skin or mucosa. (6, 73)

Further work by Milton and Lane Brown was reported by the latter at the 13th International Dermatology Congress this past year: the average survival among 50 patients with advanced malignant melanoma treated by direct inoculation with pox virus was 20 months, as against only three months for the 50 untreated controls. Local tumor destruction followed virus injection in all cases. The most favorable response was always in patients without visceral, cerebral or pulmonary metastases, the best results being obtained with skin metastases where the virus could be injected directly into the tumor. Systemic injection of virus had no effect.

The viruses used were small pox vaccine, B.P., purified suspensions of vaccinia, the Pasteur strain of neurovaccinia or rabbit pox. Optimum dosage was 400 to 600 times the normal vaccination dose of viruses. All visible deposits of melanoma were inoculated with a single injection.

Within two or three weeks the patients develop an erythematous reaction and vesication in the vaccinated tumor sites. As the inflammation subsides there is a residual blue-gray zone of pigmentation which disappears, leaving small patches of vitiligo at the vaccinated sites. There were no untoward effects in any of the treated cases.

Cell culture studies in two patients showed anti-melanoma antibody. Melanoma cells taken from these patients prior to vaccination failed to grow on the gamma globulin fraction of the serum drawn from the patients after vaccination induced tumor regression.

As to the possible mode of action of the virus, Lane Brown suggested that it probably enhances antitumor factors such as antimelanoma antibodies, and it may lead to enough tumor destruction to enable a large amount of tumor specific antigens to be released, thus permitting a competent reticuloendothelial system to recognize this antigen as foreign.

It would seem that interferon may play a role in the response to vaccinia virus and to bacterial toxins. This point deserves further study, for it may be possible to stimulate interferon synthesis more effectively by double-stranded RNA from extracts of *Penicillium funiculosum* or complexed homopolynucleotides as suggested by the recent work of Hilleman and his associates. (37, 59)

Rabies Vaccine in Malignant Melanoma:

Over 130 patients with malignant melanoma received rabies vaccine injections, the first in 1943, because she had been bitten by a dog thought to be rabid, and who remained well 10 years later, led Dr. J.B. Trunnell to suggest that a series of advanced cases be treated. These were reported by Pack in 1950 (87) and Higgins. (54) Despite the fact that the 30 cases treated at Memorial Hospital were terminal or pre-terminal, there was temporary or partial regression in two thirds of the patients.

Approximately 100 malignant patients in South America, mostly in Argentina, also received rabies vaccine injections. In 12 of these advanced cases there was apparently significant improvement. (7, see discussion by Rauschkolb).

Tagged Antibodies:

Vidal and Callahan treated a few cases with injections of rabbit gamma globulin tagged with Iodine 131, i.e., tagged antibodies against the patient's own tumor. (103) The only patient receiving such therapy who recovered also had concurrent infection and leukocytosis, and is therefore included in Series A, Case 17 of the present report.

Spleen Extracts:

Wigby and Metz reported a striking result in a man aged 43 with generalized metastases from malignant melanoma, both subcutaneous and pulmonary. (108)

Over 100 lesions were present when they began giving the patient injections of spleen extract (Armour Laboratories, derived from 325 grams of fresh spleen). This was given daily from June 15 to July 8, 1938, a total of 23 injections. Within 10 days the lesions in the chest wall began to regress. Beginning July 2, 1938, x-ray therapy was given to the pituitary in 150 r doses, totalling 1560 r to each of three portals. This was completed on August 3, 1938. The injections caused the gluteal muscles to become extremely sore and swollen. The improvement continued, the patient gained weight, and by the time the case was published the extensive metastases had almost completely regressed. They all did disappear and the patient remained free from further evidence of disease. In 1962 he developed squamous cell carcinoma of the right main bronchus which caused his death. (82)

Wigby and Metz treated four other melanoma patients with extensive regional lymph node metastases by pituitary radiation alone, without significant response. Their report suggests that spleen extracts may deserve further study as a host-stimulating agent in the treatment of malignant melanoma.

Tumor Extracts:

Rubens Duval was one of the first to use injections or oral administration of extracts of the patient's own tumor. His results were not spectacular, but the method seemed of value when begun before the disease was too far advanced, and when given as an adjunct to surgery. (94, 95)

Tumor Transplants:

Several investigators in recent years have transplanted tumors into human patients. Scanlon reported a fatal result in 1965: a melanoma was implanted into the elderly mother of a very advanced case of malignant melanoma and proved impossible to control. (96)

The recent work of Nadler and Moore at Roswell Park Memorial Institute appears to be more encouraging. (79) Patients with histologically similar incurable cancers are sensitized to each other's tumor by subcutaneously implanting a piece of tumor from patient A into patient B's thigh, and vice versa, or by incubating the tumor with white blood cells *in vitro*. After 10 to 12 days when homograft rejection had taken place, a large amount of white blood cells obtained by plasmapheresis from patient B is transfused into patient A and *vice versa*. These transplants are repeated daily for two weeks. In seven of 26 patients there was an objective response, of which two had complete responses, one malignant melanoma being in complete remission for two years when reported in 1960. The only toxic responses were nausea, occasional vomiting, chills and fever, back pain and rash, all of which occurred with leukopheresis. Locally the injected tumor cells caused erythema and induration and occasional palpable hyperplasia of inguinal lymph nodes, and occasional focal infection phenomena at the site of the tumor implants.

End Results in Infection and Toxin Treated Cases of Malignant Melanoma:

The present study comprises all patients with operable or inoperable (but not terminal) malignant melanoma known to have received toxin therapy or with concurrent infection. These have been grouped as follows:

Series A : 5 operable, 17 inoperable, with concurrent infection, fever, acute inflammation or transfusion reaction: 22 cases.

Series B: Operable toxin treated: 14 cases.

Series C: Inoperable toxin treated: 14 cases.

Fourteen of the 22 infection cases and nine of the 28 toxin treated cases remained free from further evidence of their malignant melanoma when last

INTRODUCTION

traced from five to 56 years after onset. The average survival of the 28 toxin treated cases was over three times the expected survival for this neoplasm. All but four of the toxin treated cases were recurrent, often several times, or metastatic, or both recurrence and metastases were present when toxins were begun.

DISCUSSION:

The factors which appear to influence natural resistance to malignant melanoma either favorably or unfavorably have been reviewed. Those which appear to act favorably are concurrent bacterial infections (especially streptococcal and staphylococcal), fever, heat, inflammatory episodes, transfusion reactions, agents which stimulate the lymphoid tissues or induce fever or acute inflammation, streptococcal enzymes, fibrinolysin, rabies vaccine, vaccinia virus, tumor extracts or tumor transplants combined with sensitized leukocytes, or mixed bacterial toxins (Coley toxins or MBT). The latter appear to have produced significant and lasting results in a larger number of patients than other agents, without deleterious side effects.

Among the factors which may decrease the natural resistance of the patient with malignant melanoma are extensive removal or inactivation of lymphoid tissues by surgery or heavy radiation, the use of immunosuppressive or anti-inflammatory drugs, widespread disease or advanced age.

Other factors affecting prognosis with toxin therapy are the technic of administration, especially the duration and type of febrile reaction elicited. The latter depends not only upon the dosage used but also upon the site of injection. Better results occurred when at least some of the injections were given in or near the tumor areas.

Since there is impressive evidence suggesting that bacterial infections may cause complete or partial regression of malignant tumors, including malignant melanoma, one must question the wisdom of routine administration of antibiotics before or after cancer surgery, except for life-threatening infections. (110) This point is discussed in greater detail elsewhere, as it relates to cancer of the colon and rectum. (39)

Bacterial infections, or microbial products in appropriate doses, may stimulate the functional capacity of the reticuloendothelial system and the lymphoid tissues, which are now recognized as playing a significant role in natural resistance to cancer. (1, 7, 8, 85)

A number of investigators have reported on the significant protection against lethal doses of radiation which is produced by even a single *prior* injection of bacterial toxins. Apparently this is due to their stimulation of the hematopoietic, lymphoid and reticuloendothelial tissues. (1, 19, 97, 98) Other recent studies indicate that preliminary bacterial infection or toxin therapy may markedly potentiate the response of the neoplasm to subsequent radiation, even radioresistant tumors such as fibrosarcoma or malignant melanoma. (16, 41) The last three cases in Series C suggested the possibilities of such potentiation in far advanced cases of malignant melanoma. Fletcher and Donaldson studied the effects of preliminary injections of MBT combined with x-ray therapy on the metastatic spread of the extremely malignant Fortner melanoma in hamsters. They found that with these toxins given first, the same amount of regression was obtained with almost half the dose of x-ray required in animals not pretreated with toxins. (82)

In discussing the role of natural resistance in human melanoma, White stated that immune and other factors, including the age of the patient, all appear to play a role in control of tumor growth. Since this often ephemeral control appears to exist chiefly in the early stages of the disease, he suggested that attention should be paid to the possibility of bolstering such controls at the time of surgery for melanoma. (107)

Analysis of the toxin treated cases of malignant melanoma indicates that

no cures were obtained in the terminal or preterminal stage (approximately 75 cases). Such cases were the only ones available to Coley for such treatment in the first few decades, and this led him to believe that malignant melanoma was more resistant to toxins than other types of cancer. In 1935 he stated: "While in my earlier papers I gave little encouragement for using toxins in this type of tumor, later experiences, both my own and that of other surgeons, has led me to revise my earlier pessimistic opinion. . . . I believe that the toxins offer the greatest hope for cure of this disease of all methods at our command. . . . Surgery combined with toxin therapy has proved successful in a number of cases." (28)

It would now appear that the most effective combination of therapies for malignant melanoma and other types of cancer is one that includes an attempt to stimulate and protect the host resistance mechanisms of the patient, given *prior* to any surgery except biopsy and *prior* to radiation. The need for such adjuvant therapy was first considered by the late William B. Coley (25, 80) and by Matagne, a Belgian physician. (66-69) Their observations and clinical experiences were largely based on empirical theories.

Recently Martin has clearly indicated the desirability of carefully planned combination therapy. First of all he showed that if too large a mass of tumor is present, no amount of subsequent combination therapies will prove curative. He therefore suggested that some of the tumor be removed following preliminary administration of an agent designed to stimulate host resistance. (64, 65) He found that reduction of tumor size by simple surgery restored the curative effect of subsequent chemotherapy. These studies showed that "cure" can rarely be effected on large well established tumors by chemotherapy alone, immunotherapy alone (he used zymosan, a yeast extract) or surgery alone. However, by combining these three modalities, Martin was able to obtain striking cure rates in the range of 80 to 90 per cent. These results could be nullified by simultaneous administration of an immunosuppressive drug such as cortisone. (64, 65) It is of interest to note that Coley and other surgeons obtained similar percentages of permanent results in operable and early inoperable human neoplasms treated by toxin therapy combined with surgery. (82, 91)

In analyzing the cases of spontaneous regression occurring after incomplete surgical procedures, Martin's studies suggest that by reducing the size of the neoplasm certain patients, whose natural resistance is not yet seriously weakened by the disease, may be enabled to destroy the remains of the growth unaided by infection, fever, or other "complications."

In order to obtain the highest percentage results it would appear necessary to administer a host-stimulating agent such as bacterial or yeast extracts to increase whatever immune defenses may be present.

SUMMARY AND CONCLUSIONS:

In a considerable portion of the cases of spontaneous regression of malignant tumors, including malignant melanoma, fever and infection were implicated.

The known cases of malignant melanoma with concurrent infection, fever or inflammatory episodes have been reviewed. These include a number of spectacular results, not only immediate but in some cases apparently permanent.

While the prognosis in malignant melanoma is notoriously bad, the cases assembled here, both infection and toxin treated patients, suggest that we must adopt a less pessimistic attitude about these highly malignant tumors, and that better results may be obtained in the future by the judicious combination of several modalities. One of these, which until recently has been largely ignored, is the use of bacterial toxins as a means of enhancing the resistance of the host and potentiating the response of the tumor to radiation, or to surgery. The stimulating effect of suitable dosages of certain bacterial toxins on the lymphoreticuloendothelial system is believed responsible for much of the salutary

effect of concurrent infections or of bacterial and yeast extracts. Increasing the antigenicity of the tumor cells and the fibrinolysin titre of the patients' serum may also contribute to the result. Recent studies on animals indicate that *prior* administration of bacterial toxins protects them against the lethal effects of large doses of whole body radiation. Thus timing of various therapies becomes of great importance if we are to obtain the optimum results.

The most important factors affecting success or failure with toxin therapy of malignant melanoma include the stage of the disease when toxins were begun, the potency of the preparation used, the duration and intensity of toxin therapy, and the amount of surgery and radiation given prior to the toxins.

Further intensive research is needed in order to discover many potent, stable preparations of bacterial or yeast extracts, and to try possible combination of these with other agents which may stimulate the synthesis and release of interferon or which may increase the levels of fibrinolysin in patients with malignant melanoma and other types of cancer.

SERIES A: MALIGNANT MELANOMA WITH ACUTE BACTERIAL
INFECTION OR INFLAMMATION: 22 Cases.

The name in parenthesis following the case number refers to the physician or hospital handling the case. The abstracts are listed chronologically with the exception of case 22 which was added as the report went to press. At the end of each abstract the bibliography reference numbers are given. Most of these cases were inoperable or had metastases when the infection or inflammation developed.

*Years Traced
After Onset*

1. (MOSENGEIL): Female, aged 50; inoperable malignant melanoma of nose, eyelid, cheek, ulcerated, extensive recurrent growth; numerous pigmented lesions on face, arms; primary excised; rapidly recurred; *actual cautery; slight attack of facial erysipelas; growth then ceased, healthy granulations formed; not traced subsequently.* (10; 34; 75; 76) ?

2. (BRUNS): Female, aged 47; recurrent inoperable malignant melanoma of lt. breast, metastases in lt. axilla size of walnuts; primary excised, axilla cleared 18 mos. after onset; rapid recurrence; *severe erysipelas lasting 3 wks., spread over greater part of body; complete regression, no further evidence of disease, entirely well.* (11; 21, Case 15; 34; 76, p. 33). 9½

3. (PLENIO): Female, aged 22; extensive inoperable malignant melanoma of gluteal region, extending to iliac spine and fold of buttocks onto abdominal wall, iliac lymph nodes enormously enlarged; *attempted removal followed by phlegmonous erysipelas, gangrene of skin, thrombosis, septicemia (almost fatal); during convalescence extensive neoplastic involvement all disappeared; no recurrence or metastases; entirely well when last traced.* (11; 42; 93). over
2

4. (NORTHROP): Female, aged 80; three times recurrent inoperable malignant melanoma primary in right nasal cavity; large lesion excised September 1893; metastasis in rt. cervical region promptly developed, removed; February 1894, 2 recurrent tumors 2½ cm. in diameter behind sternomastoid excised; further extensive recurrence in 1 mo. extending down nearly to clavicle, deeply attached, severe pain; exploratory incision revealed extensive infiltration, condition inoperable; *11 days later erysipelas of face and neck; pain ceased, growth regressed completely in 2 wks.; further recurrence 4 mos. later; 2 nodules enucleated from neck, 1 from inner side of cheek; end result unknown.* (84). ?

5. (DALAND & HOLMES): D. J., male, aged 42; recurrent malignant melanoma, primary at base of rt. small toe, multiple metastases to rt. thigh, rt. groin; onset, February 1927; excision, February 28, 1927; local recurrence, groin metastases in next few mos.; July 28, 1928, tarso-metatarsal amputation of 4th and 5th toes; node in rt. groin excised; recurrence in amputation scar excised November 11, 1928; about two wks. later *erysipelas of rt. buttock; many dark shot-like nodules on anterior thigh apparent by December 9, 1928; scar area became infected, indented and surrounded by infiltrating tumor; 2nd erysipelas infection, January 1929 extending over rt. hip, thigh, in region of metastases; by November 30, 1930 multiple cyst-like masses present on inner thigh, palpable nodules in foot, rt. groin and proximal rt. knee; these nodules excised November 1930; lt. inguinal herniorrhaphy, December 1933; December*

1934, cerebrovascular accident; small tumor present in rt. groin, large mass in region of rt. knee; death, February 4, 1935; presumably of cerebral metastases. (31).

8
(died)

6. (HALL): T. D., male, aged 29; malignant melanoma uveal tract lt. eye; patient kicked in face by a mule, fracturing skull, injuring lt. optic nerve; onset, about 6 mos. later, cloudy vision; 1 yr. after injury *sudden acute illness, emesis, headache, severe pain frontal sinus, requiring morphine for a wk., both eyes swollen shut (type of infection not recorded)*; suddenly lt. eye ruptured, drained jellied black to reddish contents; eye lanced 3 times, pain increased, patient requested enucleation which was performed; *complete recovery, well, symptom-free for 27 yrs.*; then began to tire easily, lost 25 lbs., brief episodes back pain; hepatomegaly noted on admission; laminectomy for compression lesion L 1, cast applied; death 48 hrs. later due to non-neoplastic embolism inferior vena cava produced by large hepatic metastasis; autopsy revealed multiple metastases to liver, adrenals, lungs, retroperitoneal lymph nodes, also recurrence or extension of primary in scar of Tenon's capsule. (49).

30

7. (MULLEDER): Male adult, physician; many times recurrent very extensive malignant melanoma with multiple metastases, primary in lt. inguinal region; patient had been operated almost yearly for recurrences and metastases in both lt. and rt. inguinal regions over a period of 5 or 6 yrs.; at final operation mass size of 2 fists pressed on iliac vessels causing increasing edema of whole lower extremity; incomplete removal by flat incision leaving rough melanotic platform about 10 by 18 cm. in diameter; wound left open at patient's express wish; many egg-sized metastases present on lt. abdomen, rt. inguinal region, lt. proximal thigh had not been removed; *very extensive erysipelas infection lasting 8 days; infiltrating melanoma metastases regressed markedly, became noticeably movable, smaller ones disappeared, quantities of melanin excreted in urine*; later metastases again began to increase in size; within a few mos. *erysipelas again developed, but was less severe; again regression occurred*; end result unknown. (77).

?
over
5

8. (MEMORIAL HOSPITAL): N.H., male, aged 40; malignant melanoma lt. shoulder, metastases to chest wall, axilla, infraclavicular region; (Pack believed some lesions were multiple primary malignant melanoma in this case); pigmented nevus excised from lt. shoulder December 1931; axillary dissection March 18, 1932; *postoperative wound infection, abscess, fever*; x-ray then given; metastases on chest excised November 23, 1932, another May 9, 1933, 3 more, September 1, 1933; *most of remaining nodules on scalp and breast then regressed spontaneously*; further lesions excised May 1, 1934, October 9, 1934, March 28, 1935; rt. radical axillary dissection April 23, 1935; very unusual dark metastatic growth; *complete regression November 1936; infection, inflammation; no further evidence disease thereafter*; in excellent health 1968. (71; 82; 89).

37½

9. (MEYER): M. M., female, aged 36; malignant melanoma lt. arm, inoperable axillary metastases; primary excised November 14, 1934; axillary metastases developed; reoperated May 16, 1935: "partial excision of lt.

- axillary mass *complicated by an abscess*; considerable amount of tumor left in axilla; this completely regressed; alive and well 1955. (5; 37). 21
10. (MORTON): M. L., female, aged 40; metastatic malignant melanoma primary in lt. anterior chest; 4 cm. nevus excised February 1934; hysterectomy for leiomyoma uteri, 1935; rt. radical mastectomy for cystic mastitis, 1936; diabetes mellitus, 1936; malignant melanoma metastases in lt. axilla 1939; lt. radical mastectomy; metastases to neck excised February and October 1940; rt. axillary metastases excised, neck explored, June 1941; *postoperative infection of neck wound with drainage*; x-ray (1500 r in 10 days), 2 more courses x-ray, 1941; cellulitis 1943; virus infection, 1955-56; *no further evidence of melanoma after infection in 1941*; remained apparently well until death, February 1959, from cerebral hemorrhage, pulmonary emboli; autopsy showed no evidence of malignant melanoma. (74; 82). 25
11. (GALGANO): Female, aged 46; malignant melanoma primary in rt. temple, pulmonary metastases; onset, 1932, lesion in rt. temple; excised; well 11 yrs.; routine chest film, February 1943 revealed asymptomatic nodule on lt. anterior intercostal space; *concurrent pneumonia, pleurisy*, August 1943; nodule in lung persisted, no progression apparent until April 1945, then new shadow in rt. hilum; deep x-ray to lungs (4799 r); did well until September 1948, then night sweats, headaches, hot flashes, dull ache in anterior chest; x-ray revealed 4 metastases in loculated pocket, pleural fluid; thoracotomy, April 1949; 10 cm. mass in rt. hilum biopsied; within 3 mos. recurrence appeared in rt. temple, 17 yrs. after onset of primary lesion; excised January 1951; further recurrence also excised; disease then progressed, steady downhill course, further enlargement of pulmonary nodules, melanuria; death, February 21, 1952, 20 yrs. after onset, 9 yrs. after pulmonary metastases. (43). 20
12. (SUMNER): Mrs. R. R., female, aged 27; malignant melanoma lt. ankle; *tumor became infected and disappeared*; February 1946; during 3rd pregnancy painless metastasis lt. groin; about February 1948, painless mass in rt. breast; again became pregnant, early October 1948; breast metastases rapidly increased in size, became painful; another mass appeared in lt. arm; during 2nd to 5th mos. of gestation several other small metastatic lesions appeared on the abdominal wall and back; *ringworm infection* about January 1949; tumors of rt. breast, lt. arm and lt. femoral region excised February 28, 1949 — all proved to be malignant melanoma metastases; larger tumors on back and abdominal wall excised March 28, 1949; normal delivery at term, May 20, 1949; small recurrent mass in femoral region excised December 6, 1949; pathologist reported "*circumscribed melanoma inguinal lymph nodes, radiation fibrosis of inguinal nodes, acute and chronic lymphadenitis*," i.e. a tissue reaction typical of radiation but no radiation had been given; another small recurrence appeared in rt. supraclavicular region July 3, 1950, excised 4 days later; no further recurrences; *sites of all previous tumors became depigmented, including 1 over eyebrow where an untreated tumor had apparently regressed completely*; alive and well August 1967, 21½ yrs. after the primary lesion had regressed following infection. (82; 101; 102). over 21
13. (B. L. COLEY): R. K., male, aged 21; twice recurrent non-pigmented malignant melanoma of rt. ankle (onset 1944); primary excised, recur-

red following bump on leg, January 1946; again excised May 1946; again recurred; lost 18 lbs. in 2 mos., felt weak, tired; fungating recurrent tumor mass 10 cm. in diameter; then developed *extensive suppurative, fibrosing inflammation around tumor, lymphadenitis in groin*; amputation, groin dissection July 23, 1946; pathologist reported small foci of persistent malignant melanoma in tissues medial and posterior to lower part of ulcer, *extensive fibrosing and suppurative inflammation of tissues surrounding large ulcer*, no evidence of metastases in groin, only *hyperplastic lymphadenitis*; following operation developed serosanguinous collection of fluid in groin; no further recurrence or metastases; obtained prosthesis, returned to work, continued to do so steadily; n.e.d., in excellent health 1968. (71; 82).

24

14. (MEMORIAL HOSPITAL): E. W. H., male, aged 27; recurrent metastatic malignant melanoma lt. axilla, primary site undetermined; mass of broken down lymph nodes involving subpectoral group excised August 20, 1946; pigmented tissues present beneath the wound; benign neuronevus on back also removed; 2nd operation at Memorial Hospital, September 24, 1946, radical lt. axillary dissection; areolar tissues in fascial plane between latissimus dorsi and subscapular muscles and chest were deeply infiltrated by black pigmentation; although dissection was clear and wide, some disease remained; prognosis guarded; *6 days later severe staphylococcus wound infection; no further metastases, remains of tumor apparently regressed*; 2 yrs. later married, had 2 children; n.e.d., in very good health thereafter. (71; 82).

22

15. (MEMORIAL HOSPITAL): Mrs. M. B., female, aged 58; subungual malignant melanoma of rt. great toe, with inguinal node metastases; (onset, September 1945); 2 local excisions prior to February 1947; great toe amputated February 8, 1947; palpable groin metastases March 1947; hip joint disarticulation refused, so radical groin dissection done, March 21, 1947; *moderate postoperative febrile episodes, fluid in wound, infection and necrosis of wound requiring skin grafts; diffuse edema of leg, erysipelas, cellulitis; no further metastases*; remained well until April 1955, then developed papillary adenocarcinoma ampulla of Vater; subtotal gastrectomy, pancreatoduodenectomy, May 12, 1955; death October 17, 1955 from recurrent adenocarcinoma, no evidence malignant melanoma. (17).

10

16. (VOGLER): Mrs. M. C., female, aged 57; malignant melanoma rt. foot, metastases to rt. groin and thigh; (onset, March 1949); *primary lesion became infected following trauma*; widely excised April 1949; pathologist reported "*marked evidence of infection and areas of atypical keratoses*"; 3 wks. later rt. groin dissection revealed metastatic area in nodes; amputation had been refused; 11 mos. later further metastases to rt. thigh, 1 of which was biopsied; further skin metastases continued to appear on rt. leg and thigh during next yr.; again refused disarticulation; not seen again until March 1953; *during this period of 3 yrs. all but 1 metastatic lesion regressed spontaneously*; another metastasis developed October 1953, was excised with remaining lesion; June 1954, numerous nodules present over rt. leg; 1 excised, 22 others irradiated (1000 r low voltage x-ray in 20 days); *all 22 lesions regressed, also some untreated nodules disappeared*; no further evidence of disease for 2½ yrs., then another nodule developed, was excised; apparently well March

to December 1958 when large *pleural effusion* occurred, Papanicolaou smears were Class I; nitrogen mustard given early 1959; *cystitis* February 1959; *continued to have episodes of pleural effusion*; repeated Papanicolaou smears negative for tumor cells; although not demonstrated was believed to be dying of widespread metastases, April 1959; death occurred about September 1959 (no autopsy). (71; 104). (died)
11½

17. (VIAL & CALLAHAN): V. P., male, aged 60; metastatic malignant melanoma, primary in rt. anterior thigh; (onset, July 1948, 2 cm. pigmented nevus); September 1948, lt. maxillary sinusitis; primary excised March 1950; recurred, irradiated without effect; tumor mass increased, many satellite pigmented skin nodules; parahydroxypropioquinone, radioactive iodine and radioactive copper given without effect; *groin mass then became infected*; generous biopsy of this lesion October 1951; *leukocytosis, lesion remained infected, suppurated for 5 mos.*; 2 injections rabbit gamma globulin tagged with I^{131} (tagged antibodies against his own tumor); *2nd caused anaphylactic reaction, December 1951*; 5 *parenchymal lung metastases present prior to this decreased in size and disappeared in 3 mos.*; patient myxedematous, requiring thyroid replacement, which he neglected at times; further metastases to rt. groin 1953; Thio-TEPA for 1 mo. without effect; 1 more injection I^{131} tagged antibodies; biopsies October 1953, January 1954 positive for malignant melanoma; *thereafter no further evidence of disease*; died suddenly at work January 27, 1959, coronary insufficiency; n.e.d. at autopsy. (9; 82; 103) 10
18. (B.L.COLEY): J.H.M., male dentist, aged 41; recurrent malignant melanoma rt. leg, rt. inguinal lymph node metastases; (onset, May 30, 1949 nevus began to enlarge rapidly); removed by electrocautery October 1949; x-ray for 9 mos., once a mo; another cycle x-ray begun March 1951; early May 1951, *ulceration appeared in cicatrix*; *Bacitracin ointment helpful*; rt. inguinal node metastases apparent June 1951, also several satellite pinhead size lesions in upper part of ulcerated area in cicatrix; 1 cm. lymph node metastasis in upper ft. femoral triangle; consulted Coley after having been advised to have amputation; June 11, 1951, recurrence widely excised, skin grafted by Coley; pathologist reported "infected malignant melanoma, margins clear;" July 2, 1951, rt. radical groin dissection, direct inguinal herniotomy; 2 metastatic nodes present; *wound failed to heal, furuncle present October 1951 requiring aureomycin*; healing finally occurred 41½ months after surgery, except for some scab formation which continued for 2 yrs.; August 1956, *infected sebaceous cyst in axilla incised, pus obtained*; in excellent health thereafter, no further evidence of disease 1968. (71; 82) 19
19. (BAKER): H.L., male, aged 46; recurrent, inoperable malignant melanoma rt. ear, metastasis to lymph node in parotid region; onset, March 1955; 3 mos. later lesion burned off by local physician; recurrence in 1 mo.; incisional biopsy of 8.8 mm. recurrence, March 12, 1956; subtotal resection ear in continuity with parotidectomy, radical neck dissection, March 21, 1956; 9 mos. later recurrent nodules present; these doubled in size by March 21, 1957; large tumor mass *grossly infected* by June 1957, fungated through skin of upper cervical region, extending over mastoid onto rt. cheek, fixed to deeper structures, bled easily; patient repeatedly refused hospitalization, only treatment "*compresses and*

prayer"; frequent hemorrhages occurred, then complete regression, leaving depigmented scar; n.e.d. thereafter; alive and well 1969. (5; 37, p. 207-211; 82)

14

20. (McCREDIE): A.R., male, aged 32, metastatic malignant melanoma primary in nevus on dorsum of lt. foot, metastases in lt. groin; primary cauterized; metastases in lt. groin present by July 1956; extensive cobalt therapy to lt. inguinal region and lt. upper thigh anteriorly; 12-14 subcutaneous metastases appeared in August and September 1956, mostly on trunk, chest wall, lt. axilla and rt. forearm; these began as tiny pin-points, gradually grew, some to size of thumb, deeply pigmented, then gradually disappeared leaving pin point of nodularity in subcutaneous tissues; finally all disappeared by October 24, 1958 except for a bluish nodule 0.5 cm. in diameter in rt. forearm; in next 6 wks. nodules continued to appear and regress; remained well until June 1959, then nausea, vomiting, melanuria, hepatomegaly; bedridden, unable to eat, marked weight loss (56 lbs.); *intermittent high fever*, marked weakness, sweating; 6 to 8 transfusions totalling 23 pints whole blood given between November 1959 and February 23, 1960; following final one, February 23, 1960, *developed chest pain, tightness, dyspnea; few days later began to improve, ate well, all symptoms ceased, gained 59 lbs. in 6 mos.; no further evidence disease*, well 1965, 9 yrs. after onset. (37, p. 211-213)

9

21. (MAYO CLINIC): male, aged 31; malignant melanoma in skin overlying 1st thoracic vertebra, with cervical lymph node metastasis; onset, April 1965, nevus present since birth increased in size, became much darker; concurrent very severe sunburn while in Mexico; patient rubbed and scratched lesion; *it disappeared*; November 1965, metastasis in rt. posterior cervical triangle; this grew rapidly for 1 mo. then stabilized; January 1966, *small pox vaccination in rt. deltoid, secondary infection and slough*; excisional biopsy of cervical lesion, wide excision of site of primary; only 1 cervical node contained metastatic malignant melanoma, *all others showed non-specific inflammatory changes*; sarcolysin given orally after surgery (50 mg. every 12 hrs. for 36 hrs.); well about 6 mos., disease then reactivated, metastases to lt. kidney, rt. shoulder, rt. arm, rt. buttock, lt. chest wall; accessible superficial metastases excised, final excision June 1967; palliative x-ray for pain due to renal lesion, without apparent benefit; death December 24, 1967, (82; 102a)

Died
2¾

22. (WARD & ACQUARELLI): male, aged 51; recurrent malignant melanoma in concha of lt. ear, with lt. submaxillary lymph node metastases; onset mid-January 1947, pin-head sized growth present 10 yrs. began to enlarge and darken; March 25, 1947: excision 2 cm. black raised lesion in concha extending to cartilage, and 1 cm. subcutaneous nodule anterior to lt. ear; latter was negative; well 5 mos., then recurrence, lt. submaxillary lymph node metastases; nodes biopsied 6 mos. after recurrence developed; February 24, 1948 auricle amputated in continuity with lt. radical neck dissection; *fistula developed; it responded to penicillin and local measures*; hospitalized 7 wks.; December 1948, gastroenterostomy for perforated duodenal ulcer; well thereafter; suspicious nodules lt. pre-auricular, lt. neck, posterior lt. neck biopsied 1949-1952, all proved negative; no further evidence disease, in good health 1967. (104a)

20

SERIES A, DETAILED HISTORIES

THE DETAILED HISTORIES OF SOME OF THE MORE INTERESTING OF THESE CASES ARE GIVEN BELOW:

CASE 2: Recurrent inoperable malignant melanoma of the left breast with axillary metastases, confirmed by microscopic examination of both the primary and the axillary lesions by Professor Schuppel.

Previous History: Female, aged 47. The family and previous personal history were not recorded. The patient had a tumor of 18 months' duration which was the size of a cherry when first noted and which increased rapidly until it was the size of an egg. It was painless at first, later becoming painful, the pain radiating to the axilla. It was soft in places firm in others and the surface was uneven, the skin adherent and ulcerated, but the growth was movable over the underlying muscles. There were two groups of enlarged lymph nodes in the axilla the size of walnuts.

Surgery: At the time the growth was excised in 1880 it was almost the size of a fist. The axilla was also cleared. The tumors were coal black, typical malignant melanoma.

Clinical Course: The postoperative course was uneventful at first, except for a slight discharge of pus. After four weeks the wound healed except for a small fistulous opening where the drainage tube had been. Recurrence took place rapidly, beginning at the fistula through which deep black nodules soon protruded. The recurrence then spread along the cicatrix which gave way and began to gape. The general condition had not yet been affected. The patient was under the care of Dr. Paul Bruns, of Tübingen, Germany.

Concurrent Infection: Four weeks after operation she developed a severe erysipelas infection which spread over the greater part of the body, first over the right shoulder and left axilla, then over the back, thorax, abdomen, buttocks, legs and both upper arms. The infection lasted three weeks, leaving the patient very much weakened and emaciated. There was constant fever during this time, but only on a few days was it over 104°F. After the erysipelas had run its course, the recurrent growth began to diminish in size and within a few weeks it had completely disappeared and the fistula remained firmly closed.

Clinical Course: Bruns examined the patient repeatedly and found no evidence of further recurrence or metastases. She remained perfectly well when last seen in 1888, eight years later, over 9½ years after onset.

Comment: Note that this patient developed an unusually severe and widespread erysipelas infection, lasting three weeks instead of the usual week or 10 days. It would appear that the reason only temporary or partial regression was observed in about 20 cases of various types of tumors who developed erysipelas is that the infection was not sufficiently severe or prolonged. This case was also cited by Kleeblatt in 1890 and Spronck in 1892.

References: (11; 21; Case 15; 34; 76, pp. 33-34).

CASE 3: Extensive inoperable malignant melanoma of the gluteal region, with metastases to the inguinal and iliac lymph nodes.

Previous History: Female, aged 22. The family and previous personal history were not recorded. The patient had a far advanced malignant melanoma of the gluteal region, extending to the iliac spine, the fold of the buttock and onto the abdominal wall. The inguinal lymph nodes were enormously enlarged. The overlying skin was blue and part of it was adherent.

Surgery: An attempt at removal was made but the growth was found to infiltrate the muscles of the hip and abdominal wall.

Concurrent Infection: Following this operation there was a severe phlegmonous erysipelas infection, with gangrene of the skin, thrombosis and septicemia. The patient was gravely ill. During convalescence the extensive tumor disappeared.

Clinical Courses: There was no recurrence or further metastases. The patient was traced entirely well and free from disease two years later.

References: 11; 42; 93.

CASE 4: Three times recurrent inoperable malignant melanoma, primary in the right nasal cavity, with metastases behind the sternomastoid muscle.

Previous History: Mrs. F., aged 80. The family and previous personal history were not recorded.

Surgery: In September 1893 a malignant melanoma of large size was removed from the right nasal cavity. She soon developed a metastatic lesion in the right cervical region which was removed at Hahnemann Hospital, Philadelphia, Pa. In February 1894 she returned with two more tumors about 2 cm. in diameter behind the sternomastoid muscle. These were easily removed.

Clinical Course: Within a month there was an extensive local recurrence. Examination by Dr. H. L. Northrop revealed an elongated mass on the right side of the neck in the line of the sternomastoid muscle, reaching from about 2 cm. above the clavicle to 3 cm. below the ear. The growth was deeply attached, not adherent to the skin and extended inward nearly to the midline of the neck, causing severe pain.

Surgery: An incision under general anesthesia revealed an extensive infiltration which was inoperable and the wound was closed.

Concurrent Infection: Eleven days later the temperature suddenly rose to 102.4°F., the skin on the right face and neck became fiery red and painful and the neck was edematous, pitting on pressure. The complication was promptly diagnosed as erysipelas and its effect upon the neoplasm was watched with great interest. Nine days after the erysipelas developed the growth was considerably smaller and more movable. The pain, which before the infection had been

severe, had entirely disappeared, and the general condition had improved. The recurrence disappeared in two weeks.

Clinical Course: The patient was discharged. Four months later she returned with a further recurrence.

Further Surgery: Three metastatic lesions were removed from the sheath of the common carotid and internal jugular vein and a small growth was enucleated from the inner side of the right cheek. The wounds healed nicely and the patient left the hospital in good condition.

Clinical Course: She was not heard from again and was believed to have died. Northrop stated: "My object in detailing this case is to show the effect of an attack of erysipelas upon sarcoma — and a melanotic sarcoma at that. . . . I suppose we are not justified in claiming that the patient . . . was more than slightly improved. But she enjoyed immunity for a longer period of time after the attack of erysipelas than after merely mechanical removal of the neck tumors." (This case was also cited by Vidal in 1910).

References: 84.

CASE 7: Many times recurrent inoperable malignant melanoma with multiple metastases, confirmed by microscopic examination by Professor Sternberg, of Vienna, Austria, following the final operation.

Previous History: S., male adult physician. Onset, about 1923 the patient developed a malignant melanoma in the left inguinal region.

Surgery: He was operated upon almost yearly during the next five or six years. The recurrence and metastases involved both the right and left inguinal lymph nodes. At these operations the involved nodes were extirpated as completely as possible. The final operation was performed at the patient's request because a mass about 10 by 15 cm. in diameter was pressing on the iliac vessels and causing edema of the left lower extremity. The tumor tissue could not be completely removed. The major part was excised by a flat incision, leaving a rough melanotic platform approximately 10 by 18 cm. in diameter. The wound was left open at the patient's express wish (he was a physician). At this time many egg size metastases were present on the left abdomen, the right inguinal region and the left upper thigh.

Concurrent Infection: The patient then contracted a very extensive erysipelas infection lasting eight days. Dr. Anton Mullender, of Stockerau, near Vienna, reported: "It was striking to observe how the infiltrating melanotic lymph nodes became smaller under the influence of this accidental infection. When the erysipelas had run its course the tumors, which had been the size of eggs, were reduced to the size of nuts, and from being immovable, had become markedly movable. Smaller nodules had entirely disappeared. In the meantime, quantities of melanin were found in the urine."

Clinical Course: The metastatic tumors later again began to increase in size.

Second Concurrent Infection: Some months later, while taking a sun cure in the south, another erysipelas infection developed which did not last as long as the first. Again the metastases regressed.

Clinical Course: No further details are given and the end result is unknown.

Reference: 77.

CASE 8: Malignant melanoma of the left shoulder, with metastases to the axilla, chest wall and infraclavicular region, confirmed by microscopic examination of the primary and the metastatic lesion by Dr. Fred Stewart at Memorial Hospital.

Previous History: N.H., Jewish male, aged 40. The family history was non-contributory. The patient was a salesman. He had had the usual diseases of childhood and an appendectomy following appendicitis many years prior to onset. He had had many pigmented nevi scattered over his body from birth.

Surgery: In mid-December 1931 a congenital nevus was excised from the left shoulder.

Clinical Course: The patient was admitted to Memorial Hospital on March 17, 1932 with a question of recurrence and axillary metastasis. At this time he had slight pain in the left axilla. Examination revealed a well developed, well nourished ambulatory white man with a scar on the left shoulder, adjacent to which was a small elevated soft black tumor the size of a match head. There was an enlarged tender lymph node in the left axilla, also one on the adjacent neck.

Concurrent Inflammation: There was also a macular, discrete, irregularly shaped skin eruption over the trunk, extending to the extremities. Freckles, rash, capillary and pedunculated capillary hemangiomas, small lipomas, flat and pedunculated nevi were scattered more or less over the entire body.

Further Surgery: On March 18, 1932, Dr. Frank Adair performed an axillary dissection and encountered two very large and several smaller involved nodes. They were not black. One was soft and thought to be inflammatory. The pectoral muscle was cut and then resutured. The recurrent nodule adjacent to the shoulder scar was excised. Stewart reported: "Mass of axillary fat 10 x 15 cm. in diameter, containing several nodes; two of them the size of marbles completely replaced by tumor tissue, non-pigmented. Two other nodes are pea-sized, one with slight pigmentation. Several smaller nodes looked normal. Second specimen is skin with a minute black superficial plaque 2 mm. wide. Malignant melanoma." (71, D 830)

Post-Operative Infection: The wound in the axilla drained quite a lot of seropurulent material and a small abscess developed on the shoulder which was opened on March 27, 1932. The temperature rose to 100.6°F. on March 18, 1932 and remained slightly elevated for about 10 days.

Radiation: Radiation therapy was then given but factors were not recorded.

Clinical Course: It was noted on November 23, 1932 that there were two or three very small lesions on the anterior chest and about three on the posterior chest. These were rather sessile, mushroom-shaped and although black, not at all typical of melanoma. (71, D 3836). The patient appeared to be in good general condition. There was no further evidence of disease in the axilla.

Further Surgery: On May 9, 1933 a nevus was removed from the center of the left nipple under novocaine anesthesia. This was reported as malignant melanoma by Stewart. (71, E 1353). On August 1, 1933 three papillary pigmented nevi were excised from the anterior chest wall. One measured 2 cm., the others 1 cm. in diameter. Stewart reported that all three showed malignant melanoma but remarked: "These don't look like metastases, resemble primary lesions." (71, E 2400).

Spontaneous Regression: In February 1934 it was noted that one black nodule remained in the area of the breast and one on top of the scalp. There

was no axillary disease. The patient was shown at the conference at this time "as an interesting case of widespread metastases treated by multiple local excisions. . . ." On March 16, 1934 it was noted by Adair that "curiously enough most of these melanomas are gone with the exception of a few in the region of the shoulder." (71)

Further Surgery: On May 1, 1934 lesions were removed from the left infraclavicular space and from the posterior aspect of the left arm. Stewart reported that the former was a malignant melanoma and that the latter was a pigmented nevus. At this time there was also a nodule on the top of the scalp. This was removed on October 19, 1934 — the 10th to be excised — and Stewart reported it was a malignant melanoma. On March 27, 1935 there was a little nodule near the site of the one previously removed from the left anterior pectoral region, also a little red area on the outer arm. These were removed by Dr. Gray Twombly on March 28, 1935, under local anesthesia. Stewart reported that the pectoral lesion was a malignant melanoma, the one on the arm being a papillary hemangioma. (71, F 7474). By April 8, 1935 there was a firm large node in the right axilla. Dr. George Pack reported on April 8, 1935: "The peculiar character of this melanoma and its unusual control by repeated excisions would justify an attempt to prolong his life further by a right axillary dissection." (71). This was performed on April 23, 1935. Stewart reported it to be metastatic melanoma. (71, G 486). The postoperative course was uneventful. On January 9, 1936 a large papilloma on the right lateral chest wall was excised in the outpatient department under local anesthesia. This was reported by Stewart to be an epithelial papilloma.

Clinical Course: The patient remained in excellent condition with no further evidence of disease until the third week in October 1936 when a very unusual dark metastatic deposit developed on the flexor surface of the right wrist. This grew rapidly and a month later it was 0.5 mm. in diameter and intensely black. This was to have been excised but five days later the patient telephoned and stated that it seemed to have almost disappeared. It did regress completely and thereafter there was no further evidence of disease. On August 16, 1937 there was a little subcutaneous swelling in the right arm which felt like a thrombosed vein. On August 26, 1937 this small nodule on the anterior aspect of the right elbow was removed and was reported as "not melanoma; sclerosing angioma (perithelial)". (71). On September 2, 1937 the patient complained that his eyes "burn, water and tire." At examination a chelazion was present on the upper right lid, also a small localized elevated tumor mass.

Further Surgery: On September 13, 1937 the latter was excised and was not metastatic malignant melanoma. On August 1, 1938 it was noted that there were numerous nevi flammeus along the chest, upper abdomen and upper back, also seborrheic keratoses. Two of the large epithelial papilloma (one on the chest and one on the back) were excised by electrocautery and the skin sutured. Keratoses, one on the left scapula, two on the right upper arm, were coagulated by monopolar fulguration on August 4, 1938.

Further Inflammation and Infection: The patient continued to have chronic conjunctivitis during the next two years and on May 23, 1940 an infected cystic mass was removed from the upper lid. Zinc oxide preparations and eye drops were prescribed. Pus was discharged from his lesion for two days.

Further Surgery: On October 9, 1941 three nevi were excised from the right upper arm. They proved to be benign pigmented papillomas. The patient complained of almost continuous headaches early in 1942. These subsided.

Radiation and Further Inflammation: On December 4, 1942 several hyperkeratoses were treated with the bulb on the right arm posteriorly, one on the left lateral arm and one on the anterior chest wall. This caused an active radiation reaction. He also had a scaling dermatitis on the scalp at this time.

Clinical Course: During October 1943 he developed pain in the right shoulder along the distribution of the cubital nerve, suggesting neuritis. Six diathermy treatments were prescribed.

Clinical Courses: The patient remained in good health thereafter. He was examined periodically by Pack. There was no further evidence of disease after 1936. He remained in excellent health in April 1968, 37 years after onset.

References: 71; 83; 89.

CASE 10: Metastatic malignant melanoma primary in the left anterior chest wall, confirmed by microscopic examinations of lesions removed from the chest wall, axillary and cervical lymph nodes.

Previous History: M.L., female, aged 40, in 1934. The patient's father died of cancer at the age of 66, her mother of heart disease at the age of about 50. The previous personal history and date of onset were not recorded.

Surgery: In February 1934 a 4 cm. nevus was removed from the left anterior chest wall at Strong Memorial Hospital, Rochester, New York. This had been present for several years, with recent slow growth. The pathologist reported pigmented nevus, but the possibility was raised that it was undergoing malignant degeneration. In December, 1935 the patient had a hysterectomy for leiomyoma of the uterus. In 1936 she had a right radical mastectomy, the pathological diagnosis being cystic mastitis with hyperplasia and acute inflammation.

Clinical Course: In 1936 she developed diabetes mellitus which was well controlled. She remained well until February 1939 when she noticed a lump in the left axilla. On examination this lesion was about 4 cm. in diameter and appeared to be attached to the chest wall.

Further Surgery: It was removed in April 1939 and proved to be metastatic malignant melanoma in the axillary nodes. In September 1939 she noticed another mass in the left axilla and was readmitted for left radical mastectomy. Pathological examinations revealed no evidence of disease in the breast but metastatic malignant melanoma was present in the axillary nodes. About a month later she noticed a swelling in the left neck. She then underwent a left radical neck dissection in November 1939. Pathological examination again showed metastatic malignant melanoma. In February 1940 a small necrotic metastatic node was removed from the left neck under local anesthesia. Another large mass of nodes was removed from the area in October 1940, and a smaller one in February 1941. In June 1941 a mass of involved nodes was removed from the right axilla and the neck was explored, but only scar tissue was found.

Postoperative Infection: At this time the patient developed infection in the neck wound, with drainage. She attempted to commit suicide.

Radiation: X-ray therapy was administered to the left cervical region (1500 r in 10 days). Another cycle of x-ray was given in September and October 1941 (1600 r), for persistent swelling.

Clinical Course: The patient improved slowly. By July 1942 she was symptom-free and in good condition, with no further evidence of disease.

Further Infection: In July 1943 she had cellulitis of the right arm — hemolytic *Staphylococcus aureus*.

Clinical Course: Thereafter she remained in good health, except for a virus infection in the winter of 1955-56. She died in February 1959 of a cerebral hemorrhage and pulmonary emboli. Autopsy showed no evidence of malignant melanoma. Death occurred 25 years after onset.

Comment: This patient had at least 10 operations. Metastases continued to develop until 1941, when infection developed postoperatively. Thereafter she was traced for a further 18 years, without evidence of disease.

References: 74; 82.

CASE 11: Malignant melanoma primary in the right temple, with pulmonary metastases, confirmed by microscopic examination following excision of the primary and biopsy of the pulmonary lesion at exploratory thoracotomy, by Dr. D. Spain.

Previous History: Female, aged 40 in 1943. The family and previous personal history were not recorded except that at the age of nine, in 1912, a small lesion of the right temple was excised from the skin, the nature of which was unknown. Onset, in 1932 another lesion appeared in the same area on the right temple.

Surgery: This lesion was excised and proved to be a malignant melanoma.

Clinical Course: A routine chest film taken in February 1943 disclosed a small nodule vaguely discernible at the level of the second left anterior intercostal space. The patient was asymptomatic.

Concurrent Infection: In August 1943 her first symptoms began when she was hospitalized for pneumonia. Chest films revealed pneumonia, pleural effusion and the nodule first apparent the previous February.

Clinical Course: The nodule persisted after the pneumonia and pleurisy cleared up. By April 1945 a new nodule was present in the right hilum.

Radiation: Deep x-ray therapy was administered (factors not recorded). A second cycle was given several months later, totalling 4700 r (2000 anterior, 2000 posterior and 700 r lateral).

Clinical Course: On September 21, 1949 the patient was first seen by Dr. Anthony R. Galgano, at Grasslands Hospital, with complaints of dull aching in the right anterior chest, night sweats, headaches and hot flashes. Chest films revealed four rounded, smooth shadows in the lung fields. The largest, anterior to the right hilum was lobulated. At the level of the ninth rib behind the heart there was a loculated pocket of pleural fluid, aspiration of which yielded some dark, creamy fluid containing a small amount of black pigment suggestive of melanin. No malignant cells were identified.

Further Surgery: In April 1949 an exploratory thoracotomy was performed which disclosed a 19 cm. fixed, dark brownish-red mass with a smooth contour in the right hilum involving the right middle and lower lobes as well as the interlobular tissue. A 1 cm. wedge of tumor was removed. The mass was soft and friable. Microscopic examination showed irregular areas of tumor with portions of intact fibrous tissue capsule. The tumor consisted of large polyhedral cells with eosinophilic cytoplasm which varied in density. The nuclei were round and oval, often large and hyperchromatic. Scattered cells were filled with yellow to dark finely granular pigment. There was invasion of the fibrous cap-

sule. The diagnosis was metastatic malignant melanoma. Three days later chest films showed a marginal hydropneumothorax, on the right. Thoracentesis yielded 160 cc. of grossly dark fluid. The patient was discharged on the 14th post-operative day.

Clinical Course: By July 1950 a recurrence was present in the skin over the right temple. This was 17 years after onset of the primary lesion.

Further Surgery: This tumor was excised and proved to be recurrent malignant melanoma.

Clinical Course: Thereafter the course was steadily down hill and by February 1952 there was melanin in the urine. Shortly before death, chest films revealed further enlargement of the lung metastases. Death occurred on February 21, 1952, 20 years after onset of the primary malignant melanoma, and nine years after pulmonary metastasis was first noted.

Comment: In reporting this case in 1953 Galgano noted that when pulmonary metastases develop in malignant melanoma death usually follows within a year. At Presbyterian Hospital, in New York, the longest survival with pulmonary metastases was four years, after onset of cough. In Galgano's case the patient lived nine years after pulmonary metastases were first seen. He also noted the long interval between the excision of the primary lesion and the development of the pulmonary metastases — 11 years. In this case the concurrent pneumonia and pleurisy may have stimulated this woman's resistance so that her disease remained stationary much longer than is expected in this type of tumor.

Reference: 43.

CASE 12. Malignant melanoma of the left ankle. The tumor was not examined by the pathologist, but the metastases in the right breast, left arm and left femoral region were examined by several pathologists.

Previous History: Mrs. R.R., female, aged 27, at onset. The family history was not recorded. The patient had had no serious illnesses or operations. She had had two uncomplicated pregnancies.

Concurrent Infection: In February 1946 a pigmented tumor which was present on the left ankle became infected and disappeared. The exact date of onset is not recorded.

Clinical Course: During her third pregnancy the patient developed a painless lump in the left groin. This was not treated. About February 1948, a painless lump developed in the right breast. In early October 1948 the patient again became pregnant and the lesion in her breast rapidly increased in size and became slightly painful. At the beginning of this pregnancy another mass was first noticed in the left arm near the shoulder. During the second to fifth months of gestation several other small tumors developed in the abdominal wall and back. The patient also had a ringworm infection of the left shoulder which was successfully treated by a local physician. She was first seen by Dr. Wilbur S. Sumner of Jacksonville, Florida in February 1949. Examination revealed a well developed, well nourished white woman, not acutely ill. She had a firm, slightly tender, freely movable mass about 6 x 6 cm. in diameter in the right upper quadrant of the right breast. The borders were irregular and the mass felt somewhat cystic. There was no lymphadenopathy. The abdomen was distended and the uterus could be palpated 4 cm. above the umbilicus. Fetal heart tones could be heard. In the abdominal wall there were three masses similar to the ones in the breast, one in the midline above the umbilicus, one over the costal

cartilage on the left and a third in the left lower quadrant. They varied from 1 to 2 cm. in diameter. The cervix was soft and no pelvic masses were palpable. Over the left arm and shoulder and extending somewhat to the back was an area of scaly lesions characteristic of healing ringworm infection. On the anterior surface of the left arm there was a 2 x 3 cm. mass similar to the one in the right breast. Scattered over the back were subcutaneous nodules like those in the abdominal wall. In the left femoral region another mass 4 x 5 cm. in diameter was noted.

Surgery: The patient was admitted to St. Luke's Hospital, Jacksonville, Florida. On February 8, 1949 under sodium pentothal and cyclopropane anesthesia, the tumors in the right breast, left arm and left femoral region were excised. (101).

Clinical Course: The incisions healed without complications. After the diagnosis of malignant melanoma was established, a search for the primary tumor was made but none was found. However, just above the internal malleolus of the left ankle a depigmented area 1 x 1.5 cm. in diameter was noted. On questioning, the patient stated that 3½ years before, she had had a black mole which became infected and disappeared. As Sumner regarded the condition as incurable, it was thought that no definitive treatment should be instituted.

Further Surgery: However, on March 28, 1949 the larger tumors on the abdominal wall and back were excised in Sumner's office under local anesthesia. All were deeply pigmented and exceedingly friable and most were torn in the process of removal so that soot-colored fluid escaped into the incisions. At the completion of this "most depressing procedure, it was expected that the patient would promptly have local recurrence with fungating ulceration." (101)

Clinical Course: However, all the incisions were well healed by April 4, 1949. The patient had a normal delivery at full term of a normal male child on May 20, 1949. She was cared for by a local physician and the placenta was not examined for malignant melanoma. She was seen again by Sumner on November 11, 1949. At this time there was a 2 cm. mass beneath the scar in the left femoral region, but no other lesions were found. Chest x-rays and eye-ground studies were negative for metastases. The uterus was normal and the patient was menstruating normally and regularly.

Further Surgery: On December 6, 1949 a superficial femoral dissection was performed at St. Luke's Hospital. The incision healed per primum. The pathologist reported: "Melanoma of inguinal lymph nodes (circumscribed); fibrosis of inguinal nodes (irradiation); acute and chronic lymphadenitis." Sumner stated: "It is interesting to note that the pathologist reported a tissue reaction typical of irradiation. No such therapy had been given in this patient." (101)

Clinical Course: She was followed periodically by Sumner and remained free from further evidence of disease until July 3, 1950 when a mass approximately 2.5 cm. in diameter was noted in the right supraclavicular region. Again x-rays and eyeground studies were negative for metastases.

Further Surgery: An attempt to remove this lesion was made in Sumner's office on July 7, 1950. "Most of the node was removed piecemeal, and it was believed that not all of it had been removed. Again it was felt that a surgical blunder had been made and that a fungating mass would develop. However, the incision healed." (101)

Clinical Course: The patient was not seen between August 22, 1950 and September 13, 1952 when examination revealed no evidence of tumor and chest

films were again negative for metastases. Urinalysis showed no evidence of melanin. "A most interesting observation was made at this visit. In most of the areas in which the patient had had malignant melanoma, the skin had become depigmented; and over an area on the inner surface of the eyebrow, in which the patient thought she had had a tumor that had never been excised, not only was the skin depigmented, but the eyebrow was devoid of pigment." (101) The patient was again seen by Sumner on February 4, 1953. At this time there was no apparent change in her condition or appearance. For photographs made on that date see Sumner's reports. (101, 102) Thereafter she was examined periodically by Sumner. She remained in excellent health with no further evidence of metastases in August 1967, 21½ years after the primary lesion had regressed following infection. (82)

Comment: After finding these interesting changes (depigmentation) in 1953, Sumner requested a review of all the sections and the pathologists all confirmed the diagnosis of malignant melanoma. It was then noted that some disintegration of the tumor cells could be seen in the tissue from the original surgical specimens. Sumner observed that according to Pack and Scharnagel, pregnancy produces marked acceleration of the growth of malignant melanoma. In this case the first metastatic lesion was noted in the left groin during the patient's third pregnancy. Another appeared in February 1949, but caused no symptoms until she again became pregnant in October 1948. During the first months of this pregnancy, multiple metastases developed. However, the natural resistance of this patient must have remained fairly active, because examination of the tumors showed some disintegration. The most interesting changes were noted in the tumors removed in December 1949, 6½ months after confinement. The pathologist then reported a tissue reaction typical of irradiation, with necrosis, fibrosis and acute and chronic lymphadenitis. It is now believed that the regression of the primary lesion following infection in 1946 increased the natural resistance of this patient, but not sufficiently to offset the stimulus of her subsequent pregnancies. Sumner probably saved this woman's life by removing most of the tumor tissue and thus enabling the patient's immune responses to destroy the remains of the tumors and cause a final lesion to regress spontaneously.

References: 82; 101; 102.

CASE 14: Recurrent metastatic malignant melanoma of the left axilla, primary site unknown, confirmed by microscopic examination at Memorial Hospital by Dr. Fred W. Stewart.

Previous History: E.W.H., male, aged 27, of Oahu, Hawaiian Islands. The family and early personal history were not recorded except that in April 1946 the patient was struck on the left shoulder by a tidal wave. He was first seen by Dr. P. F. Alsup of the Alsup Clinic in Honolulu on June 11, 1946. Onset, about a week or 10 days previously he had first developed a swelling in the left axilla under the margin of the pectoral muscles. He gave no history of infections involving the fingers, hand or arm, but stated that he had a small lesion on the dorsum of the left hand which he "had scraped off while fishing along the coral reefs" about a week or two before the axillary swelling appeared. The patient swam and dived a great deal and this might have been caused by coral or sea urchin. He was given penicillin without effect. He was a well nourished male with freckles all over the body. No liver or spleen enlargement and no lymphadenopathy were present except the mass in the left axilla.

Surgery: On August 20, 1946 Alsup removed a large mass of what appeared to be broken down lymph nodes involving the subpectoral group. During the procedure he noted pigmented material in the tissues beneath the mass. Dr.

Sumner Price, the pathologist reported: "Histological examination shows a lymph node in which there is a free distribution of pigment, some of which is undoubtedly hemorrhagic in origin. There are also a few scattered bacterial deposits — such as cocci. In addition there is a peculiar distribution of pigment which indicates that it is probably melanin. A definite portion of tumor tissue is found presenting a pseudoperitheliomatous arrangement around the blood vessels. This is common in a number of melanotic tumors. The lesion is apparently not primary in the axilla, and the most likely sources would be in the skin, perhaps the region of the toes, or the meninges, or the eye, or adrenal. Many of the tumor cells are comparatively free of pigment. In some areas there is a suggestion of vascular invasion. In such a case the prognosis should be guarded, since it is entirely possible that multiple metastases will appear clinically within a short time. There is little recommended in the way of treatment because if the lesion is metastatic it will probably soon be diffusely disseminated. The prognosis is grave. Diagnosis: Pseudo-peritheliomatous melanoma, primary source undetermined." (71). A few days later a small growth was excised from the patient's back. This was examined and reported to be a benign neuronevus. Chest x-rays were negative. Ophthalmological examination revealed a very small pigmented lesion situated between 12 and one o'clock and well toward the periphery of the left eye. Fundus examination of the right eye showed no evidence of pigmentary changes in the surrounding structure and no evidence of destruction within the retina, choroid or media. This lesion in the left eye was regarded as a benign melanoma, although the possibility of its being a melanoblastoma in an initial stage was considered. The patient was admitted to Memorial Hospital on September 19, 1946. No further evidence of disease could be detected except for a recurrent mass in the left axilla. The tiny macule in the retina of the left eye did not impress Dr. Joseph A. Urban as the primary. Another chest plate taken that day revealed no evidence of lung metastases. On September 24, 1946, a radical left axillary dissection was performed by Urban, including a wide ellipse of skin. At operation the areolar tissues in the fascial plane between the latissimus dorsi and the subscapular muscles and the chest wall were densely infiltrated by a black pigmentation. Several firm nodes were excised from the axilla, the dissection being carried up to the costoclavicular ligament. Although dissection was clear and wide, some disease remained. The wound was drained through a stab wound on the lateral flap. Drs. Foote and Stewart of Memorial Hospital reported the tissue in the fascial plane as rather low grade malignant melanoma and voiced the opinion that the primary tumor might have arisen in this region. All the nodes removed revealed only benign hyperplasia and contained no melanoma. Urban stated that because of the peculiar pathology of this lesion, the usually rapid, fatal course of the disease might not intervene.

Postoperative Infection: While the drain still remained in the stab wound, the patient took a tub bath, and the wound became infected, apparently a staphylococcus infection. Two weeks after operation the wound was clean.

Clinical Course: The patient was discharged about October 16, 1946 and returned to the Hawaiian Islands, after being seen once again at Memorial Hospital on November 6, 1946, when he appeared to be in excellent condition. After delaying marriage for three years at Urban's suggestion, to see if he remained free from further evidence of disease, he married and had two children. There has never been any further metastasis, the function of the arm has been good and the patient remained in excellent health when last traced in January 1968, 21½ years after onset.

References: 71; 82.

CASE 15: Subungual malignant melanoma of the right great toe, with metastases to the labia minora and the inguinal lymph nodes, confirmed by microscopic examination by Drs. Sophie Spitz and Fred W. Stewart of Memorial Hospital.

Previous History: Mrs. M.B., Italian female, aged 58, of New York, N.Y. The family history was negative for cancer or tuberculosis. The patient had had one daughter. An appendectomy and apparently a hysterectomy had been performed in 1941, for she did not menstruate thereafter. She had had no severe illnesses but had been a poor eater for years. She was the wife of a junk dealer on the lower East Side and was very poor. Onset, in September 1945 her right great toe cracked and while cutting the nail there was some bleeding and what was thought to be a hematoma under the nail.

Concurrent Infection: The daughter stated that after this there was no pigmented area beneath the nail but an infection in the corner of the nailbed developed. No medical care was given until about a year after onset.

Surgery: Since the lesion did not heal, she had two operations and a diagnosis of malignant melanoma was established. She lost four pounds in the seven months prior to admission to Memorial Hospital. At examination on February 3, 1947, in the Mixed Tumor Clinic, the patient appeared to be a rather pale, thin, nervous, poorly developed, wrinkled woman. There was considerable piling up of granulation in the dorsal aspect of the right great toe and a moderate amount of edema of this toe. Examination of the introitus revealed a 2 x 3 mm. deeply pigmented lesion on the inferior right labia minora which was flush with the mucosa of the vagina. This lesion was unknown to the patient. There were also several large discrete lymph nodes in the right groin, the largest 1 cm. in diameter. The patient complained of pain in the affected toe. She had a corneal opacity on the right side, present since childhood. The nail of the right toe was absent and the lower nail bed was occupied by a tough, friable, granulomatous lesion with a bluish tinge, which bled easily. On February 7, 1947 the right great toe was amputated under spinal anesthesia. The patient was discharged two days later.

Postoperative Infection: She developed a low grade infection of the operative scar. The foot remained painful and tended to swell and redden around the amputation site.

Further Surgery: There was no drainage at examination on readmission on March 20, 1947, and no further evidence of infection. However, two femoral lymph nodes were palpable on the right side. The patient was advised to have a hipjoint amputation but this was refused. Therefore, a radical groin dissection was performed under spinal and pentothal anesthesia on March 21, 1947. This was reported as showing metastatic malignant melanoma.

Postoperative Fever, Inflammation, Cellulitis: There was a moderate febrile episode to 101.6°F. on the second postoperative day, and a rise of 1° or 2° for another two days. On March 27, 1947, 30 cc. of fluid was aspirated from the groin apex under a thin, partially necrotic flap. On March 31, 1947 the wound was widely debrided of necrotic material. Azochloramid dressings were started. As the wound did not heal satisfactorily, Padgett pinch grafts were applied on April 9, 1947, about 95% of which took. The patient was discharged on April 19, 1947, at which time the entire defect was not filled with skin. Prognosis was regarded as a "5 to 15% chance of five-year survival." At home the wound was dressed three times a week by a visiting nurse and wet dressings were applied by the family. Diffuse edema of the leg developed. The patient was advised to use ace bandages. On August 25, 1947 it was noted that there

was definite cellulitis with some inflammation of the thigh. Sulfadiazine was given for two weeks. She then had an attack of erysipelas involving the edematous right thigh which lasted two weeks. She was advised to take penicillin (300,000 units daily for three or four days). During October or early November lymphedema continued, with several sinuses on the upper right thigh. This responded to the application of a tailored elastic stocking. By January 5, 1948 the lymphedema was markedly improved. In April 1948 there was an abrasion over the lower aspect of the groin dissection and ophthous-stomatic ulcers in the buccal gutter on the right side and on the tip of the tongue. She was advised to have her few remaining very sharp, carious teeth extracted or filed down. This cleared up under treatment.

Clinical Course: The patient appeared symptom-free except for some edema of the thigh and pain in the anterior right thigh, especially at night. Seconal was given for sleep. The continued pains were believed due to scar contraction. Beginning in the fall of 1950, if the patient became excited she had severe precordial pain and "became stiff" according to her daughter, but this responded to brandy. Thereafter she had these attacks about once a month. At this time the pains in the right knee were attributed to arthritic changes and to the gait she had adopted since losing her great toe. She remained relatively well until July 1951 when a discoloration appeared on the nail of her left great toe. She was readmitted for a few hours on November 28, 1951 at which time examination revealed no lesion of this toe. Dr. Theodore R. Miller also saw the patient and stated: "This is the most remarkable cure of a subungual melanoma that I have ever seen." (71). She remained free from further metastases and in her usual health until late April 1955, when she had shaking chills which were treated by the usual home remedies. During the next two weeks the patient was first aware of right upper quadrant pain, also nausea and emesis. The urine was dark, but there was no change in the character of the stools. By May 1, 1955 she was somewhat jaundiced. She was examined at Memorial Hospital on May 4, 1955. Palpation of the right upper quadrant caused discomfort and revealed a definite tender mass beneath the liver consistent with the gall bladder. The liver was down 5 cm. and Dr. Lemuel Bowden believed that the obstructive jaundice was due to a neoplasm which he suspected was a second primary rather than metastatic malignant melanoma. The patient was readmitted the next day. A pancreatoduodenectomy was performed on May 12, 1955, revealing a tumor approximately 2 x 2 cm. in diameter completely surrounding the ampulla of Vater, causing obstruction and dilation to three times normal size of the biliary and pancreatic ducts. The pancreas was edematous, many nodes were present around the common duct and the head of the pancreas. Following exploration the common duct was entered. Obstruction was noted at the ampulla but no stone was recovered. A subtotal pancreatoduodenectomy and cholecystectomy was performed with antero-colic Hofmeister anastomosis of the stomach and jejunum. The common duct was joined to the proximal jejunal segment, and a T-tube drain inserted. Regional nodes were negative for tumor. Dr. Sophie Spitz reported that the tumor arose in the mucosa of the duodenum. The mucosa of the main pancreatic duct showed *in situ* carcinoma at its origin. The ampulla of Vater was involved. There was direct invasion of the pancreas in continuity with the duodenal lesion and metastases to one node lying between the duodenum and the pancreas: "Papillary adenocarcinoma, principally low grade, but with Grade II." (71). The postoperative course was uneventful. In early July 1955 she complained of pain in the right upper quadrant with some radiation to the back and emesis once or twice during the day, especially after meals. This continued and she lost 10 pounds during July. She also had persistent, steady, moderately severe back pain around the level of the first and second lumbar vertebrae. She was readmitted on Aug-

ust 8, 1955 with what was believed to be intra-abdominal metastases. X-rays at this time were negative. She improved quite a bit after her discharge on August 18, 1955, gained weight and had a better appetite. This was only temporary, ascites then developed, the disease progressed causing death on October 17, 1955, 10 years after onset of the malignant melanoma from which she had entirely recovered.

Reference: 71.

CASE 17: Malignant melanoma primary in the right anterior thigh, with metastases in the right groin and many satellite nodules in the skin, confirmed by microscopic examinations following operations at Harper Hospital, Detroit, Michigan, and at the University of Michigan Medical Center, Ann Arbor.

Previous History: V.P., male, aged 60, in 1948. The family history was negative for cancer, tuberculosis and diabetes; the patient never had hay fever or asthma but he had two episodes of dermatitis on his hands due to chemicals. His only infections had been occasional colds. In May 1949 he had a stasis ulcer secondary to an old thrombophlebitis and varices. Onset, in July 1948 he first noticed a 2 cm. pigmented nevus on the right anterior thigh.

Concurrent Infection: In September 1948 he had a left maxillary sinusitis.

Surgery: In March 1950 the brown lesion on the thigh, which had become ulcerated, was removed at Harper Hospital.

Clinical Course: Metastases developed in the right groin.

Radiation: In April and May 1951 the area was treated by x-ray therapy without effect, "the metastatic tumor reportedly growing unabated," with many satellite pigmented nodules in the skin.

Chemotherapy: In August 1951 parahydroxypropioquinone, radioactive iodine and radioactive copper were given with no evidence of regression.

Further Concurrent Infection: The metastases in the groin then became ulcerated and infected.

Further Surgery: On October 10, 1951 a generous biopsy of the groin tumor was performed at University of Michigan Medical Center in Ann Arbor, to obtain material for antibody purposes.

Further Concurrent Infection: The white blood count rose from 7950 two days prior to surgery to 9650 two days after surgery. By November 23, 1951 it was 11,350. The ulcerated neoplastic area remained opened and discharged pus and necrotic tumor tissue for five months. Complete healing occurred in March 1952.

Tagged Antibody Therapy: On December 6, 1951 antibodies to this patient's malignant melanoma (rabbit gamma globulin) containing radioactive iodine (27 mc.) were administered. Five days later the white blood count was 7850. Regression of the metastatic tumors was then noted. Chest films taken December 17, 1951 showed at least five parenchymal lung lesions characteristic of metastases. By January 3, 1952 the groin lesions were 40% smaller and chest films showed that the lung lesions were less prominent. Another injection was given on January 4, 1952 (170 ml. containing 124 mg. of rabbit gamma globulin with 69.2 mc. of I^{131}). During this injection the patient had an episode interpreted as anaphylactic shock: considerable difficulty in breathing, face ex-

tremely flushed, blood pressure 78/50; pulse 108; respiration 32; emesis of 700 cc. of brownish fluid.

Clinical Course: On January 18, 1952 chest films showed continued regression of the pulmonary metastases had occurred with only a simple residual lesion present in the sixth left anterior interspace. On March 14, 1952 chest films showed complete disappearance of the remaining lung metastasis had occurred. On May 20, no tumor was apparent. A pigmented area of skin, where a previous tumor had been, was biopsied and reported as follows. "Melanin pigment in phagocytes throughout dermis in specimen received. No nevus cells identified other than melanospores." The patient became completely myxedematous and required thyroid replacement which he neglected from time to time. Further metastases developed in the groin.

Chemotherapy: Beginning July 20, 1953 he received thio-TEPA (Triethelenethiophosphamide) for a month, with no change in the size of the inguinal mass.

Further Tagged Antibody Therapy: On October 23, 1953 a third injection of I¹³¹ tagged antibody was given by Dr. Bierwaltes.

Further Surgery: On October 26, 1953 biopsy of a right inguinal nodule was reported as amelanotic melanoblastoma. On January 24, 1954 the right inguinal mass 5 cm. in diameter was excised. The pathologist reported "Metastatic malignant melanoblastoma; abundant pigment."

Clinical Course: Thereafter there was no clinical or x-ray evidence of tumor. On January 27, 1958 the patient died suddenly at work of coronary insufficiency. Autopsy at University Hospital revealed no evidence of tumor. This was 10 years after onset of the primary tumor on the thigh and six years after infection and his first treatment with tagged antibodies.

Comment: In citing this case as a spontaneous regression, Block and Hartwell (9) stated that the treatment which this patient received (i.e., tagged antibodies) had been uniformly unsuccessful in a significant number of other cases. The above case appears to have been the only one to develop concurrent infection, and this factor may have been responsible for the result obtained.

References: 9; 82; 103.

CASE 18: Infected recurrent malignant melanoma of the right leg with metastases to the right inguinal lymph nodes, confirmed by microscopic examination at Memorial Hospital following operations in 1951.

Previous History: J.H.M., male, aged 41, dentist, of Bayonne, New Jersey. The family history was negative for cancer, tuberculosis or diabetes. The patient had had no serious medical illness. Onset, on May 30, 1949 he first noticed that a nevus on his right leg, which had been present since birth, was "growing very fast and was raised."

Surgery: He consulted his family physician, Dr. Raymond I. Driscoll, who removed the lesion by electrocautery.

Radiation: X-ray therapy was then given in Jersey City once a month for nine months. (dosage and factors not recorded). A second cycle of monthly treatments was begun in March 1951.

Concurrent Ulceration or Infection: In early May 1951 an ulceration was noted in the area of the cicatrix and he was advised to use Bacitracin ointment which he did with good results. About June 1, 1951 he accidentally noted a

lymph node in the right groin. At examination on admission to Memorial Hospital, June 1, 1951, there was a small ulcerated area in the outer aspect of the middle third of the right leg, in the proximal part of which there were several pinhead size grey black spots. Surrounding the ulceration there was an erythematous area about 3 cm. in diameter with depilation, undoubtedly due to the irradiation. In the upper part of the right femoral triangle, not really in the inguinal region, there was a 2.5 x 1 cm. lymph node, very firm, hard and fixed to the deep structures but not to the overlying skin. No other nodes were palpable in the groin, superficially or deeply.

Further Surgery: The patient had been advised to have a hip joint disarticulation before he consulted Dr. Bradley L. Coley, but Coley felt that more conservative surgery might be advisable. He therefore removed the recurrent lesion on the leg by wide local excision and applied a skin graft from the right thigh. The leg and thigh were placed in a light plaster cast along the posterior region. The temperature rose to 100°F. that day. The pathologist reported: "Infected recurrent melanosarcoma, margins clear."

Clinical Course: The postoperative course was satisfactory. The skin graft took about 100%. By June 29, 1951 the wounds were practically healed.

Further Surgery: On July 2, 1951 a right radical groin dissection was performed, also a direct inguinal herniotomy. The pathologist reported three lymph nodes were present in the specimen. The largest consisted of firm, glistening, opaque, greyish tan tumor tissue. At one pole of the node numerous scattered small hemorrhages were present and there was a solitary well defined area of brownish black pigmentation representing melanin deposition. The second largest node was 1.5 cm. in diameter and on section was seen to be completely replaced by a soft, in areas almost diffuent, tumor tissue containing abundant diffusely distributed brownish black melanin pigment. The smallest node, 1 cm. in diameter, was grossly unremarkable. The next day the temperature rose to 101.4°F., returning to normal the next morning.

Clinical Course: There was a small amount of superficial necrosis in the mid-portion of the lateral flap of the wound. By August 1, 1951 the wound was cleaner.

Delayed Wound Healing: On September 19, 1951 Coley stated: "There is some peculiar failure of the epithelium to cover the area from which the skin graft was taken. It behaves almost like a superficial wound such as a burn upon which skin from another person has been applied, and which appears to remain for awhile and then gradually melt away. I am quite unable to understand why this defect in healing is taking place. Scarlet red ointment to be used today." (71)

Further Surgery: Because the donor site had still failed to heal by September 26, 1951, Coley was suspicious of further recurrence and specimens were taken for biopsy on that day. The pathologist reported "granulation tissue."

Further Infection: An inflammatory area suggesting a furuncle then developed in the area, but by October 10, 1951 it had almost disappeared under aureomycin. There was a marked change for the better in the epithelialization of the donor site while being treated with chlorezium. The area finally healed by October 31, 1951, 4½ months after surgery. However, the skin in this area continued to have a peculiar appearance with scab formation in several areas 0.5 — 2 cm. in diameter over the next two years. There was no further evidence of recurrence or metastases. In August 1956 the patient consulted Dr. H. McLeod Riggins about a redundant swelling in the superficial portion of the axilla. Riggins excised the area and found an infected

sebaceous cyst which, on histological examination showed no evidence of malignancy. Pus was obtained.

Clinical Course: The patient continued to practice dentistry. He enjoyed excellent health, with no further evidence of disease when last traced on July 8, 1968, over 19 years after onset.

References: 71; 82.

CASE 19: Recurrent inoperable malignant melanoma of the right ear, with metastasis to a lymph node overlying the lower pole of the parotid gland, confirmed by microscopic examination by the Armed Forces Institute of Pathology. (For microphotos and pictures of the patient see 5).

Previous History: H.L., male, aged 46. The family and early personal history were non-contributory. Onset, in March 1933 a "dark spot" was first noticed on the right ear. Three months later the lesion was "burned off" by a local physician.

Clinical Course: A month later a recurrent nodule appeared at the original site which slowly enlarged during the next eight months. The patient was admitted to the Veteran's Hospital in Portland, Oregon on March 12, 1956. Examination revealed a firm, subcutaneous 8.8 cm. nontender, bluish nodule on the antitragus of the right ear. There was a firm node palpable in the upper cervical region just beneath the lobe of the ear. No other significantly enlarged nodes were apparent and no suspicious nevi. Chest films were normal.

Surgery: An incisional biopsy of the tumor of the ear was performed and reported as epidermoid carcinoma. On March 21, 1956 subtotal resection of the ear was performed in continuity with parotidectomy and radical neck dissection. The pathologist then reported malignant melanoma with metastasis to one lymph node overlying the lower pole of the parotid gland.

Clinical Course: The postoperative course was uneventful. A plastic prosthesis was constructed for the ear and the patient was discharged on March 30, 1956. He remained without evidence of recurrence until December 1956 (nine months) when a 5 mm. deeply situated subcutaneous nodule was noted just posterior to the angle of the jaw. A poorly defined 1 cm. subcutaneous nodule was also palpable at the posterior limits of the neck dissection. Hospitalization was refused by the patient. By March 1957 the nodule behind the angle of the jaw had doubled in size and the posterior nodule was also larger. Hospitalization was again refused.

Concurrent Infection: By June 1957 the large tumor mass was grossly infected and had fungated through the skin of the upper cervical region, extending up over the mastoid and onto the right cheek. It was fixed to the deeper structures and bled easily and much of it was black. The patient was in considerable pain but he again refused hospitalization. He returned home and applied compresses to the infected tumor area, also vaseline. There were frequent hemorrhages from the fungating mass, but the tumor gradually decreased in size and the area finally healed.

Clinical Course: The patient did not return for subsequent follow up examinations and was believed to have died of his disease. He reappeared on July 15, 1958 in apparent good health. Examination disclosed marked scarring in the upper right cervical region, at the former site of the massive, fungating, recurrent tumor. There was a most unusual loss of pigmentation in the scarred

areas. There were no palpable cervical nodes, and no evidence of tumor on complete physical examination. Chest films were normal. The patient attributed his cure to prayer. He was followed periodically thereafter and remained entirely well on January 13, 1969, almost 14 years after onset.

Comment: In reviewing the 13 known cases of spontaneous regression of malignant melanoma Baker stated that in two of these patients the tumor disappeared without any factors being noted which might have contributed to the regression. Incomplete surgical excision of the tumor or its metastases preceded regression in five instances. Significant infection of the tumor was present in two of the cases. Confinement appeared to have a significant role in two cases in which widespread dissemination of tumor occurred during pregnancy, with rapid regression two to six months following delivery. Baker believed that these various factors "probably merely trigger the unknown mechanism known as host resistance. The understanding of this mechanism may prove important to the field of cancer."

References: 5; 37 (Case 16, p. 207); 82.

CASE 20: Metastatic malignant melanoma primary on the dorsum of the left foot, with metastases in the left groin, confirmed by microscopic examination following excision of the groin mass at Toronto General Hospital.

Previous History: A.R., male, aged 32. The family and previous history and date of onset were not recorded.

Surgery: In May 1955 a mole on the dorsum of the left foot was cauterized by a local physician. In July 1956 he noted a lump in the left groin. Excision of this mass was performed at Toronto General Hospital by Dr. W. B. Bigelow, on December 15, 1956 and reported to be malignant melanoma.

Radiation: 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.

Clinical Course: During August and September 1958, 12 to 14 subcutaneous metastases appeared, mostly on the trunk, chest wall and left axilla, and in the right forearm. These began as tiny pin points which gradually grew over a period of two or three weeks, in some instances to the size of a thumb. After another two weeks they became deeply pigmented.

Spontaneous Regression: These lesions then gradually disappeared, leaving a pin point of nodularity in the subcutaneous tissues. The patient returned on October 17, 1958. Examination revealed three subcutaneous nodules: one, 1 cm. definitely pigmented, was in the right infraclavicular region; another was in the left axilla and the third was in the right forearm. They appeared to be regressing metastatic subcutaneous metastases. At examination seven days later it was noted that these nodules had disappeared except for a bluish nodule 0.5 cm. in diameter in the skin of the right forearm. Since this nodule appeared to involve a vein, it was suggested that these lesions might have been thromboses in the veins rather than metastases. At examination on December 19, 1958, the patient reported that these skin nodules had continued to appear and disappear. The lesion on the forearm looked like a thrombosis at this time except that it was painless and non-tender.

Clinical Course: At examination on March 16, 1959 the liver was not palpable and a chest film was normal. The patient was seen on June 4, 1959 because of nausea and vomiting. At this time the liver was not enlarged but

urinalysis revealed melanin. This finding was confirmed on July 10, 1959. By August 28, 1959 the liver edge was four finger breadths below the right costal margin. During the next five months the patient lost 56 pounds, weighing only 85 pounds by February 1960.

Concurrent Fever and Transfusion Reaction: He became completely bed-ridden, unable to eat, with intermittent high fever, marked weakness, sweating and vomiting. He was admitted to Scarborough General Hospital six or eight times between November 1959 and February 1960 receiving six to eight transfusions totalling 23 pints of blood. On February 23, 1960, following administration of the third pint of blood at his final transfusion, (A, Rh negative), he developed some chest pain, tightness and dyspnea. Accordingly the procedure 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; he began to eat well and the nausea and vomiting gradually subsided.

Clinical Course: On May 13, 1960 the patient was admitted to Princess Margaret Hospital for study. "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 melanocarcinoma." He was discharged on May 20, 1960. By August 19, 1960 his weight was restored to 144½ pounds — a gain of 59 pounds in six months. There was clinical evidence of a minimal degree of bilateral gynecomastia. Multiple physical and laboratory examinations during the next five years revealed no further evidence of disease. Plasma from this patient was given to another patient with lung metastases from malignant melanoma, with no improvement. Plasma from this case and from all but one of the blood donors (of February 23, 1960) was injected into metastatic malignant melanoma in a third patient, without any response.

References: 37, p. 211.

CASE 21: Malignant melanoma primary in the skin overlying the spinous process of the first thoracic vertebra with a lymph node metastasis in the right posterior cervical triangle, confirmed by microscopic examination following radical neck and axillary dissections, at the Mayo Clinic.

Previous History: Male, aged 31, civil engineer. The family and early personal history were not recorded. In April 1965 the patient noted that a nevus which had been present since birth had increased in size and become alarmingly darker in color. He consulted a physician who was also concerned and who took a photograph of the lesion. (102a, Fig. 1).

Concurrent Sunburn: Because of a recent very severe sunburn acquired in Mexico, the patient was advised to return for excision of the nevus after subsidence of the acute inflammatory process (erythematous reaction).

Clinical Course: At about this time the patient rubbed and scratched the lesion. Because it seemed to disappear, he dismissed all further thought of it until early November 1965 when a mass appeared in the right posterior cervical triangle. It grew rapidly for one month and during the second month it remained relatively stable.

Vaccination: In early January 1966 the patient was given a small pox vaccination in the right deltoid area. Examination at the Mayo Clinic that month revealed a hard, fixed 2 cm. mass in the right posterior triangle, and a pale, slightly atrophied area of skin at the site of the lesion which had disappeared. Careful examination for other sites of primary malignant melanoma, including ophthalmological examination, revealed no other source of a pri-

mary lesion. There was an erythematous area over the right deltoid muscle, the site of the recent small pox vaccination, with evidence of slough and secondary infection in this area.

Surgery: Excisional biopsy of the cervical mass revealed malignant melanoma. Right radical neck and right radical axillary dissections were then performed, with wide excision of the original nevus. Pathological examination revealed only a solitary cervical lymph node involved by the neoplasm. *All other nodes, both cervical and axillary showed non-specific inflammatory changes.* The involved cervical lymph node was almost totally replaced by solid sheets of tumor cells. In the skin lesion a band of subepidermal fibrosis, with prominent vascular channels and a scattering of chronic inflammatory cells, was present in the upper dermis. Numerous pigment filled macrophages were clustered about the area. No definite residual malignant cells were found, although a rare degenerating, atypical cell was present in the junctional zone of the epidermis.

Prophylactic Chemotherapy: The patient was given sarcolysin as an adjuvant to surgery (50 mg. orally every 12 hours for 36 hours).

Clinical Course: Convalescence was uneventful. He remained entirely well when the case was reported in 1966. The disease reactivated in June 1966, presenting as a metastatic nodule on the anterior chest wall. Subsequently metastases developed in the left kidney, right shoulder, right arm, right buttock and left chest wall, and there was an enlarged node in the left axilla.

Further Surgery: On June 27, 1967 one of the last localized lesions in the left chest wall was excised. The left axillary nodes were also removed and showed no evidence of metastasis.

Radiation: Palliative x-ray therapy was given for relief of pain due to the renal metastasis, without apparent benefit.

Clinical Course: The disease progressed, causing death on December 24, 1967, 2 $\frac{3}{4}$ years after onset.

Comment: In this case radical right cervical and axillary node dissections removed the tissues which presumably had received the most obvious immunological stimulus and which might have helped prevent further activation of the disease. Possibly if only the involved node had been removed, thus preserving the lymphatics which showed non-specific inflammatory changes, and if sarcolysin had not been administered, the disease might have been controlled.

References: 82; 102a.

CASE 22: Recurrent operable malignant melanoma, primary in the concha of the left ear, with metastases in the left submaxillary lymph nodes, confirmed by microscopic examination following excision of the primary, recurrent and metastatic lesions, at Wadsworth Veterans Administration Hospital, Los Angeles, California.

Previous History: J.O., male, aged 51 (in 1947). The patient had a small pinhead growth on his left ear which had been present for approximately 10 years. About mid-January 1947 it changed from brown to black and increased in size. Examination on admission, March 18, 1947, revealed a 2 cm. black raised lesion occupying the concha of the left ear and a 1 cm. subcutaneous nodule anterior to the left ear.

Surgery: On March 25, 1947 an excisional biopsy was performed taking a 1 cm. margin and extending down to the cartilage. The preauricular node was submitted to pathology. A split thickness graft was placed in the surgical defect. Microscopic examination revealed malignant melanoma extending to the cartilage, but no evidence of metastases in the node.

Clinical Course: The patient requested an emergency discharge to leave the state. Recurrence became apparent in August 1947 within five months after surgery. However, the patient failed to return until February 1948 when he was readmitted with a small lump in front of the left ear which had been present for six months. Examination also revealed a firm nodule in the region of the left submaxillary lymph nodes.

Further Surgery: These nodes were biopsied and revealed metastatic malignant melanoma. On February 24, 1948 the auricle was amputated in continuity with a left radical neck dissection. There was no evidence of metastases in the surgical specimen.

Postoperative Infection: Convalescence was complicated by the development of a fistula which responded to penicillin and local measures.

Clinical Course: The patient was discharged on April 13, 1948. On December 13, 1948 he was readmitted with a perforated duodenal ulcer.

Further Surgery: He underwent gastroenterostomy and there was no evidence of local or intra abdominal metastases. In June 1949 a suspicious nodule was biopsied in the left preauricular area but microscopic examination was negative for malignancy. The patient had subsequent biopsies of suspicious nodules removed from the left neck and posterior left neck (1950) and the submental area (1952). All were negative for malignancy.

Clinical Course: He remained well and free from further evidence of disease in 1967, 20 years after onset.

References: 104a.

Comment: Analysis of the 22 cases in Series A suggests that a delicate balance may exist between the patient's local and systemic resistance and the neoplasm. Certain factors such as pregnancy, physical or psychic trauma or immunosuppressive drugs may lower this resistance so that metastases or recurrence may develop. Others, such as bacterial infections, fever, a local or systemic inflammatory episode, or a transfusion reaction, may stimulate resistance sufficiently to cause "spontaneous" regression, or to prevent or delay the development of metastases or recurrence. If the disease is very extensive or far advanced when such "complications" develop, they may have little or no effect, or may cause only temporary improvement. (Case 7). The results in many of these cases suggest that permanent control may be obtained even in the presence of metastases, and may be more apt to occur if much of the tumor is removed surgically, during or following enhancement of host resistance by infection or other factors.

CONCURRENT PREGNANCY

Concurrent Pregnancy: The following case is another example indicating that pregnancy may temporarily lower a patient's resistance to malignant melanoma. (See above, Series A, Case 12 for the other example). Usually cases in whom "spontaneous" regressions occur have acute concurrent infection, fever or an inflammatory episode, but in the following case the only possible factor

of this sort was a breast abscess which occurred prior to regression of her metastases.

Diagnosis: Malignant melanoma of the right forearm, recurrent, with multiple metastases of the left waistline, right flank and right upper arm and breast, confirmed by microscopic examinations by Dr. J. O. Mercer, pathologist.

Previous History: Female, aged 38, of Stratford, New Zealand, wife of a sheep farmer. The family history was negative for cancer in 1942, but in the next 25 years three of the patient's brothers died of cancer and a fourth living in Ireland developed a skin cancer on the ear requiring plastic surgery. The previous personal history was not recorded. The patient had three children 10, 8½ and 4 years of age. She had had an area about the size of a thumb nail on the extensor surface of the right forearm, which though normal in color, was a little elevated above the skin surface. Onset, about the middle of 1942, possibly following a scratch with a pin, part of this area became black.

Surgery: This lesion was excised in July 1942 and the pathologist reported: "A circumscribed tumor composed of small nevoid cells with irregular 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." (3).

Clinical Course: Two months later a black area appeared in the scar and by May 1943 this black lesion was the size of a marble.

Further Surgery: Wide excision was then performed down to the deep fascia. 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 tissues and local fat. The appearance is quite unlike that previously reported on. It is malignant melanoma." (3).

Radiation: The patient was then referred to Dr. E. P. Allen, Radiologist, of New Plymouth Hospital, New Zealand. She received a tumor dose of 4,700 r in 17 days to the forearm through opposing fields. At this time she appeared fit, with no evidence of residual disease.

Clinical Course: In late August 1943 she again became pregnant. She was again seen by Allen on November 8, 1943, at which time she remained free from recurrence. During the next five months multiple bluish subcutaneous nodules appeared, up to the size of marbles, on the left waist line, right flank and right upper arm. These were regarded as blood-borne metastases, and the prognosis was considered hopeless.

Further Surgery: To confirm the diagnosis a lesion on the right upper arm was excised on March 10, 1944. The pathologist reported: A lymph node, the structure of which was almost entirely obliterated by tumor, consisting of solid masses of darkly staining polyhedral cells. There was little pigment present. The tumor was considered to have become more cellular and less well differentiated.

Confinement and Breast Abscess: Her confinement, April 26, 1944, was preceded by a hemorrhage. By May 14, 1944, 18 days after the birth of a normal child, the patient had developed further metastases in the right scapular and inguinal regions. Localized tumor masses were also noted in the left breast, but it was not certain that these were of the same nature, because the patient had a concurrent breast abscess on that side. The latter subsided without treatment.

Clinical Course: When seen again on July 10, 1944 to Allen's surprise all the nodules noted previously had disappeared, except for a small node in the

right groin. The patient was feeling well and was gaining weight. Small crescentic areas of pigmentation were seen on the temporal sides of both discs, but they did not appear to be neoplastic in nature. The patient was followed at intervals. She remained free from further evidence of recurrence or metastases and in very good health in 1967, almost 25 years after onset of the primary lesion and nearly 23 years after regression of the multiple metastases. For years she suffered from migraine headaches, at least once a week, but after 1959 she rarely had one. She stated in 1967 that she felt these were due to overwork (5 a.m. to 8 p.m. regularly): milking, child care, housework, gardening, helping with the sheep. She added that in 1966 she had worked for eight months in a department store "without a day's illness." In 1967 she "retired" and gained about 35 pounds, her height being approximately five feet five inches. She remained in good health with no further evidence of metastatic malignant melanoma on September 20, 1968, over 26 years after onset.

In reviewing the sections in 1955 the pathologist stated: "The original report that the (primary) tumor was a pigmented nevus should certainly be qualified by the statement that, in the light of a modern view on the histology of melanoma, it was clearly a malignant tumor when it was first removed." In reporting the case in 1955 Allen stated: "The sequence of events strongly suggests that the metastases developed as a direct response to the stimulus of pregnancy, and that they were in fact so dependent upon the stimulus that upon its withdrawal they themselves disappeared. The speed of their disappearance is in itself remarkable, regression being complete 11 weeks after delivery. . . . There was no local recurrence after excision." (3). He suggested that the stimulus of pregnancy may have led to the activation of malignant cells which up to that time had been lying dormant.

References: 3; 82.

EFFECTS OF TOXIN THERAPY ON PREGNANT PATIENTS

No untoward effects were produced on either the mother or the fetus in a terminal case of malignant melanoma treated by Dr. L. A. Crowell (28). This woman received only intramuscular injections. Three other pregnant women are known to have received mixed bacterial toxins. One patient was given intramuscular injections in the fourth month of pregnancy for a sarcoma of the leg, inoperable except by amputation which had been refused. She had a complete regression, and a normal child was born at full term. She remained well and free from recurrence when last traced 21 years later. (91, XIII. Series A, Case 12). The other two women received intravenous injections of these toxins in the first trimester of pregnancy and aborted within 24 to 49 hours. Toxins were resumed in the first instance, combined with radiation, with complete regression of the reticulum cell sarcoma of the humerus. This patient remained in good health in 1969, 22 years later. The other patient succumbed to her osteogenic sarcoma within a year. (71).

EFFECT OF PREGNANCY ON SURVIVAL OF PATIENTS WITH MALIGNANT MELANOMA

White, *et al.* (106) analyzed pregnancy data for 71 women aged 15 to 39 with malignant melanoma. Thirty of these patients became pregnant between one year prior to and five years after diagnosis was established. In 10 no history of pregnancy could be obtained. Five year survival was slightly higher in the women who became pregnant than in the nonpregnant. Thus no deleterious effect of the pregnancy on survival could be demonstrated.

SERIES B: PRIMARY OR RECURRENT OPERABLE
MALIGNANT MELANOMA TREATED BY TOXIN THERAPY

The diagnosis was confirmed by microscopic examination in each instance. The name in parenthesis following the case number refers to the physician, surgeon or hospital handling the case. The abstracts are listed chronologically according to the type of toxin preparation used and the date of the first injection. At the end of each abstract the bibliography reference numbers are given. For a brief description of the various formulae used in making these mixed toxins of *Streptococcus pyogenes* and *Serratia marcescens* see references 80 and 81.

*Years Traced
After Onset*

1. (W.B. COLEY): L.B., female, aged 39; recurrent malignant melanoma of neck, primary in congenital nevus; lesions 2.5 cm. in diameter excised April 1895; metastases to cervical lymph nodes within 4 wks.; removed surgically by Coley September 20, 1895 when 7 cm. in diameter; toxins (Buxton VII) postoperatively, 17 i.m. in 25 days; *did not prevent metastases to lower dorsal spine*, apparent 6 wks. after last injection; death, February 26, 1896; autopsy showed metastases to lung, liver, ovary, retroperitoneal lymph nodes, large mass destroying front of sacrum and nodules up spine. (22; 28; 71) 1
(died)
2. (WEEKS): Age and sex not given; recurrent malignant melanoma of eye; enucleation of eye at 2nd operation, autumn 1900; toxins (Buxton VI) then given for considerable period; *no further recurrence; alive and well* 3 yrs. after 2nd operation; not traced subsequently. (23) over 3
3. (McDERMOTT): Mrs. B., aged 45; recurrent malignant melanoma of retina, involving orbit; onset, summer of 1904; operation refused until October 1904, eye then enucleated; following summer had mild case of typhoid fever; November 1906, recurrence in scar; excised; toxins (Tracy X) every 48 hrs. for 3 mos. in temporal region and forehead; dose increased to 6 minims, severe reactions; larger doses not tolerated although patient weighed 210 lbs.; *in perfect health* 3½ yrs.; then metastases to lumbar region, liver; severe pain; toxins not resumed until jaundice present, morphia required every 2-4 hrs.; *after toxins were given no further morphia required, as severe pain was almost entirely controlled*; disease gradually progressed with gradual emaciation, then sudden coma, death June 15, 1910. (24; 25, Case 91 in Table; 26, Case 6 in text; 28). 6
(died)
4. (HARE): Mrs. J.E.M. aged 56; malignant melanoma of heel, with enlarged popliteal lymph nodes; pigmented nevus injured, became painful, increased very rapidly in size; primary excised, hipjoint disarticulation advised, refused; enlarged popliteal nodes removed; patient referred to Coley for consultation; he advised toxins (Tracy XI) which were given by Hare under Coley's direction for 2 yrs., with considerable febrile reactions; wound healed slowly; *complete recovery, no recurrence or metastases*; died at 84, cerebral arteriosclerosis and chronic nephritis, July 3, 1937. (26; 82). 26
5. (W.B. COLEY): M.N.A., female, aged 17; malignant melanoma of proximal thigh; onset, early 1912; excised at another hospital when

about 6 cm. in diameter, April 30, 1912; toxins (Tracy XI) begun 3 wks. later, continued by family physician for nearly 2 yrs. (100 doses); *marked reactions, to 103°F.; complete recovery, no recurrence or metastases*; married, had 2 children, several miscarriages; in excellent health until 1959, then symptoms of gastric ulcer, cholecystitis, requiring cholecystectomy for gallstones, spring 1959; during 1965-66 she gradually became totally blind; no evidence of recurrence or metastases 1969. (26, Case 5; 28; 82).

57

6. (W.B. COLEY): Mrs. M.B.G., aged 54; malignant melanoma of lt. groin; onset, May 1911; excision at another hospital, May 22, 1912; toxins (Tracy XI) begun 5 wks. later, 7 in pectoral muscles in 12 days, *only 2 adequate febrile reactions*; metastases to brain, with terminal pulmonary edema causing death February 7, 1913. (71; 82).

21

mos.

7. (SPESSOOD): Mrs. L. H., aged 30; recurrent malignant melanoma, primary in nevus on arm, metastasis in axilla; primary removed by electric needle; recurrence 9 yrs. later; excised summer of 1920; metastases developed in axilla following influenza, January 1922; removed at operation at Mayo Clinic, March 23, 1922; they advised toxins (Tracy XI), which were given by Spessood for 6 wks.; then developed tonsillitis so toxins discontinued; abdomen enlarged rapidly, multiple small metastases to back, arm, breast and pelvic region; "blanket of x-ray given," caused nausea, vomiting, severe pain requiring large doses of morphia; toxins resumed for 3 wks. at the end of which *the smaller metastases began to disappear*; alive with disease; end result unknown. (28; 82).

11

8. (B.L. COLEY): Mrs. D.L., aged 38; twice recurrent malignant melanoma of calf of rt. leg; onset 1937, pigmented nevus began *to enlarge*; *overlying skin became infected and broke down*; lesion excised elsewhere September 1937; recurrence in 6 mos.; again excised, October 1940; 3rd excision by Coley early 1941; few x-ray treatments given; March 1941, pain in nasal sinuses and cervical region due to sinusitis; groin dissection March 19, 1941; "hyperplasia;" toxins (Parke Davis XIII) begun 11 days after this operation, 7 i.m., 1 i.v., reactions 102° - 104.2°F.; *no further recurrences or metastases*; in excellent health August 1968. (71; 82).

31

9. (GRAY): L.L.M., male, aged 34 at onset; recurrent malignant melanoma, primary in skin over lt. clavicle with metastases to sternal notch, lt. axilla, latissimus dorsi muscles, rt. cervical region; patient and family had higher than average number of pigmented nevi; patient had over 130 removed by electrocautery, 1933; onset, October 1956, lesion beneath skin of sternal notch noted; October 1958, nevus over lt. mid-clavicle began to enlarge; electrodesiccation by family physician (incomplete eradication); rapid recurrence; January 1959, wide excision by Gray; metastatic lesions in sternal notch above umbilicus also excised, positive for metastatic malignant melanoma; May 1959, some thickening beneath scar in sternal notch; upper pectoralis removed, lt. axillary dissection, also nodes in lt. cervical region and superior mediastinum, which involved removing median 2/3 of lt. clavicle and splitting sternum; no evidence of metastases found in any of these areas; October

1959, metastasis in rt. cervical region, increased to 4 cm. in diameter; in December 1959, rt. radical neck dissection; January 1960, another metastasis in lt. axilla, removed May 1960; rt. radical mastectomy (multiple metastases present); June 7, 1960: toxins (Johnston XV), 67 in 5 mos., 61 i.v., 6 i.m.; febrile reactions averaged 101°F. (minimum 100.6°F., maximum 105.1°F.; chills occurred after most i.v. injections, none severe; another nodule apparent, November 1960 in lt. arm; urethane i.v. at regular intervals for 10 mos.; *no appreciable effect from toxins or chemotherapy*; death, March 17, 1962. (82).

(died)
5½

10. (MOUND): K.L., male, aged 67; metastatic malignant melanoma lt. groin, primary site unknown; mass in groin apparent December 1961, following steroid therapy for pain in low back, rt. hip and ankle in previous yr.; groin mass excised, May 1962, 6 mos. after it became apparent; toxins (Johnston XV) begun June 29, 1962: 20 i.v. in 33 days; febrile reactions averaged 101.4°F.-102.4°F. (maximum 103°F.) with severe chills; *complete recovery, returned to work, no further evidence of metastases*; in good health 1968, only illness a myrocardial infarction 1963. (82).

6½

11. (MAZZARA): Mrs. V.D'A., female, aged 25; malignant melanoma on shoulder (in area where shoulder straps could irritate it); onset, late January 1962, nevus present for some time in this area rapidly enlarged; excised February 22, 1962; toxins (Johnston XV) begun March 6, 1962: 128 in 26 mos., i.v., almost daily at 1st, decreasing to 1 a wk. from June 1962 until last dose May 29, 1964; reactions averaged 102° - 102.5°F. (maximum 104.6°F.); *no recurrence or metastases*, in excellent health 1969. (82).

7

12. (CHANDLER & FLETCHER): J.H.D., male, aged 64; malignant melanoma nasal mucosa; onset, January 1963, epistaxis; polypoid mass lt. lower turbinate cauterized a wk. later; biopsy excision January 1963; toxins (Johnston XV) begun February 20, 1963, 10 i.v. in 20 days; radical operation March 11, 1963, wide excision inferior turbinate, lt. lateral naris ala; 20 more injections toxins then given; did very well until acute bowel obstruction, causing death October 24, 1963; autopsy revealed asymptomatic vertebral metastases, no other evidence of disease. (16; 82)

10 mos.

13. (CHANDLER & FLETCHER): G.P., male, aged 45; malignant melanoma of skin in lt. preauricular region, metastases to cervical nodes; onset, August 1960, small nevus apparent; punch biopsy, August 1960, positive for malignant melanoma; more radical excision 2 mos. later, n.e.d. in this specimen; did very well until January 1963, metastatic lt. cervical node then excised; few other shotty cervical nodes palpable when toxins begun March 26, 1963: (Johnston XV), 46 i.v. in 14 mos., reactions averaged 101.2° - 103°F. (maximum 103.8°F.); 10 days after 1st injection lt. radical neck dissection and lt. subtotal parotidectomy; patient resumed heavy work as millwright and continued working during treatment except for 1 day a mo. when injection was given; *no further evidence of disease, in very good health* until about June 1967, then large cerebral metastasis in frontal region surgically removed; in good health until about March 1968, then further cerebral

*Years Traced
After Onset*

metastases; death April 13, 1968, after convulsive type seizures; no other lesions except those in the brain found at autopsy. (16; 82).

died
7½

14. (CHANDLER & FLETCHER): M.W., female, aged 40; recurrent malignant melanoma lt. distal leg; onset, April 1961, following minor injury; excised October 1961 (specimen lost); punch biopsy of recurrence April 1963; a further recurrent lesion dark brown to black, 1.5 x 0.8 cm. in diameter, present prior to toxins (Johnston XV), April 26, 1963: 10 i.v. in 10 days, then wide excision with skin graft; 6 more i.v. after surgery; reactions averaged 101° - 103°F. (maximum 104.2°F., none at all twice) *tolerated treatment well, no pain, graft healed*; n.e.d. until August 1964, then palpable inguinal nodes; groin dissection that month; no further evidence of disease; remarried; in excellent health, May 1968. (16; 82).

over 7

SERIES B, DETAILED HISTORIES

CASE 1: Recurrent malignant melanoma of the neck, confirmed by microscopic examination of the recurrent tumor and at autopsy.

Previous History: L.B., female, aged 39, of Red Bank, New Jersey. The family history was non-contributory. The patient had always been in good health. She had an apparently congenital nevus of the left side of her neck beneath the ear.

Surgery: In April 1895 it was removed by Dr. E. M. Field when about 2.5 cm. in diameter.

Clinical Course: Within four weeks the growth recurred locally and grew slowly. The patient was referred to Dr. William B. Coley and was admitted to Memorial Hospital on September 20, 1895. At this time the lesion was approximately 5 cm. in diameter, rather firmly attached to the deeper structures in the left cervical region.

Further Surgery: Coley removed this tumor and found it was entirely encapsulated, and involved the cervical lymph nodes.

Toxin Therapy (Buxton VI): Injections were begun on September 20, 1895 and were given in large doses intramuscularly in the hope of preventing recurrence. A total of 17 were given in 25 days.

Clinical Course: The patient was discharged on October 2, 1895 in apparently good health. Six weeks later she developed some pain in the back and legs and was treated for rheumatism. The pains increased in severity and the patient was readmitted to Memorial Hospital. At this time a small growth 4 cm. in diameter was discovered in the lower dorsal spine, also several small nodules 0.5 to 1.5 cm. in diameter near the sacroiliac synchondrosis. The pains in the legs were very severe and there was some loss of sensation. These symptoms increased and later paralysis developed. Death occurred on February 26, 1896. Autopsy showed metastases in the liver, lung, one ovary and the retroperitoneal lymph nodes, as well as a large mass at the back of the pelvis destroying the front of the sacrum. This was contiguous with the nodules extending up the spine.

Comment: In this case the toxins had absolutely no effect on the course of the disease. Perhaps, as Matagne suggested, operable cases should receive injections before as well as after surgery. It would appear that 25 days is rarely sufficient duration of toxin therapy to control the disease in malignant melanoma.

References: 22; 28; 71.

CASE 3: Malignant melanoma of the retina, recurrent in the orbit, confirmed by microscopic examination at Boston City Hospital.

Previous History: Mrs. B., aged 45. Onset, during the summer of 1904, the patient complained of pain and failing vision in the right eye. She was examined by Dr. Alling and a diagnosis of detached retina, probably malignant melanoma, was made. This was confirmed by Dr. Herman S. Knapp of New York.

Surgery: The patient refused operation until December 8, 1904, when the eye was enucleated in Boston City Hospital.

Typhoid Infection: During the summer of 1905 she had a mild typhoid infection.

Clinical Course: She remained in good health and free from recurrence for almost two years, until about November 1, 1906, when a small black growth was noted in the scar of the orbit. Dr. T. S. Mc Dermott, of New Haven was consulted.

Further Surgery: On November 21, 1906 the recurrent growth was removed but Mc Dermott stated that because of the anatomical situation he could not cut very far into healthy tissue. The recurrence was about the size of a cornea.

Toxin Therapy (Tracy X): Injections were begun on November 24, 1906 and were given every other day into the temporal region and forehead, the highest doses being 6 minims. Although the patient was a large woman, weighing 210 pounds, Mc Dermott found that he could not give more than 6 minims because of the severe reactions that always followed. They were continued for four months, until March 27, 1907.

Clinical Course: The patient remained perfectly well for three years. At examination on February 27, 1910 Mc Dermott found no evidence of disease. Shortly thereafter, she began to have pain in the right lumbar region. A month later jaundice developed, with severe pain.

Further Toxin Therapy: The injections were then resumed. McDermott reported: "The severe pains were almost completely controlled by the toxins, but they were not able to control the disease." She was taking $\frac{1}{4}$ gr. of morphine every two to four hours prior to toxin therapy, and after the injections were begun she had no pain and required no further morphine.

Clinical Course: The disease progressed, with gradual emaciation. On June 15, 1910 she suddenly became comatose and died. This was six years after onset.

Comment: In this case the preliminary course of toxins in 1906 was given after surgical removal and was continued four months, none of the injections being given intravenously. Possibly if the toxins had been resumed as soon as back pain developed in 1910, instead of delaying until liver metastases and jaundice were present, the disease might have been controlled.

References: 24; 25 (case 91 in Table); 26 (case 6 in Text); 28.

CASE 4: Malignant melanoma of the heel, with involvement of the popliteal lymph nodes, confirmed by microscopic examination by three pathologists.

Previous History: Mrs. J.E.M., female, aged 56. The family history was non-contributory. The patient had a pigmented nevus on her heel. Sometime prior to consulting Dr. Oaka S. Hare, in Bluefield, West Virginia, this nevus was injured, became painful and began to increase in size very rapidly. Upon examination he found enlarged nodes in the popliteal space.

Surgery: The nevus was excised and proved to be malignant melanoma. Two of the pathologists advised hip-joint amputation. This was not done, but the affected popliteal nodes were removed. Soon after this Hare took the patient to New York to consult Dr. William B. Coley. The latter concurred in the diagnosis and advised toxins.

Toxin Therapy (Tracy XI): Hare stated that Coley's suggestions were followed in detail, as to dosage and duration of treatment, and there was considerable reaction to the injections, i.e., fever and chills. The site from which the nevus was removed was very slow in healing. Scarlet red was used as a dressing and in the course of time the area healed. Toxin therapy was continued through September 1913, with intervals of rest, a total duration of over two years.

Clinical Course: The patient made a complete recovery and there was no further evidence of disease. She died on July 2, 1937, at the age of 84, of cerebral arteriosclerosis and chronic nephritis, almost 26 years after the toxins were begun.

References: 26, 82.

CASE 5: Malignant melanoma of the upper thigh, confirmed by microscopic examination following surgical excision in Richmond, Virginia.

Previous History: M. N. A., female, aged 17, of Richmond, Virginia. The family and previous history were non-contributory. The patient first menstruated at the age of about 12. Onset, early in 1912 she first noticed a small tumor in the proximal thigh. This steadily increased in size until it was as large as a hen's egg.

Surgery: Under general anesthesia the growth was excised on April 30, 1912 by Dr. Stuart McGuire. An elliptical incision 18 cm. long was made well outside of the indurated area. The tumor did not extend down to the fascia and was removed completely.

Toxin Therapy (Tracy XI): Injections were begun by Dr. William B. Coley three weeks later, the initial dose being 0.5 minim which produced considerable reaction, a severe chill and a temperature of 103°F. The patient proved to be very susceptible to the toxins and it was impossible to increase the dose more rapidly than by 0.25 minim. She returned home where the treatment was continued by the family physician for nearly two years, during which she received over 100 injections.

Clinical Course: There was no recurrence or metastases. The patient was examined periodically by Coley. She remained in perfect health, married in 1923, had two children (in 1928 and 1936), also several miscarriages. After the second confinement she was troubled with stress incontinence (feces) which persisted. Her health remained good until 1959 when symptoms of gastric ulcer and cholecystitis developed requiring cholecystectomy for gallstones in the spring of 1959. In 1965-66 she gradually became totally blind and was confined to a nursing home. She remained free from recurrence in January 1969, 57 years after onset, at the age of 74.

References: 16 (case 5); 28; 82.

CASE 6: Malignant melanoma of the left groin confirmed by microscopic examination after surgical excision at Beth Israel Hospital, New York.

Previous History: Mrs. M.B.G., aged 54, of Brooklyn, New York. The family and previous personal history were non-contributory. The patient had been married 23 years previously, was a widow and had two children. She had had no illnesses at all prior to onset, which occurred in May 1911, when a growth the size of a pea appeared in the left groin. It increased to the size of a walnut.

Surgery: This growth was excised at Beth Israel Hospital on May 22, 1912. The patient was then referred to Dr. William B. Coley for toxins.

Toxin Therapy (Tracy XI): Injections were begun at Memorial Hospital on June 27, 1912, five weeks after operation. The initial dose was 0.5 minim given into the pectoral muscles. A total of seven intramuscular injections were given in 12 days gradually increasing the dose to 3 minims. Only two marked febrile reactions occurred, the maximum being 105°F. with a chill lasting 20 minutes on July 9, 1912. The patient was discharged two days later.

Clinical Course: The disease later metastasized to the brain, causing death on February 7, 1913, 21 months after onset.

Comment: Compare the result in this case with those in which the toxins were given for a considerable period, gradually decreasing the frequency.

References: 71; 82.

CASE 8: Twice recurrent malignant melanoma of the leg, confirmed by microscopic examination at Memorial Hospital.

Previous History: Mrs. D.L., aged 38, of New Britain, Connecticut. The family and previous personal history were negative for cancer, tuberculosis or diabetes. The patient had had slight sinus trouble off and on and was of a very nervous and apprehensive nature. She had had no allergies or infections. Her menses had always been regular, with onset at the age of 12. She was married and had two children, the youngest seven years of age, and had had no miscarriages. A small pigmented nevus was present on the back of the calf of the right leg at about the middle third. It remained small for years. In October 1937 she noticed that it had increased in size.

Concurrent Infection: The overlying skin then broke down and became infected.

Surgery: A doctor was consulted who excised the lesion.

Clinical Course: In about six months there was a recurrence.

Further Surgery: This was excised and the patient was told to forget all about it. In October 1940 a second recurrence developed. This time the bluish tumor was a little larger and the patient was referred to Dr. Bradley L. Coley in New York. He excised the growth early in 1941.

Radiation: A few x-ray treatments were given.

Clinical Course: The patient was admitted to Memorial Hospital on March 18, 1941. She had a sinus infection and complained of pain in her nasal sinuses and in the cervical region. There had been no loss of appetite or weight. Examination showed a well developed, well nourished woman with a few pigmented moles on the side of her neck. On the back of her right leg there was a linear scar with quite a good deal of induration around it, also skin discoloration due to x-ray therapy and applications of gentian violet. At the upper end of the scar there was an induration about 2 cm. in diameter. There was no definitely palpable lymphadenopathy in the groin.

Further Surgery: Coley did a groin dissection under general anesthesia on March 19, 1941. Dr. Fred W. Stewart reported that the nodes were hyperplastic with one area of giant cells.

Toxin Therapy (Parke Davis XIII): Injections were begun by Coley on March 31, 1941 and were given daily for eight days. The first seven were given intramuscularly in doses of 1, 3, 5, 8, 11, 12, 14 minims. Febrile reactions averaged 102° to 103°F. with slight chills three times and one severe chill lasting 20 minutes. The final dose was given intravenously and caused a severe chill for 20 minutes and a febrile reaction of 104.2°F. and vomiting.

Clinical Course: Coley decided that the patient's mental and nervous condition indicated a need for rest and freedom from all therapy, so she was discharged on April 1, 1941. The groin wound had healed unusually well. She remained free from recurrence or metastases and in excellent health except for

some anxiety neurosis. She was last traced on October 12, 1968, 31 years after onset.

References: 71; 82.

CASE 9: Recurrent malignant melanoma, apparently primary in a nevus over the left mid-clavicle, with regional metastases, the first beneath the sternal notch, others in the skin above the umbilicus, in the right cervical region and in the axilla and latissimus dorsi muscle, confirmed by microscopic examinations following excisions and node dissections.

Previous History: L.M.M., male, aged 34 at onset, married high school mathematics teacher. The family history was negative for cancer. The patient's father died of a cerebral hemorrhage at 67. His mother had hypertension and a cerebral hemorrhage with left hemiplegia and almost complete recovery at the age of 47. Many members of the family had a higher than average number of nevi of the skin, none malignant. The patient also had a great many pigmented nevi on the scalp, neck and trunk. As a child he had had mumps and possibly measles. In 1933 he had approximately 13 large nevi removed by electrocautery under local anesthesia by Dr. Carter, of Clarksburg, West Virginia. Because of the discomfort, he was admitted to a hospital shortly thereafter and approximately 100 more were said to have been removed under general anesthesia by electrocautery. Onset, in October 1956, a small nodule appeared beneath the skin in the sternal notch. In October 1958, a lesion over the left mid-clavicle began to enlarge and protrude.

Surgery: This nevus was removed by electrodesiccation by the family physician, but the procedure did not result in complete eradication of the growth.

Clinical Course: It began to recur rather rapidly. The patient was first seen by Dr. David Gray, of Charleston, West Virginia, in January 1959.

Further Surgery: Under regional block anesthesia the recurrent lesion was widely excised by Gray. Clinically it appeared to be malignant melanoma. He also excised the nodule beneath the skin in the sternal notch which had been present for over two years. There was pigment in this nodule and it was reported to be metastatic malignant melanoma. At this time a medium brown nevus 3 cm. above the umbilicus in the midline showed some exfoliation. This was excised completely and reported to be superficial malignant melanoma. In May 1959 there appeared to be some increase in the thickening beneath the scar in the sternal notch. Gray then removed the upper portion of the pectoral muscles of the left axilla and the underlying lymph nodes, as well as the nodes in the lower left neck and the superior mediastinum. This involved removing the median two-thirds of the left clavicle and splitting the sternum. Clinically there was no evidence of metastases in any of these areas.

Clinical Course: The patient made an excellent recovery and remained symptom-free for five months. He then noted a small lump in the right mid-cervical region. This lesion remained about 2 cm. in diameter for two months. In December 1959 it began to enlarge.

Further Surgery: In January 1960 Gray performed a right radical neck dissection. At this time the lesion was 4 cm. in diameter. Two enlarged metastatic lymph nodes were found lying along the internal jugular chain. The nodes in the superior cervical, submaxillary and supraclavicular areas were all negative.

Clinical Course: On routine follow-up examination, May 7, 1960, a small nodule was felt in the region of the latissimus dorsi muscle.

Further Surgery: This was removed under block anesthesia and proved to be another metastatic lymph node. For this reason the patient was readmitted the next day and a radical right mastectomy was performed with a more thorough dissection of the posterior axilla. The resected specimen showed multiple metastatic malignant melanoma nodules.

Toxin Therapy (Johnston XV): Injections were begun by Gray on June 7, 1960. During the next five months he received 65 injections intravenously and five intramuscularly. These caused febrile reactions averaging 101°F (maximum 105°F.). The six intramuscular injections caused little or no reaction, no chills. After most of the intravenous injections chills occurred but were not severe, usually only "chilly sensations," often in two cycles about two hours apart. He also experienced nausea, lethargy and discomfort after injections. When the school term began the patient resumed teaching full time, but received his injections in the evenings three times a week.

Clinical Course: Shortly after the toxins were stopped a nodule appeared in the subcutaneous tissues of the left arm, underlying the anterior border of the deltoid muscle. This was about 2 cm. in diameter on November 19, 1968, non-tender, movable but quite firm. The patient appeared to be quite well except for this lesion.

Chemotherapy: After evaluation it was decided to administer urethane intravenously and this was given at regular intervals for 10 months with no appreciable effect upon the course of the disease.

Clinical Course: Cerebral metastases developed. The patient finally expired on March 14, 1962, 51½ years after onset. Autopsy was not permitted.

Comment: Note that in this case toxin therapy was not begun until after the fourth operation, three of these consisted of radical procedures with the removal of lymph nodes in the pectoral region, left axilla, right cervical region, right radical mastectomy, etc., i.e., the lymph nodes in the region of the tumor and its metastases had largely been removed and the vascular and lymphatic channels through which the toxins must circulate had been seriously disrupted by scar tissue. It would appear that to be most effective toxins should be begun prior to surgery. Where this is not possible a more prolonged postoperative course may be required.

References: 32.

CASE 11: Malignant melanoma of the left shoulder, confirmed by microscopic examination at Swedish Hospital, Brooklyn, New York, following excision.

Previous History: Mrs. V. D'A, aged 25. The family and previous personal history were non-contributory. The patient had two children. Onset, in late January 1962 a nevus in the supraclavicular region of the left shoulder, just where her shoulder straps rested, began to enlarge rapidly. She consulted Dr. Anthony J. Mazzara and he arranged to have her admitted for surgery at once. However, her mother died at this time and the operation was postponed for about two weeks.

Surgery: On February 22, 1962 Mazzara excised the lesion widely at the Swedish Hospital. At this time it was about 4 cm. in diameter, but there were no satellite nodules in the specimen.

Toxin Therapy (Johnston XV): On March 6, 1962 Mazzara began the injections which were all given intravenously. During the first three weeks they

were given almost daily. Nine were given in April, nine in May, six in June and thereafter four a month until May 29, 1964, a total of 128 in 26 months. Febrile reactions averaged 102° to 102.5°F. (maximum 104.6°F.). Occasionally no reaction at all was elicited. The first 10 days of treatment the patient remained in the hospital, thereafter all injections were given in Mazzara's office.

Clinical Course: She remained in excellent health with no evidence of recurrence or metastases at periodic examinations. The last observation was January 1968, six years after onset.

Reference: 82.

CASE 13: Malignant melanoma of the skin in the left preauricular region, with metastases in the left cervical nodes, confirmed by microscopic examination following excision at the University of Oregon Medical School Hospital.

Previous History: G.P., male, aged 45, millwright, of Monroe, Oregon. The patient's mother had died at the age of 49 of cancer of the colon. In 1949 the patient sustained a traumatic amputation of the third, fourth and fifth digits of the left hand. He was allergic to penicillin. He had always been in good health, working full time in a large sawmill. In August 1960 he first noticed a small dark nevus over the left preauricular region.

Surgery: This was biopsied in August 1960 and pronounced malignant melanoma. Two months later a more radical excision was performed which yielded no evidence of disease.

Clinical Course: The patient was seen at frequent intervals and did very well, with no evidence of recurrence or metastases until January 1963, 2½ years later.

Further Surgery: At this time a left superior cervical node was removed and again reported to be malignant melanoma.

Toxin Therapy (Johnston XV): Injections were begun by Fletcher on March 26, 1963 and nine were given intravenously in 11 days, causing febrile reactions averaging 101.6° to 102.4°F. (maximum 103.4°F., none at all on two occasions). Chills occurred after all but two of these injections. When the toxins were begun there were a few shotty nodes palpable in the cervical region.

Further Surgery: Ten days after the first injection a left radical neck dissection and left subtotal parotidectomy was performed, April 8, 1963.

Further Toxin Therapy: Injections were resumed on April 18, 1963 and 35 more were given, at first weekly, then monthly during the next year, all intravenously. Febrile reactions averaged 101.5° to 103°F. (maximum 103.8°, minimum, 100.6°F.). Chills occurred after all but five injections, lasting an average of 30 to 60 minutes. The patient was able to work full time during his treatment as a millwright running a busy sawmill. His only problem was nausea and emesis on the day of his injection. He usually stayed home those days, returning to work a full shift the next day. Routine examinations revealed no further evidence of disease until October 1963, the month in which the frequency of injections was decreased from weekly to monthly. At this time a mobile nontender node was found high in the axilla, approximately 1.5 cm. in diameter. There was no history of infection or skin break in that arm.

Clinical Course: This node remained the same size during the next seven months. There was no further evidence of disease until June 1967 when a large cerebral metastasis developed in the right frontal region.

Further Surgery: After preliminary administration of steroids, this was successfully removed by a neurosurgeon.

Clinical Course: The patient remained free from further evidence of disease when last seen at the University of Oregon Medical Center on February 20, 1968. He expired on April 30, 1968 in Eugene, Oregon, after convulsive type seizures. Death was apparently due to further cerebral metastases. It occurred 7½ years after onset.

References: 16; 82.

CASE 14: Recurrent malignant melanoma of the left distal leg, confirmed by microscopic examination at the University of Oregon Medical Center, Portland, Oregon.

Previous History: Mrs. M. W., aged 40. The family history was negative for cancer or other familial diseases. In 1945 the patient had a tumor removed from the left ovary, a uterine suspension and an appendectomy. All tumors were benign. In 1954 her tonsils and adenoids were removed. In 1957 a growth was removed from around the trachea (not thyroid) and was reported to be benign. The patient had smoked a pack of cigarettes daily for 25 years. In April 1961 she sustained a moderate injury to the left posterior lower leg. The lesion failed to heal and in October 1961 she consulted her local physician, who excised it. The specimen was lost and no diagnosis was made. The leg continued to ache and there was soreness in the unhealed lesion for two years. The patient was then seen by another physician.

Surgery: On April 1, 1963 a punch biopsy revealed malignant melanoma. She was then referred to the University of Oregon Medical Center. At this time a dark brown to black lesion was present 1.5 by 0.8 cm. in diameter on the posterior calf. No other lesions were apparent, and there was no inguinal lymphadenopathy.

Toxin Therapy (Johnston XV): Injections were begun by Dr. William S. Fletcher on April 22, 1963 and were given daily for nine days intravenously prior to more radical surgery. Febrile reactions averaged 101° to 103°F. (maximum 103.4°F., minimum 100.2°F.). Chills occurred after all but one dose, lasting 15 to 45 minutes. The patient tolerated the treatment well.

Further Surgery: On May 6, 1963 the recurrent lesion was widely excised and a split thickness skin graft was applied.

Further Toxin Therapy: Beginning May 10, 1963, four days after operation, injections were resumed and given daily for six days intravenously. Reactions ranged from none at all to 104.2°F., after the initial dose. Chills occurred after five of the injections, lasting 15 to 40 minutes. Again these were well tolerated, there was no pain and the skin graft healed well.

Clinical Course: The patient remained in good health, with no evidence of disease at follow-up examinations over the next 13 months. In June 1964 there was palpable lymphadenopathy.

Further Surgery: A groin dissection was performed in August 1964.

Clinical Course: The patient remarried prior to May 1967. She remained in excellent health, free from further evidence of disease in August 1968, over 8½ years after onset.

References: 16; 82.

SERIES C, INOPERABLE MALIGNANT MELANOMA TREATED BY
BACTERIAL TOXIN THERAPY
4 SUCCESSES, 10 FAILURES

The diagnosis was confirmed by microscopic examination in each case. The name in parenthesis following the case number refers to the physician or surgeon handling the case. The abstracts are listed chronologically according to the type of toxin used and the date of the first injection. At the end of each abstract the bibliography reference numbers are given. For a brief description of the various formulae used in preparing these mixed bacterial toxins the reader is referred to references 80 and 81. (Detailed histories are given following the abstracts).

*Years Traced
After Onset*

1. (G. R. FOWLER): Male, adult; recurrent inoperable malignant melanoma of lt. tonsil and fauces; 1st operation, external pharyngectomy, diseased area removed consisted of tonsil, anterior faucial pillar, half of velum, portion of floor of mouth; recurrence apparent 4 wks. after wound had healed, on lateral wall of pharynx; incisional biopsy; toxins (Buxton VI) begun May 1895, i.m. every 36 hours, deeply in lt. arm; febrile reactions to 103°F., chills; treated as an ambulatory case; *recurrent neoplasm changed from red to glazed white necrotic tissue, completely disappeared in 3 wks., area healed*; frequency then decreased to every four days, later once a wk., total duration less than four mos.; *entirely well 2 yrs.*, then another recurrence; further toxins advised, but patient did not return; death 1898, extensive infiltration lt. cervical region. (25; 42) (died)
3 yrs.
2. (MATAGNE): Female, aged 40; recurrent inoperable malignant melanoma proximal arm, axillary metastases; onset, late 1899 or early 1900; primary growth over biceps removed; rapid recurrence before wound had healed; toxins (Buxton VI formula prepared by Matagne himself), March 24, 1900 when main growth was 7 cm. in diameter, with 2 smaller nodules; *rapid regression during 1st wk., later increased growth*; injections continued, febrile reactions to 106°F.; formalin applied locally to tumor; shoulder disarticulation advised, finally performed after toxins had been given for 7 mos.; axilla found to be full of metastases; no further recurrence or metastases, in excellent health when last reported 1941. (66; 67; 68; 69) 41 yrs.
3. (GREENWOOD): J. B., male, aged 67; very extensive recurrent inoperable malignant melanoma rt. posterior triangle of neck at mid-clavicle; onset, December 1911; incisional biopsy, 2 days later incomplete though extensive operation, inaccessible portions of growth infiltrating beneath vertebrae untouched; very prompt recurrence, extremely rapid growth, increased to 8 cm. in 8 days; toxins begun March 3, 1911 given steadily, aggressively and persistently, at 1st in pectoral muscles, gradually nearer tumor, finally in or near site of growth; at 1st every 48 hrs., later less often, total of 105 in 22 mos.; *treated entirely as an ambulatory case; complete regression, no further recurrence or metastases*; remained in good health until death from acute bronchitis, 1935; no evidence of malignant melanoma at death. (History deserves special study in detail). (25, p. 136; 26, Case 2; 28; 45; 81, Case 17; 82) 14 yrs.
4. (W. B. COLEY): E. R. D., male, aged 46; malignant melanoma lt. 2nd toe with groin metastases; primary developed in nevus on toe, spring 1906;

toe amputated 18 mos. after onset; 3 yrs. later groin metastases size of goose egg incompletely removed at Mayo Clinic, February 5, 1912; hard mass 6 to 8 cm. in diameter present in unhealed portion of wound when toxins were begun, February 20, 1912 (Tracy XI); 12 i.m. in 30 days, slight febrile reactions; *marked improvement evident in 1 wk.*; injections continued by family physician after return home, 2 a wk., only 1 marked reaction with chills elicited; total duration 6 mos.; *complete regression*, remained in good health until mid-summer, then cerebral metastases, death October 20, 1912. (25, Case 80: 71; 82)

(died)

6½ yrs.

5. (GRAHAM): W. B., male, aged 33; recurrent malignant melanoma (Grade IV), primary in calf of leg, groin metastases; onset, early in 1911; excision of primary June 26, 1911; pea-sized recurrence in lower cicatrix, hard nodules in groin within 2½ mos.; mass size of man's fist in Scarpa's triangle, overlying skin red, glistening; area incised, hoping it might be inflammatory; 10 lb. wt. loss, back pain; explored at Mayo Clinic, May 13, 1912, specimen removed, wound packed open; toxins advised, given daily (Tracy XI) beginning May 31, 1912, small doses, mild reactions; *within 10 days pain and tenderness ceased, growth smaller, more movable, harder; improvement marked in 4 wks., patient felt better*; injections stopped for a wk., thereafter given twice a wk.; disease no longer controlled, death December 6, 1912. (71; 83)

(died)

2 yrs.

6. (W. B. COLEY): Mrs. C. P., many times recurrent inoperable malignant melanoma rt. shoulder, metastases in surrounding tissues and axilla; onset, December 1911; primary and several recurrences cauterized with acid, May to November 1912; 1st excision December 1912; at 2nd operation February 4, 1913 discrete, disseminated, pin-head nodules were scattered near scar, matted metastatic lymph nodes in axilla; 3rd operation incomplete, May 1913; patient referred to Coley as "hopeless," had lost 10-15 lbs.; toxins (Tracy XI) begun May 18, 1913, 13 i.m. in 19 days, no reaction until final dose; continued at home by family physician, 3 small doses a wk.; stopped for 3 wks. August 1913; small swelling appeared on shoulder, several wks. after her return home, others then developed, they increased in size more rapidly after toxins were stopped; recurrent nodules excised by Coley August 29, 1913; injections resumed 3 times a wk.; 4 more metastases on back and shoulder excised by Coley November 4, 1913; toxins resumed given steadily, total of 128 in 1 yr.; *patient well, no further evidence of disease until some mos. after toxins were stopped*; metastases then developed in heart, liver, lungs, omentum; death, November 10, 1914; *patient felt quite well until shortly before death*. (71; 82)

(died)

3 yrs.

7. (W. B. COLEY): H. S., male, aged 58; recurrent, extensive malignant melanoma mucous membrane over superior maxilla; onset, spring 1911, shortly after extraction of 2 teeth; February 1912, partial resection superior maxilla; radical neck dissection refused; cervical nodes continued to enlarge, local recurrence within a few mos.; untreated next 4½ yrs.; Coley consulted when tumor extended from ear nearly to upper thyroid cartilage and from angle of jaw to corner of mouth, protruding 6½ cm.; buccal portion was black; incomplete though extensive operation, external carotid tied, December 15, 1916; toxins (Tracy XI) begun 16

days later, 3 days after 1st radium pack to lt. neck (9,000 mch.); few more doses toxins, moderate reactions; another radium pack, February 7, 1917, to antrum; tumor then increased rapidly in size, *no apparent benefit* from toxins and radium; general health failed, death May 22, 1916. (17, Case 11).

(died)
5 yrs.

8. (W. B. COLEY): E. E. C., male, aged 33; three times recurrent malignant melanoma primary in nevus on rt. lip, with lymph node metastases; nevus removed by barber with caustic, 1912; patient had several other congenital nevi on trunk also 1 on rt. arm; May 1918, metastases to rt. neck; removed surgically; recurred twice; 3rd operation at Mayo Clinic; referred to Coley, March 1919; node in rt. neck excised; March 15, 1919, toxins (Tracy XI) 3 or 4 very small doses i.m. in wk.; radium pack March 28, 1919; injections continued at home alternate mos.; slow-growing mass then appeared in upper scar behind sternomastoid; toxins resumed by Coley, September 20, 1920, very small doses i.m., no marked reactions; radium tubes inserted, another radium pack (2,200 mch.) to neck; toxins continued 3 times a wk.; *tumor in neck almost disappeared*; 1 more bare tube of radium inserted into remains of growth; toxins continued at home until February 4, 1921, resumed for a few wks. in April 1921; *no further evidence disease during 1921 and most of 1922*; disease then became generalized, death March 15, 1923, 10 yrs. after onset, 4 yrs. after toxins were begun. (28; 71; 82).

(died)
10 yrs.

9. (HARMER): F.H.F., male, aged 35; twice recurrent inoperable malignant melanoma scapular region, primary in pigmented nevus, metastases to axilla; onset, June 1911; excision 5 wks. later; local recurrence, October 1911, excised shortly after it appeared; immediate recurrence after this operation, grew rapidly to 6½ cm. in diameter, metastases in axilla; toxins begun November 15, 1911 (both Parke Davis XII and Tracy XI used in this case); during treatment further metastases developed in pectoral region and back; *extensive metastases all disappeared or sloughed out under large doses given both into the tumors and i.m.* (in pectoral muscles); maximum dose, 53 minims; total 195 injections in 26 mos.; by August 1913, *good appetite, no evidence of disease*; patient then disappeared on "spree," returned 19 days later haggard and weak; toxins resumed, *disease no longer controlled*; multiple metastases on abdomen, arms, breast, back, spinal cord; death, February 16, 1914. (Detailed history deserves special study, histological examinations made of tumors during treatment showed different effects produced by injections into the lesions as compared with those not injected.) (28; 50; 51; 81, Case 27; 82).

2¾ yrs.
(died)

10. (B.L. COLEY): Mrs. S.P., aged 41; inoperable malignant melanoma, primary in pigmented nevus on back along vertebral line, with bilateral axillary metastases; onset, spring 1933; primary lesion removed by electrocautery by local physician, July 1933; local recurrence, bilateral axillary involvement in 4 mos.; December 5, 1933, Coley cleared the lt. axilla; then gave 3 radium packs to rt. axilla; recurrence on back excised December 20, 1933; toxins (Parke Davis XIII) begun 8 days later, given i.v. and i.m., febrile reactions to 105°F.; rt. axillary metastases then excised; toxins resumed for 11 days; 3rd course toxins, July 1934; no fur-

ther evidence disease until December 1935 when another lesion appeared in rt. axillary region; dissected free, December 31, 1935; toxins resumed; although there was *no further evidence of disease*, 5th course toxins given July 1937, good febrile reactions, chills; in excellent health until 1956, then arteriosclerosis, hypertension; 2 myocardial infarctions 1956-7; in apparently fair health until death in her sleep, of apparent coronary thrombosis, January 23, 1963. (28; 71; 82).

30 yrs.

11. (CHANDLER & FLETCHER): D.M.M., female, aged 58; malignant melanoma lt. eye, multiple metastases in lt. auricular region, rt. chest and over entire body (subcutaneous and intracutaneous); onset 1957, decreased vision; lt. eye enucleated October 1958; very well 2½ years, then metastasis to lt. hand, excised June 1962; wider excision 2 wks. later; 2 nodules lt. lumbar, rt. thoracic area excised September 1962; January 14, 1963: toxins (Johnston XV), 52 in 15½ mos., 48 i.v.; reactions averaged 100.6 to 102.6°F. (maximum 103.6°F., none 4 times); *occasionally felt pain in tumors during reactions; during 3rd wk. of treatment 2 metastatic nodules behind ear enlarged slightly, then receded and enlarged several times during continued toxin therapy; felt exceptionally well, led normal life, in excellent general health during treatment, no new lesions appeared in 16 mos.; 2 nodules 2 cm. in diameter then developed deep in lt. axilla, June 1964; remained in good health another yr.; then disease progressed, widespread metastases with central nervous system involvement, flaccid paralysis, causing death October 30, 1965.* (16; 82)

(died)
8 yrs.

12. (CHANDLER & FLETCHER): Mrs. E.B., aged 53; recurrent malignant melanoma lt. knee, with over 20 metastases to lt. thigh, groin, rt. breast, axillae, rt. groin, rt. supraclavicular region (2½ cm.); onset, June 1961; primary excised that mo.; widely re-excised August 1961 (no tumor found in specimen); lt. groin nodes enlarging November 1961; lt. groin dissection, November 13, 1961, histologically negative for metastases; lesion on thigh biopsied, May 1962, positive; 45 mg. nitrogen mustard perfused via iliac vessels, June 1962; numerous satellite lesions appeared on leg, thigh next 2½ mos.; 27 present when toxins begun, August 31, 1962; 44 i.v. in 5½ mos.; x-ray to rt. supraclavicular region (800 r), September 12 to 17, 1962; *this lesion decreased in size, less local and radicular pain; daily red flare about some metastases, also markedly increased skin temperature over lesions during febrile reactions (to 106°F. when oral temperature was only 101° to 102°F.); further metastases developed immediately after frequency of injections reduced to 2 a wk.; 1 regressed, 5 others appeared; further radiation February 3 to 23, 1963 (4,000 r to lt. medial thigh nodules); toxins continued weekly during March 1963; lesions irradiated in February disappeared by April 1963; further x-ray to thigh May 6, 1963, caused regression of treated lesions in about 8 wks.; 2½ mos. after toxins stopped, supraclavicular metastases which had almost regressed completely the previous fall, began to recur; Velban then given for 8 wks., no benefit; severe pain rt. arm increased, requiring neurosurgery; death, November 22, 1963.* (16; 28)

(died)
2½ yrs.

13. (CHANDLER & FLETCHER): D.H., male, aged 50; malignant melanoma behind rt. ear, arising in compound nevus, metastases to rt. cervical and supraclavicular region (50 involved nodes), and later extensive metastases to duodenum and head of pancreas (inoperable); onset 1957; primary excised November 11, 1958; regional metastases biopsied; rt.

radical neck dissection, wide excision rt. posterior auricular region; 50 of 80 nodes positive; no further evidence of disease at follow up examinations, only vague ulcer symptoms, beginning about May 1962, continuing during next yr.; May 1963, sudden onset generalized weakness, stools became dark; g.i. series revealed large mass in duodenum; explored June 28, 1963; lesion $6\frac{1}{2}$ by $2\frac{1}{2}$ cm. in diameter almost surrounded 2nd portion duodenum, metastases also involved liver, large extensions in mesocolon, pancreas and gallbladder; enlarged nodes in mesentery and along common duct; no attempt at removal; toxins (Johnston XV) begun 12 days later, 9 i.v. in 15 days, 1 marked reaction from slight overdose (105.6°F . and hypotension); other reactions averaged $101.8^{\circ} - 103^{\circ}\text{F}$.; chills lasting 15 - 30 minutes occurred after all but 1 dose; metastatic mass continued to increase in size considerably; X-ray then given ending September 5, 1963 (3,500 r in 45 treatments); *gained 25 lbs., felt well, marked regression evident in several g.i. series until March 30, 1964 when regrowth evident*; disease progressed, retroperitoneal, supraclavicular and lt. and rt. inguinal metastases; trimethylcolchicinic acid given for 2 days, May 14-16, 1964, causing intense vomiting; downhill course, death August 24, 1964. (16; 82)

(died)
7 yrs.

14. (CHANDLER & FLETCHER): Mrs. M.M.P. diabetic female, aged 79; four times recurrent, very extensive malignant melanoma of scalp, with dermal lymphatic metastases involving almost entire scalp; onset, pigmented nevus, mid-1950; excised August 1957; recurred 1 mo. later; widely re-excised shortly thereafter: "superficial malignant melanoma;" further local recurrences removed, January 17, 1958, October 17 & November 10, 1960 ("junctional nevi"); pruritis of scalp, further recurrence excised March 1961: definitely malignant melanoma; skin grafted; latter broke down, numerous recurrent nodules bordered it; vaccinia virus inoculated into some of the lesions without effect; tumors increased in size; July 11, 1961, nitrogen mustard perfused via superficial temporal artery, without effect, then through lt. temporal artery also without effect; perfusion, 5-FU through lt. external carotid, no benefit; lesions grew, coalesced, extending over entire scalp from mid-forehead to mid-occiput, ear to ear; skin grafted area completely black with melanin, other $\frac{2}{3}$ covered by multinodular lesions, verruca like, black, almost confluent; toxins (Johnston XV), October 8, 1962: 8 into tumors in lt. scalp, 9 i.v. in 69 days, 4 moderate reactions (none at all 5 times); *no apparent change in lesions*; January 1963, 5 i.t. injections 5-FU in scalp lesions, no effect whatever, January 15, to March 12, 1963, X-ray to posterior occiput (4,000 r tumor dose); *little immediate effect, but by mid-April 1963 complete regression pigment and nodularity in treated area with white skin formation in its place*; further x-ray to lt. temporal region, April 15 to May 17, 1963 (4000 r tumor dose); *marked decrease in nodularity and depigmentation followed*; skin grafted area not treated, and in this region lesions continued to grow, with ulceration; 3rd area, lt. frontal and parietal region irradiated, September 24 to October 10, 1963 (4000 r tumor dose); *this area showed some regression, notable healing of ulcers, pruritis no longer a problem*; did fairly well until January 1964, then excessive bleeding from ulcerated areas in skin grafted portion, causing severe anemia requiring transfusions; disease progressed, probable widespread metastases to viscera present at death, March 6, 1964. Autopsy refused. (16; 82)

(died)
 $6\frac{1}{2}$ yrs.

SERIES C, DETAILED HISTORIES

CASE 1: Recurrent inoperable malignant melanoma of the left tonsil and fauces, confirmed by microscopic examinations following both operations.

Previous History: Male adult salesman. The family and previous personal history were not recorded.

Surgery: The patient was operated upon by Dr. George R. Fowler, of Brooklyn, N.Y. at St. Mary's Hospital for a malignant melanoma of the left tonsil and fauces, by external pharyngectomy. The diseased area which he removed included the tonsil, anterior faucial pillar, half of the vellum and a portion of the floor of the mouth.

Clinical Course: Recurrence took place four weeks after the wound had healed. A portion of this new growth was removed for biopsy, but further surgery was considered inadvisable.

Toxin Therapy (Buxton VI:) Injections were begun by Fowler in May 1895 following this second operation. They were given deeply into the muscles of the left arm. A sharp chill followed each dose with a febrile reaction of 103°F. The injections were given in the Outpatient Department of the hospital every third day, the patient returning home to bed. On the day before each injection he was able to continue his work as a salesman. When the toxins were begun there was a red recurrent growth at the site of the operation. Fowler stated that during the treatment "the whole region became white and glazed — a remarkable change." At the end of three weeks, the new growth in the lateral pharyngeal wall had disappeared and, the parts having healed, the frequency of the injections was decreased to one every four days, then to one a week, the total duration being less than four months.

Clinical Course: On December 12, 1895, three months after discontinuing the injections, the patient was presented before the Brooklyn Surgical Society, at which time no trace of disease could be found. Two years later he again consulted Fowler because of further recurrence. He was advised to resume toxin therapy at once, and promised to report to the hospital for this purpose. He failed to do so. Fowler learned that the patient died in 1898 with extensive infiltration in the cervical region, over three years after onset.

Comment: This appears to be the first case of malignant melanoma to be treated by toxin therapy. The history indicates the need for more sustained treatment in recurrent inoperable cases; possibly if this man had followed Fowler's advice and resumed treatment in 1897, a permanent result might have been obtained.

References: 25; 42.

CASE 2: Recurrent malignant melanoma of the bicipital region of the arm, with axillary metastases, inoperable except by interscapulothoracic amputation, confirmed by microscopic examination by Professors Huon and Thirier, of Mons, Belgium.

Previous History: Female, aged 40. The family and previous personal history were not recorded. The patient developed a malignant melanoma on the anterior aspect of the biceps in the region of the humeral artery.

Surgery: The growth was removed surgically by Drs. Descamps and Restiaux, of Mons.

Clinical Course: Even before the wound was entirely healed recurrence was evident. The patient was therefore referred to Dr. J.H.J. Matagne, of Brussels,

for toxin therapy. At this time the largest tumor mass was 7 cm. in diameter, situated near the humeral artery in the proximal third of the arm, and there were two adjacent smaller nodules.

Toxin Therapy (Buxton VI Formula as Made by Matagne): Injections were begun by Matagne on March 24, 1911. He always made them daily into the tumor tissue when this was possible, beginning with a dose of 5 cg., gradually increasing this by 2.5 cg. daily or every other day until a febrile reaction of 102° to 104°F. was elicited. The reactions usually consisted of a violent chill which began about 30 minutes after injection and lasted 30 minutes. There was no set maximum dose. During the first week of treatment decrease in size was apparent, and the rate of regression was so rapid that Matagne became hopeful of an ultimate cure. However, from time to time further recurrent nodules developed in the tumor area. Each time this happened Matagne felt that he had "lost the ground he had gained." He therefore advised shoulder joint disarticulation, which was refused. He then continued the injections and also applied formalin to the tumor. Finally the patient seemed to become more sensitive to the toxins. The febrile reactions became more and more marked (105.8° to 107°F.), and after almost seven months it was considered no longer possible to continue the treatment. Matagne again suggested surgical intervention and the patient finally agreed. At this time the axilla was filled with metastatic nodes.

Further Surgery: A shoulder-joint disarticulation was performed on October 20, 1900 by Professor Thirier, assisted by Drs. Marcel Heger and J. Goosens. The postoperative course was uneventful.

Clinical Course: There were no further recurrences or metastases. Restiaux, of Mons, reported in 1901 that the patient was in excellent health. She was last traced well and free from disease by Matagne in 1941, 41 years after onset.

Comment: In reporting this case in 1905 Matagne stated: "The success obtained in this case is all the more extraordinary since this type of neoplasm is of extreme malignancy and one which usually recurs in a matter of weeks." He added that the case suggested the advisability of using toxin therapy *before* surgical intervention in order to produce permanent results. As to the duration of treatment necessary prior to operation, he felt that this was a question which only experience would demonstrate, but that he considered two to four weeks of injections into the tumor or its vicinity was sufficient, and that toxins could then be continued after the operation. In concluding his paper which presented cancer patients apparently cured by Coley's method combined with surgery, Matagne stated that he did not think surgery alone could give as good results as he had obtained in his series of cases given pre-operative toxins. He stated he did not believe injections given after operation gave as good results as those prior to surgery.

References: 66; 67; 68; 69.

CASE 3: Recurrent malignant melanoma of the right posterior triangle of the neck, confirmed by microscopic examination by Dr. W. Gough, pathologist, who stated: "The tumor has a fibrous stroma, containing large numbers of irregular cells containing black pigment. . . . a typical malignant melanoma."

Previous History: J.B., male, aged 67, of Leeds, England. The patient was strongly built and in fairly good health when he first consulted Mr. H.H. Greenwood, F.R.C.S. (England) on February 2, 1911, complaining of a lump on the right shoulder which he had first noticed about December 1, 1910. A month after onset it began to be painful, and by February 1, 1911 the pain caused by

the irritation of his suspenders interfered with his work. The tumor mass $2\frac{1}{2}$ cm. in diameter was at the base of the posterior triangle of the neck at about the mid-clavicle. It was fairly hard and fixed, and was adherent to the skin which was normal in appearance save for a black speck the size of a pinhead. There was no obvious inflammation around the growth, which was increasing in size.

Surgery: On March 1, 1911 Greenwood excised a small portion under local anesthesia. It proved to be solid, the cut surface black. Sections were reported to be malignant melanoma. Two days later the growth was dissected out. It proved to be very extensive, about 8 cm. in diameter and black throughout. Toward the midline, although the carotid sheath was stripped clean, there remained small inaccessible portions burrowing in front of the vertebrae. The wound was closed without drainage. When the stitches were removed on the seventh day the wound was well healed.

Clinical Course: Three days later a black growth was found breaking down the scar, pushing through the suture marks. Eight days after recurrence was first noted the cavity was filled by a mass as large as the original growth.

Toxin Therapy (Tracy XI): Injections were begun by Greenwood on March 21, 1911, the initial dose being 0.5 minim diluted in 20 minims of sterile water and injected deeply into the pectoral muscles below the right nipple. Half an hour later the patient had a slight chill with a temperature of 101°F . and a feeble, rapid pulse. An hour later profuse perspiration occurred. In four hours the temperature was normal and the patient felt well enough to eat a hearty meal. Injections were continued in increasing doses every 48 hours, the site being gradually nearer the tumor, so that in a month's time the dose was 20 minims given directly into the tumor. Nux vomica was administered by mouth during the first two weeks, as the pulse was weak and irregular. Greenwood stated that the administration of nux vomica had "an unmistakable benefit." (Personal communication to Coley) (28) After the first month the injections were given twice a week, then once a week, the regular dose being 10 minims. At the end of a year the frequency was decreased to every two weeks and finally to once a month. On three occasions the general reaction was so severe that the injections were stopped for 7, 11 and 14 days respectively. Locally each injection gave rise to a hard, braunish swelling as large as a walnut, which subsided in 10 to 14 days. On November 14, 1911, after an injection into the tumor site, the reaction was so severe that the patient collapsed and was semi-conscious for four hours, although the temperature was only 103.4°F . Following this reaction the patient was confined to bed for three days and away from work for two weeks. In describing the effects of the toxins Greenwood stated: "By May 2, 1911, the visible black portions of the growth had disappeared and the growth was manifestly smaller. He returned to work on this day and except for the fortnight referred to above, has worked uninterruptedly since. The injections have been given in the afternoon, and he has always been fit for work the following morning. (He was granted a half holiday on his injection days.) Now, $1\frac{1}{2}$ years after treatment was begun, there is no sign of recurrence, his general health is excellent, his weight has increased slightly, and his monthly injection causes little general reaction." He added: "It will be conceded, I think, that (1), the growth was, as evidenced by the rapidity of the recurrence, of a high degree of malignancy. (2) the action of the toxins is due not merely to necrosis — shrinking of the growth was discernible before any injection was made into the tumor. (3) A certain degree of immunity is acquired. . . . (4) The treatment can be carried out at the surgery or in the out-patient department — the patient should be under supervision for four hours after each injection. It is desirable that the general health be attended to during the treatment. An overdose produces its most obvious effects on the cardiovascular and

nervous system." (45) Greenwood further described the effects in this case in his letters to Dr. William B. Coley: "The severity of the reaction was very precise and could be prophesized exactly: (1) The nearer the neck, the quicker and more severe the reaction. (2) The longer the interval, the quicker and more severe the reaction. (3) Only when injections were given daily and steadily increased did anything like a cumulative effect occur, and then it seemed rather that the patient had not had time to recover his strength. The reaction lasted about two to four hours, according to the dose — but immediately the sweating stage was over he got up and ate a hearty meal." (28) He added that the temperature usually rose to 101°F. in half an hour, and was sometimes followed by a chill, varying in intensity. *Summary of Toxin Therapy*: A total of 105 injections were given in about 22 months. Site: at first intramuscular, gradually working nearer the tumor, finally into the tumor, later into the site of the former growth after it had disappeared. Dosage and frequency: at first every other day, 0.5 to 20 minims; April to August 1911, 10 minims three times a week; then twice weekly; August 1911 to January 1912, 10 minims once a week; during the whole of 1912, 5 minims at first once a week, later once in two weeks, finally once a month.

Clinical Course: Greenwood reported to Coley in July 1913 that the patient remained absolutely free from further recurrence or metastases, that he was in splendid health and weighed 12 pounds more than he had at the beginning of toxin therapy. The site of the former growth was marked by a hollow, covered by a clean scar with no trace of pigment. Greenwood examined him periodically. He remained free from further evidence of disease until his death from acute bronchitis in 1925, at the age of 81, 15 years after onset. His family physician, Dr. Lacey Bathhurst reported that at the time of his death "there was not the slightest suspicion of a neoplasm, either primary or metastatic, in his chest." (82)

References: 25, p. 136; 26, Case 2; 28; 45; 81, Case 17; 82.

CASE 6: Several times recurrent inoperable malignant melanoma of the right shoulder, confirmed by microscopic examinations by Dr. James Ewing, at Memorial Hospital, with metastases in the surrounding tissues and the axilla.

Previous History: Mrs. C.P., aged 60, of New Haven, Connecticut. The patient's maternal grandmother had died of cancer of the breast. The patient had had no serious illnesses except typhoid fever at the age of 38. Onset, in December 1911 she first noticed a reddish brown spot on the skin of the right shoulder, resembling a birth mark or pigmented nevus. Three or four months after onset she burned it off with an acid. It recurred in about a week. Again she cauterized it. These recurrences and cauterizations were "repeated several times" by the patient and later by her local physician, the final one being in May 1912.

Surgery: The lesion soon reappeared and gradually increased in size for six months. In December 1912 it was removed surgically by Dr. Otto G. Ramsay, of New Haven. By February 1, 1913 there was a small recurrent pigmented growth in the scar and a mass of enlarged lymph nodes in the axilla. At the second operation, February 4, 1913, Ramsay found several discrete disseminated nodules the size of a pin head scattered throughout the tissues near the scar, and a mass of matted metastatic nodes in the axilla. Another incomplete operation was performed in May 1913. The patient was then referred to Dr. William B. Coley as a hopeless case. At times there had been slight pain in the shoulder, but never enough to trouble her very much. However, she had lost 10 or 15 pounds in weight and had become somewhat weak.

Toxin Therapy (Tracy XI): Injections were begun by Coley on May 18,

1913 and 13 were given in 19 days in doses of 1 to 6 minims ending June 6, 1913. The final dose caused the only febrile reaction (104.4°F.) and a slight chill. The patient was discharged on June 7, 1913. The injections were continued after her return home about three times a week, increasing the dose to 10 minims.

Clinical Course: Beginning August 7, 1913 the toxins were omitted for three weeks at Coley's suggestion. During July a small swelling appeared in the right shoulder. Several others then developed which continued to increase in size. This increase was more rapid after the toxins were stopped on August 7, 1913. The general health was excellent during this time, her only symptom being "slight tingling" about the shoulder and right arm and soreness near the elbow. The patient was readmitted to Memorial Hospital on August 28, 1913.

Further Surgery: The next day Coley excised the recurrent tumor.

Further Toxin Therapy: Injections were resumed on September 5, 1913 with a dose of 1 minim. Two days later a dose of 1½ minims was given. Neither of these caused any reaction. The patient was discharged home on September 8, 1913. The injections were continued three times a week by the family physician, the maximum dose being 8½ minims.

Clinical Course: Two new growths the size of marbles appeared during the next two months, one in the region of the spine on the right side, the other at the tip of the shoulder. There was no pain and no loss of weight. The patient was readmitted to Memorial Hospital on November 4, 1913.

Further Surgery: Coley excised three nodules the size of peas to marbles from the right shoulder region and another 3½ to 4 cm. in diameter in the lumbar region of the spine. These were reported by Ewing to be malignant melanoma without pigment. The patient was discharged on November 9, 1914.

Further Toxin Therapy: The injections were again resumed by the family physician and were continued steadily. In the spring of 1914 the patient wrote to Coley that no further recurrences or metastases had appeared. She added: "I am very well and all seems quiet on my shoulder, for which I am most thankful. I have been using your toxins one year today, and have had 128 injections . . . I am sure you will rejoice with me." Apparently the toxins were stopped about April 1, 1914.

Clinical Course: During the next few months metastases developed in the heart, liver, lungs and omentum, causing death on November 10, 1914, three years after onset.

Comment: This case suggests the need for more aggressive use of the toxins, begun earlier in the course of the disease, as in Greenwood's case.

References: 71; 82.

CASE 8: Three times recurrent malignant melanoma of the neck, confirmed by microscopic examination by Dr. James Ewing, after the fourth operation in March 1919.

Previous History: E.E.C., male, aged 33. The patient's mother had a few small nevi. Otherwise the family history was non-contributory. The patient had always been healthy. He had several congenital pigmented nevi, one on the lip, one in the pectoral fold, one in the suprapubic region, one beneath the right nipple, one on the right arm as well as several on the back. In 1912 a nevus was removed from the right lip by a barber with a caustic. There was no local recurrence. In May 1918, six years later, a mass appeared in the right cervical region which was diagnosed as tuberculosis.

Surgery: This was excised but recurred and on July 5, 1918 a second operation was performed at Mandan, North Dakota. This was reported to be non-malignant. Recurrence again developed and on September 30, 1918 a third operation was performed at the Mayo Clinic, the diagnosis at that time being malignant melanoma. The following March the case was referred to Dr. William B. Coley. Examination on admission to Memorial Hospital, March 12, 1919 showed a hard fixed mass in the right side of the neck on the posterior margin of the sternomastoid. The next day, under ether anesthesia a lymph node the size of an olive was removed from this region by Coley.

Toxin Therapy (Tracy XI): Injections were begun by Coley on March 15, 1919, the initial dose being 0.5 minim which caused a febrile reaction of 103.4°F. They were continued three or four times a week, the maximum dose being 2 minims.

Further Surgery: After about four weeks' treatment another node was removed from the posterior border of the sternomastoid, under local anesthesia. This was the size of a pea, hard, firmly attached to the surrounding tissues and was reported by Ewing as being dense fibrous fat tissue, with no evidence of tumor.

Radiation: One radium pack treatment was administered on March 28, 1919 (6085 mch.). The patient then returned to North Dakota.

Further Toxin Therapy: He is believed to have had further toxin injections at home for a time, alternate months, but the site, dosage and frequency were not recorded. During the entire course of treatment he had only six chills and the maximum dose was 5½ minims.

Further Surgery: In July 1919 another lesion was excised from the right hip.

Clinical Course: No further evidence of disease was noted until a year later, in July 1920, when a slowly growing mass appeared high up on the operative scar posterior to the sternomastoid. By September 1920, it was the size of an olive, painless and attached to the deeper structures. A chest plate was negative for pulmonary metastases at this time.

Further Toxin Therapy: Coley resumed the injections on September 15, 1920 at Memorial Hospital but only five were given that week in doses of ½ to 1¼ minims. The maximum febrile reaction was 102.6°F. and one chill occurred.

Further Radiation: On September 22, 1920 four bare tubes of radium were inserted into the right side of the neck. Two days later the radium pack was applied (2,200 mch.).

Further Toxin Therapy: Thereafter the toxins were continued three times a week until the patient returned home. On October 27, 1920 it was noted that the right cervical region was inflamed and tender to palpation, but no definite metastasis was felt. There was a small crusted area at the site of the radium treatment. By November 5, 1920 the tumor in the neck had almost disappeared.

Further Radiation: One bare tube of radium was inserted into the remains of the growth.

Further Toxin Therapy: The patient returned home and injections were continued until February 4, 1921, when they were suspended until April. During this time the patient regained his normal weight. On April 1, 1921 he wrote that he had not had any recurrence or symptoms whatsoever. He added: "There is just a very small lump where you inserted the last radium needles. The sore where you put the first radium is just about healed up. Personally, I am of the

opinion that I am entirely cured. . . ." The toxins were apparently continued for a few more weeks, but the exact duration was not recorded.

Clinical Course: The patient remained free from further evidence of disease during 1921, but it later became generalized causing death on March 15, 1923, in Mandan Deaconess Hospital, Mandan, North Dakota. This was 13 years after the primary lesion was cauterized and four years after toxins were begun.

Comment: This history indicates that recurrent malignant melanoma can not be controlled permanently by brief courses of intramuscular injections administered during and following radiation. The toxins were never administered aggressively at any time in this case.

References: 28; 71; 82.

CASE 9: Twice recurrent malignant melanoma of the scapular region, primary in a pigmented nevus, with axillary metastases, confirmed by microscopic examination after the first and second operations at Massachusetts General Hospital, Boston, Massachusetts. Dr. Whitney reported: "Large cells, many of them containing black pigment with little intercellular substance between, and irregularly infiltrating the periphery."

Previous History: F.H.F., male, aged 46, structural iron worker, of Somerville, Massachusetts. The family history was negative for cancer or tuberculosis. The patient had always been well except for pneumonia 20 years previously. Onset, without known cause, a pigmented nevus in the scapular region began to enlarge early in June 1911.

Surgery: Five weeks later, on July 14, 1911, Dr. Homans excised the growth with a 5 cm. margin of skin at Massachusetts General Hospital. The patient was seen every two weeks thereafter and no recurrence was noted until October 22, 1911 when a small lesion was seen on the outer aspect of the scar. Three days later the patient was admitted and Dr. Farrar Cobb excised the recurrence.

Clinical Course: The patient was first seen by Dr. Torr W. Harmer two weeks later at which time another recurrence 6½ cm. in diameter was present in the scar and there was a palpable mass in the axilla about 3 cm. in diameter.

Toxin Therapy (Parke Davis XII): Injections were begun by Harmer on November 15, 1911. Within 12 days a mass 4 cm. in diameter appeared in the scar. The two lesions became confluent, but under continued toxin therapy they entirely sloughed out in a month, leaving a thin soft scar. Harmer stated: "During this time however, a recurrence appeared in the upper scar, which became 6 by 9 by 2½ cm. in size. This whole mass was entirely sloughed out by January 13, 1912. It ruptured in three weeks with local injections, but increased in size until it measured 5 by 8 cm. There were several "erysipeloid" attacks when the whole pectoral region would become red, hot, tense and tender. A second metastatic lymph node appeared in the axilla and another on the neck. The latter became the size of a cherry, but entirely disappeared in a month. The axillary masses became 3 to 5 cm. in diameter during these erysipeloid attacks, but within a month decreased considerably and never became any larger until treatment was discontinued 11 months later. The upper axillary mass, which was present prior to toxin therapy, was no larger and just as movable 26 months later. The entire breast tumor sloughed out with cutaneous appearance of dark pigment by August 1913, and never recurred. Harmer stated that one bluish black mass about 6½ cm. in diameter regressed under local injections to an apparently fibrous mass of dull red color about 2 cm. in diameter. During this period another pigmented mass was developing within less than 10 cm. of the

one which was regressing. The second lesion increased to about 2½ cm. during the time that the other one was regressing."

Further Surgery: Both masses were then excised under ether anesthesia with an elliptical area of skin, subcutaneous tissue and fascia about 15 x 17 cm., and 14 sections were made from these two tumors. In reporting the case in 1914 Harmer showed microphotos of characteristic portions of the treated tumor in Fig. 3 in marked contrast to Fig. 5 and 6, the untreated lesion. (50) This is the only known case in which such a comparison was made of the different histological effects apparent in a tumor which had received injections into its substance and another near by which had not been so injected. Harmer stated that *the tumor was being destroyed by an inflammatory process.*

Clinical Course: By August 1913 the patient was in excellent condition with good appetite and no evidence of internal metastases. The other masses had sloughed out or been excised as stated above. The patient then disappeared on a "spree," returning 19 days later haggard and weak.

Further Toxin Therapy: Injections were resumed, but the patient never regained his former tolerance for the toxins. He had been taking 40 to 50 minims at a dose prior to this spree, but when he returned 4 to 8 minims produced as severe reactions as he had formerly experienced with only the larger doses. Metastases began to appear on the abdomen, arms, breast and back. The final injection was given on January 28, 1914. He received a total of 195 injections in 26 months, the maximum dose being 53 minims. Both intramuscular and intratumoral routes were used.

Clinical Course: The disease progressed causing death on February 26, 1914, 2¾ years after onset.

Comment: This patient received the Parke Davis XII preparation of Coley toxins, one of the weakest, yet by increasing the dosage to about three or four times the usual dosage suggested by Coley complete regression occurred. The case clearly indicates that even though new metastatic lesions may develop during the course of toxin therapy, one may gain control of the disease by persistent treatment. This case might have remained well had he not gone on a spree, and had the injections been continued for at least a year after regression occurred. The interesting observations as to the comparative effects of local and intramuscular injections indicate the importance of using at least some intratumoral injections. Intramuscular injections appear to be of little value in such cases, but a combination of intravenous and intratumoral and possibly intradermal in the vicinity of the lesions appears to be the most effective.

References: 28; 50; 51; 82.

CASE 10: Recurrent malignant melanoma of the back along the vertebral line, with bilateral axillary metastases, confirmed by microscopic examination by Dr. Fred W. Stewart at Memorial Hospital, of the recurrent growth and the metastases.

Previous History: Mrs. S.P., aged 41, of Greenvale, Long Island, N.Y. The family history was negative for cancer. The patient had always been healthy except for the usual diseases of childhood. She was married in 1909 and had five children between 1910 and 1919, all normal deliveries. The menstrual history was normal. An oophorectomy was performed in 1924. Onset, in the spring of 1933 the patient first noticed a pigmented nevus on her back. This increased in size very slowly until it was as large as a pea, pedunculated and papillary in shape.

Surgery: This lesion was removed by a local physician by electrocautery in July 1933.

Clinical Course: The following November a mass about 5 cm. in diameter appeared in the left axilla and a smaller one about 2 cm. in diameter developed in the right axilla. The patient was first seen by Dr. Bradley L. Coley on November 27, 1933. At this time there was local recurrence as well as metastases in both axillae.

Further Surgery: The tumor in the left axilla was removed by Coley at the Hospital for Special Surgery on December 5, 1933. The patient was transferred to Memorial Hospital on December 18, 1933. Examination on admission revealed a small healed incision on the back along the vertebral line, associated with a bluish black pigmented area. The left axilla showed a recently healed incision. The right axilla showed a mass in its lower portion approximately 2.5 cm. in diameter which was slightly movable.

Radiation: Three radium pack treatments were given to the right axilla on December 19, 20 and 21, 1933 (8,000 mch. each).

Further Surgery: On December 20, 1933 the recurrent melanotic area on the back was excised, an elliptical incision 6 x 10 cm. being made around the lesion. The patient was allowed to go home for Christmas but was readmitted on December 27, 1933.

Toxin Therapy (Parke Davis VIII): Injections were begun by Coley on December 29, 1933. The first eight were given intramuscularly in doses of 1 to 12 minims, then three intravenous injections were given, the dose being 1/60 minim. Febrile reactions ranged from 99.2° to 105.4°F. the latter after the first intravenous dose.

Further Surgery: On January 3, 1934 the mass in the right axilla was excised.

Further Toxin Therapy: Injections were resumed on January 9, 1934 and continued daily until January 20, 1934, three being given intravenously, the other eight intramuscularly in this first course. A second course was given from March 9 to 23, 1934, consisting of seven intramuscular injections. A third course, given between January 7 and 17, 1935, consisted of four intramuscular injections and two intravenous.

Clinical Course: The patient was readmitted to the Hospital for Special Surgery on February 2, 1935, because of thickening of the scar in the right axilla, which was thought to be a recurrence. This was excised and proved to be scar tissue without trace of malignancy. On December 26, 1935 the patient again consulted Coley, because of soreness in the right axilla of three weeks duration. There had been no loss of weight. Examination revealed a definite recurrence 5 cm. in diameter in the right axillary region.

Further Surgery: An axillary dissection was performed by Coley on December 31, 1935 at the Hospital for Special Surgery.

Further Toxin Therapy: A fourth course of injections was given between February 10 and 29, 1936, consisting of seven intramuscular injections (1 to 7 minims) and eight intravenous (1/60 to 1/2 minim), causing chills and marked febrile reactions. A fifth course was given between July 13 and 25, 1936, as a prophylactic against further recurrence, consisting of three intramuscular (2 to 4 minims) and eight intravenous injections (1/50 to 1/5 minim). A sixth and final course was given between January 18 and 29, 1937, consisting of 10 intramuscular injections (2 to 9 minims).

Clinical Course: The patient never had any further evidence of disease. She remained in excellent health until 1956 when she developed arteriosclerosis and hypertension. On August 9, 1956 and May 26, 1957 she had two myocardial infarctions from which she recovered. She remained well and free from further evidence of malignant melanoma until she died in her sleep, January 23, 1963, almost 30 years after onset. Death was believed due to a coronary thrombosis.

Comment: This patient received toxins for a longer period than any other case of malignant melanoma. The permanent result in this case was probably due to this prolonged intermittent treatment. This occurred even though the toxins were not begun until bilateral axillary metastases and recurrence were present.

References: 28; 71; 82.

CASE 11: Malignant melanoma of the left eye, with multiple small distant metastases in the left auricular region, right chest and entire body, confirmed by microscopic examinations at the University of Oregon Medical School, Portland.

Previous History: Mrs. D.M.M., aged 58 of Salem, Oregon. The patient's paternal grandfather had had a squamous cell carcinoma of the lip. Two brothers had rheumatoid arthritis and a sister had diabetes. The patient had diphtheria in childhood. She was allergic to penicillin. She was in exceptionally good health until about 1957 when she noticed decreased vision in her left eye. This was not improved by changing her glasses (optometrist). The vision decreased gradually until she began to notice yellow floating objects in her field of vision. She consulted a physician in the fall of 1958 and was told she had a tumor in her eye.

Surgery: The left eye was enucleated in October 1958.

Clinical Course: The patient did very well, with no further evidence of disease for over 3½ years, until June 1962, when a nodule was noticed between the left thumb and the index finger.

Further Surgery: This was removed and pronounced malignant melanoma. The area was more widely excised two weeks later without further evidence of malignancy. In September 1962 two more metastatic nodules were removed from the left lumbar and the right thoracic areas.

Clinical Course: She then developed two more subcutaneous nodules, one behind the left ear, the other in the right lumbar region in the posterior axillary line. She was then referred to the University of Oregon Medical School Hospital. Findings on admission were entirely normal with the exception of small subcutaneous and intracutaneous nodules over multiple areas of the body, the three most prominent were a) one 2 mm. in diameter behind the left ear; b) one 3 mm. in diameter in the right posterior axillary line and c) one 2 mm. in diameter in the right upper chest wall. The right eye was negative. The liver appeared to be a little thickened but was of normal size. There was no evidence of metastases to the lungs, soft tissue or bones.

Toxin Therapy (Johnston XV): Injections were begun on January 14, 1963 and 52 were given in the next 5½ months, four intratumoral and 48 intravenous. Febrile reactions averaged 100.6° to 102.6°F. (maximum, 103.6°; none at all four times). Following the third injection on January 18, 1963 the patient noted pain in the tumors. Two of the three larger nodules had almost disappeared by February 1, 1963, after 13 injections had been given. The 12th injection was the first to be given into one of the tumors. During February 1963 the frequency

was decreased to nine a month. By February 15, 1963 one of the nodules had almost doubled in size and another had appeared in the right flank. The reactions during February were mild; none following the intratumoral injection on February 28, others averaged 100.8° to 101.4°F., once 102.6°F. By March 14, 1963 the nodule on the abdomen measured 6 by 6 mm. and the one on the flank 8 by 8 mm. During April 1963 only four injections were given, one into one of the tumors, without reaction, and three intravenous (100.2° to 100.9°F.). The nodules on the flank and abdomen remained unchanged.

Further Surgery: On May 1, 1963 the lesion behind the left ear was removed.

Further Toxin Therapy: During May five injections were given. The lesions all remained stationary in size, except for the one in the abdomen which decreased slightly. In June 1963 four injections were given, in July three, none of which caused reactions over 102.6°F. (most were 100.2°F.). By July 10, 1963 the lesion in the abdomen was the same size but the one in the flank had increased slightly to 1.2 by 0.8 cm. During August and September 1963 only one injection was given, but these caused more marked reactions (102.2°F and 103.6°F.). The lesions decreased slightly during August and by September 6, 1963 had increased to 1.5 by 1.5 and 1.7 by 1.3 cm. Further slight increase was noted on October 2, 1963. In October 1963 two injections were given and in November one, causing febrile reactions of 102°, 103° and 102.2°F.; no injections were given in December 1963, two in January 1964, none in February, one in March and two in April 1964. It was noted on April 29, 1964 that two of the four nodules which had been 2 to 3 mm. in diameter when the toxins were begun were no longer present, one having been excised, the other having disappeared and never recurred. The other two lesions had remained stationary in size, with periods of enlarging and regressing over the previous seven months. During this period the patient felt exceptionally well, actually in excellent health and continued to lead a normal life.

Clinical Course: In June 1964 two 2 cm. nodules were palpated deep in the left axilla, which had not been apparent before. This was the first evidence of an increase in her metastatic disease in 16 months. She apparently remained in good health for another year. The disease then progressed with widespread metastases and involvement of the central nervous system, causing flaccid paralysis. Spinal fluid cytology was positive for malignant cells on September 27, 1965. Death occurred on October 30, 1965, eight years after onset.

References: 16; 82.

CASE 12: Numerous recurrent and metastatic malignant melanoma of the left leg, thigh, breast and groin; primary in a pigmented lesion on the left knee, confirmed by microscopic examination following biopsy of the metastases at the University of Oregon Medical School Hospital, Portland, Oregon.

Previous History: Mrs. E.B., aged 53. There was no family history of cancer, nervous or mental disease, but a strong family history of heart disease. The patient had her tonsils and adenoids removed in 1913. In 1933 she had a right oophorectomy for a cystic ovary, appendectomy and myomectomy (uterine fibroid). In 1936 and 1945 she had Caesarian sections. In 1938 she had a placenta praevia. In 1954 she developed rheumatoid arthritis. She sustained a whiplash injury in 1955. Onset, in 1961 she first noticed an enlarging pigmented lesion on her left knee.

Surgery: This was excised in June 1961 and reported to be malignant melanoma. On August 6, 1961 the area was widely re-excised. No tumor was found

in this specimen. In November 1961 enlarging nodes were apparent in the left groin. On November 13, 1961 a left radical groin dissection was performed. This specimen was also negative for further evidence of melanoma histologically.

Clinical Course: The patient remained fairly well until May 1962 when a suspicious lesion was noted on the left proximal thigh.

Further Surgery: Biopsy of this nodule was positive for malignant melanoma.

Chemotherapy: In June 1962 45 mg. of nitrogen mustard was perfused into this leg via the iliac vessels.

Clinical Course: Numerous satellite lesions then appeared on the left leg shortly after this procedure and continued to appear on this leg and thigh during the next 2½ months. The patient was referred to the University of Oregon Medical School Hospital in late August 1962. At this time physical examination revealed a somewhat thin but vigorous woman in no acute distress, except for pain in the right shoulder and arm. There were numerous small, very superficial light brown pigmented areas on the left leg. Approximately 5 cm. below the inguinal ligament on the lateral left thigh there was a raised 6 by 7 mm. somewhat erythematous nodule and there was marked induration deep to the groin incision. There was also a lesion 5 cm. below the ligament on the medial side of the thigh. There was marked erythema and induration on the proximal portion of the scar where the primary had been removed from the knee. There was induration throughout the perfusion and radical groin dissection incisions, which were either recurrences or cicatricial. The liver was palpable two fingers breadths below the costal margin, but it was not nodular. There was a thickened area on the upper outer quadrant of the right breast. There were several small nodes in the right axilla, the right groin and the left axilla. Pelvic examination was negative except for the induration in the region of the scars of the left groin and the hypogastric region. There was a definite 2½ cm. hard mass on the lower end of the right sternomastoid muscle which unquestionably accounted for her severe shoulder-arm pain on the right side. X-rays of the cervical spine, right shoulder and chest were all normal. All initial laboratory studies were within normal limits.

Toxin Therapy (Johnston XV): Intravenous injections were begun on August 31, 1962. The first dose caused pain in the right neck, legs and groin during the chills, but less pain was noted in the right shoulder and left knee following the third injection. During the febrile reaction the skin temperature rose as high as 106°F. over the tumor masses and each day a "red flare" was noted about some of the skin nodules during the febrile period after each toxin injection. The peak reaction occurred two or three hours after each injection at first, but after the x-ray treatments were begun it occurred six or seven hours after injection. The patient stated that she felt better after seven injections had been administered.

Concurrent Radiation: Beginning September 12, 1962 she received daily x-ray treatments for six days totalling 800 r to the right supraclavicular tumor mass. The tumor decreased in size under this combined therapy and there was less local and radicular pain. She then received 4,000 r to the medial aspect of the left knee delivered in 21 days resulting in moderate decrease in size of the tumor mass and definite symptomatic improvement, i.e. motion was less painful. She also received 4200 r to the medial aspect of the thigh given in eight days.

Further Toxin Therapy: A total of 17 intravenous injections were given in the first 21 days of treatment, the febrile reactions averaging 102° to 103°F. (maximum 104°, minimum, 101.8°F.). Chills occurred after all but four of these injections lasting from five to 22 minutes. The patient was discharged home

on September 20, 1962. Thereafter only two injections a week were given (as an out-patient). As soon as the frequency of the injections was decreased new lesions began to appear on the thigh and by September 27, 1962 there were 27 metastases present. By October 18, 1962 four of these had regressed. A week later the lesion in the left knee was causing pain and appeared to be growing. During the next 2½ months the lesions increased and by January 21, 1963 there were 31 present. In February 1963 pain increased, requiring aspirin and percodan.

Further Radiation: From February 3 to 21, 1963 x-ray therapy was given to numerous metastases on the left thigh through a lead cut out, totalling 4200 r.

Further Toxin Therapy: Injections were given weekly during March 1963. Complete regression of the metastatic nodules irradiated in February was apparent during the first week in April 1963.

Further Radiation: Further x-ray was given to other lesions in the left thigh between April 8 and May 6, 1963 (totalling 3700 r). These lesions also disappeared after about eight weeks.

Clinical Course: By June 1963 it was evident that the right supraclavicular mass, which had been irradiated early in October 1962 and had regressed to almost complete disappearance, was beginning to recur.

Further Chemotherapy: Velban was begun on August 5, 1963 and was given for four weeks in increasing doses. The supraclavicular mass continued to increase in size, and caused much pain in the right arm.

Further Surgery: On September 6, 1963 a bilateral cervical dorsal rhizotomy was performed for intractable pain in the right arm and shoulder. The patient was fairly comfortable thereafter.

Clinical Course: The disease progressed causing death on November 22, 1963 about 2½ years after onset.

Comment: In this case the toxins were not begun until the disease had recurred and both regional and distant metastases were present, and groin dissection and perfusion of the lower extremity had been performed. The latter appeared to hasten metastatic spread. Toxin therapy was not aggressively administered (nine into the tumors, no marked febrile reactions). The first new lesion to develop after the toxins were begun occurred shortly after the frequency of the injections was reduced to two a week. No evidence of regression was noted except in the areas which were given x-ray therapy. However, there was definite evidence of local reaction in the tumors after the third injection, i.e., increased heat and erythema. Perhaps if larger doses had been given more frequently a more marked effect might have been apparent. Such cases appear to respond more readily to toxins if the injections are begun prior to chemotherapy or radiation or extensive surgery.

References: 16; 82.

CASE 13: Malignant melanoma primary in the right posterior auricular area with metastases to the right cervical and right supraclavicular nodes and extensive inoperable metastases involving the duodenum, the head of the pancreas, the liver and the gallbladder, confirmed by microscopic examinations at the University of Oregon Medical School Hospital, Portland, Oregon.

Previous History: D.H., male, aged 50, of Hood River, Oregon. The family history was negative for cancer, tuberculosis and heart disease. The patient was

run over by a wagon at the age of five. He had herpes zoster in 1955. He had had a mole behind his right ear for ten years prior to onset in 1957 when a change became apparent. The patient did not mention this to his physician until November 1958.

Surgery: The lesion was excised on November 11, 1958 and was reported to show a "central malignant change in a compound nevus." Subsequent biopsy of the right cervical and supraclavicular nodes also revealed metastatic malignant melanoma. He was admitted to the University of Oregon Medical School Hospital where a right radical neck dissection was performed and a wide excision of the right posterior auricular region was also done. The pathologist reported that 50 of the 80 nodes in the specimens were positive for malignant melanoma.

Clinical Course: The patient was discharged three weeks later improved. He was followed closely in the tumor clinic and no further evidence of disease was found until May 1963, when after going fishing he noted onset of generalized weakness present on awakening. His stools then became dark. Three weeks after onset of weakness the patient returned to the tumor clinic. His hematocrit at this time was 25. He then admitted that for about a year he had had some ulcer type symptoms. It was felt that he was bleeding from a peptic ulcer or tumor and he was therefore readmitted on June 10, 1963. Physical examination revealed a pale, white male in no distress. The chest showed marked dorsal kyphosis and decreased breath sounds. The abdomen was scaphoid, the liver reached the costal margin, the spleen tip was not felt, the bowel sounds were active, there were no masses but some tenderness was felt to deep palpation in the epigastrium. Rectal examination was negative. There was no cervical, axillary or inguinal lymphadenopathy. Barium enema on June 6, 1963 was essentially negative. An upper G.I. series and small bowel series was completed on June 17, 1963 and revealed a lesion $6\frac{1}{2}$ by $2\frac{1}{2}$ cm. in diameter probably within the wall of the descending duodenum but possibly invading it from without; this was believed to be metastatic malignant melanoma. There also appeared to be a mass along the lesser curvature of the distal aspect of the duodenal bulb as well.

Further Surgery: On June 28, 1963 an exploratory laparotomy revealed an almost napkin ring lesion on the second portion of the duodenum with metastases to the liver, large extensions to the mesocolon, pancreas and gallbladder, and with enlarged lymph nodes at the root of the mesentery and along the common duct. None of the tumor was resected. After finding these extensive inoperable abdominal metastases it was felt that toxin therapy offered the only chance for control and that possibly following initial toxins the lesion might be irradiated.

Toxin Therapy (Johnston XV): Injections were begun by Dr. William S. Fletcher on July 10, 1963, 12 days after operation. A total of nine were given in 15 days. The febrile reactions averaged 101.8° to 103° F. (minimum 100° , maximum 105.6° F., from an overdose). Chills occurred after all but one injection, lasting 15 to 60 minutes. The patient tolerated these well with the exception of the maximum reaction which caused shock due to slight overdosage on his fourth day of therapy (blood pressure 70/40). He responded well to shock therapy and was well the next day.

Clinical Course: A repeat G.I. series on August 12, 1963 showed that the mass had grown considerably.

Radiation: He then received 45 x-ray treatments through anterior and posterior fields totalling 3500 r., ending September 5, 1963.

Clinical Course: A third G.I. series was then made and revealed a decrease in the size of the duodenal metastases. The patient felt well and had gained 20

to 25 pounds in weight. There was no evidence of intestinal obstruction. Regression continued until March 30, 1964 when an upper G.I. series showed progression of amount and degree of involvement compared with previous series done at six week intervals. During these six months anemia had been a constant problem although no gross bleeding was evident. By April 16, 1964 an extrinsic pressure defect upon the proximal ureter was reported on intravenous pyelogram, presumably due to retroperitoneal metastases. By May 5, 1964, a tumor mass was present in the right supraclavicular fossa which was positive for malignant melanoma. Left inguinal lymphadenopathy had also been present for many months, and at this time there was also a left iliac mass and a right inguinal node lying over the femoral artery. The laboratory studies remained within normal limits for liver, urine and blood.

Chemotherapy: He was started on trimethylcolchicinic acid on May 14, 1964 but could not tolerate more than two days of therapy because of intense vomiting.

Clinical Course: The disease progressed causing death in August 1964, seven years after onset.

References: 16;82.

CASE 14: Very extensive four-times recurrent malignant melanoma of the scalp, with dermal lymphatic metastases involving almost the entire scalp, confirmed by microscopic examinations following several excisions of recurrences or metastases at the University of Oregon Medical School Hospital, Portland, Oregon.

Previous History: Mrs. M.M.P., aged 79. The family history was negative for cancer, tuberculosis, heart, kidney or lung disease. The patient had had a hysterectomy in 1914 for removal of a "bleeding tumor of unknown cell type." In 1947 she fractured her left humerus, in 1954 her right clavicle, with no residual deformities. Beginning about 1950 she had rather severe diabetes. Originally she took 18 units of insulin a day but by 1963 she was taking 40 units daily. Onset, a pigmented nevus developed on the right temporal region in the summer of 1950.

Surgery: This was excised at the University of Oregon Medical School Hospital in August 1957.

Clinical Course: One month later recurrence developed.

Further Surgery: This was widely excised shortly thereafter and reported as "superficial malignant melanoma with more than adequate margins." Further local recurrences in the operation site were removed on January 17, 1958, October 17, and November 10, 1960. Each time these were read as active junctional nevi of the scalp. During this time the patient did well and was asymptomatic except for some itching of the scalp. However, in March 1961, further local recurrences were excised and reported to be definitely malignant melanoma. This area was covered with a skin graft. Areas of the graft broke down and further recurrent malignant melanoma appeared. By May 1961 numerous elevated pigmented lesions bordering the graft were apparent.

Vaccinia Virus Inoculations: On July 7, 1960 most of the lesions were inoculated with vaccinia, without effect. The tumors continued to spread.

Chemotherapy: On July 11, 1961 the scalp was infused with nitrogen mustard via the superficial temporal artery. The tumors slowly continued to spread. In December 1961 the affected area was perfused with 5-Fluorouracil through cannulation of the left external carotid. No apparent benefit was noted. The

lesions slowly grew and coalesced. From March to June 1964 she had a full course of Velban without benefit. By October 1962 the entire scalp was black from the mid-forehead back to the mid-occiput, extending down to the tops of the ears on both sides. About a third of the scalp was covered by a skin flap which was completely black with melanin. The other two thirds of involved scalp showed multinodular lesions, most of which were verruca-like, black, and scattered though almost confluent for the most part.

Toxin Therapy (Johnston XV): On October 8, 1962 injections were begun by Dr. William M. Fletcher. A total of 17 were given in 69 days, eight being into the scalp tumors and nine intravenous. Four fairly adequate febrile reactions occurred (101.8° - 102°F.), but none at all occurred after five of the injections. Chills occurred after eight of the injections lasting 20 to 50 minutes. In this case there was no definite increase in skin temperature over the tumor areas during these rather mild reactions, but the patient experienced severe back pain during one of the chills. No change was noted in the lesions.

Further Chemotherapy: In January 1963 five injections of undiluted 5-FU were made directly into the tumor in the left scalp, without causing any change whatsoever in the lesions. They continued to progress slowly.

Radiation: A small field in the posterior occipital region then received x-ray therapy between February 15 and March 12, 1963 (4000 r tumor dose). There was little immediate effect but by mid-April 1963 complete regression of the darkness and the nodularity of the skin had occurred with white skin formation in its place. Therefore further radiation was given on the left temporal region from April 15 to May 17, 1963 (4000 f tumor dose). This was followed by marked decrease in the nodularity and depigmentation of the area. The patient continued to do fairly well but during this time the tumor on the skin grafted area continued to progress (the whole right scalp). The radiologist did not want to treat this area because of the known notorious tissue reaction in grafted areas. However, a third field over the left frontal and parietal region was treated between September 24 and October 10, 1963 (4000 r tumor dose). This area showed some regression but the most notable observation was the healing of the ulcers and the lack of pruritis which had bothered her intensely for several years until toxins and radiation had been administered.

Clinical Course: The patient continued to do fairly well with interval growth in the tumor nodules and ulceration of two large areas in the skin grafted portion of the scalp. By January 1964 she began to have excessive bleeding from this area and was hospitalized with profound anemia (22%). She felt well otherwise and was comfortable. She was transfused to 40% by January 29, 1964. She continued to bleed slowly and was thought to have liver metastases due to an increase in her BSP of 30% on January 24, 1964. She expired on March 6, 1964, of poor fluid and oral intake and poor control of her diabetes. At this time it was believed that widespread visceral metastases were present, but autopsy was refused. Death occurred over $6\frac{1}{2}$ years after onset.

Comment: In this case toxin therapy was not begun until five excisions and a skin graft had been performed and three chemotherapeutic agents had been administered (two by perfusion, one orally), without any apparent benefit. The patient's advanced age, her diabetes and her very extensive disease were also deleterious factors. Only 17 injections were given in 69 days without adequate febrile reactions and these did not produce any apparent effect upon the tumors. However, this "priming" appeared to markedly potentiate the radiosensitivity of these usually rather radioresistant tumors so that marked regression occurred in the irradiated areas, more marked in those treated just after the toxins were administered than in the later series. If toxins and radiation had

been begun earlier in this case, before skin-grafting or chemotherapy, it is possible that the disease might have been controlled. The scarring of so many surgical procedures as well as the perfusion undoubtedly decreased the vascular channels through which the toxins must reach the neoplastic cells, as well as affecting the lymphoid tissues deleteriously, thus limiting the possible benefits of toxin therapy. Nevertheless, the history suggests that even a brief course of toxin injections can have a "priming" effect on subsequent radiation. Recent studies on animals by Ainsworth (1) and Cole (13) indicate that better results may be obtained if radiation is begun immediately after the initial toxin injections, rather than waiting three months as was done in this case.

References: 16; 82.

CONCLUSIONS: These 28 toxin treated cases in Series B and C suggest the great importance of sustained toxin therapy, using a preparation and dosage adequate to elicit febrile reactions averaging 101-104°F. It is of interest to note that in Case 10, the only area in which a further lesion appeared was the area which had been irradiated (radium pack). A permanent result was finally achieved in that case by further surgery and toxins. Case 12, 13 and 14 in Series C suggest the value of preliminary toxins in rendering a radioresistant tumor more sensitive to subsequent radiation.

Most of the patients in Series B and C had had one to three recurrences, or metastases were present when toxins were begun. Successful results were usually obtained, in both operable and inoperable melanoma, if toxins were given persistently for considerable periods, gradually lessening the frequency of the injections. It is now apparent that if toxins are given as an adjuvant to surgery it is best to begin the injections *before the operation*, in order to offset the stress of surgery and in order possibly to increase the antigenicity of the tumor. They should then be continued after the operation, as this appears to stimulate wound healing and lessen the chance of recurrence. Matagne, an eminent Belgian physician who used toxin therapy successfully for many decades, believed it was best to administer toxins for a month prior to surgery (See Series C, Case 2 for such a case). That his theory is sound is borne out by the results in cases receiving such therapy, and by several recent reports which indicate that tumor immunity is best elicited by absorption of necrotic tumor tissue during regression.

Present studies with animal tumors indicate that microbial products which are not pyrogenic or toxic to the animal may prove to be equally effective as regards their tumor destructive activity. Thus it may no longer be necessary in treating patients to elicit marked febrile reactions and chills, especially when using toxin therapy as an adjuvant to surgery or to potentiate the response of tumors to radiation. (48a; 84a).

INOPERABLE MALIGNANT MELANOMA TREATED BY VACCINIA VIRUS

As mentioned in the introduction, two investigators in the United States (12, 53) and three in Australia (6, 53, 83) have been using vaccinia virus inoculations in the treatment of malignant melanoma. Detailed histories are not available on the cases treated in Australia.

Burdick and Hawk, working at the Cleveland Clinic, reported in 1964 that of the advanced inoperable malignant melanomas who received injections of vaccinia virus, three had shown temporary improvement in the cutaneous tumors without apparent alteration in the overall clinical course; five showed no change whatsoever. One patient then under treatment was responding favorably. Burdick stated: "Two factors seem to have had a favorable influence on the result: *Patients who responded best have had multiple small tumors and have exhibited a generalized hypergic reaction to the cowpox, as manifested by chills, nausea, vomiting and malaise for several hours after injection into the tumor.*" (13)

Detailed histories of two of Burdick's cases are available for analysis and are given here, first as brief abstracts, then in detail. One other case is known to have received two injections of vaccinia virus without apparent effect. This patient also received 17 injections of MBT and is therefore listed as Case 14, Series C, the inoperable toxin treated group.

Possibly inoculations of vaccinia virus may stimulate host resistance mechanisms (including interferon?) in patients whose disease or advanced age have not rendered them anergic. Burdick's comments about the type of reaction that accompanied favorable responses is of interest. Other physicians noted that patients receiving toxin therapy who had marked febrile reactions with chills did better than those with little or no reaction. (91, Monograph #3)

Series D, Vaccinia Virus Treated Cases, Brief Abstracts

1. (BURDICK): Female, aged 69; inoperable malignant melanoma primary on dorsum of lt. foot, metastases to lt. groin and lt. thigh; onset, spring 1957; ulcerated lesion involving dermis and epidermis excised 18 mos. later; lt. groin dissection several wks. later; within a few mos. many subcutaneous nodules in lt. groin; region again dissected free of metastases; 17 nodular lesions present in periphery of scar, February 1960; hepatomegaly, indurated region in lt. inguinal region melanuria, metastasis to lung by May 1960 when 1/2 vial vaccinia virus injected into a metastatic nodule causing *modified, accelerated vaccinia reaction with redness, swelling, induration, beginning 4 days later*; similar injections continued wkly, gradually reducing frequency to 3 wk. intervals; dose increased to 5 vials in 0.5 ml. saline; for 8 hrs. after 2nd and 3rd injections systemic reaction occurred: fever, malaise, vomiting; thereafter such symptoms were largely obviated by prior injection of phenothiazine; *all nodules showed regression, particularly the smaller lesions, which practically disappeared after a yr. of treatment*; irregular, edematous, asymptomatic erythema then developed on large areas of the glabrous skin; *in 10-14 days edema and erythema subsided leaving completely depigmented areas; concomitant with this cutaneous reaction the remaining metastatic nodules disappeared, induration of the lt. inguinal region showed remarkable resolution, liver no longer palpable, no further melanin in urine, chest films negative*; thereafter vaccinia injections given every 3 mos.; *patient asymptomatic, n.e.d. until early May 1965, nearly 5 yrs. after 1st vaccinia injection*, then noted swelling of lower extremities; metastases in paravertebral region revealed at exploratory operation, no other evidence of disease; alive, doing own housework at 77 years, July 1965, but with continuing anemia

and general debility metastases believed present; she is believed to have died about February 1966 of metastases to retroperitoneal space and spine. (12; 13; 82)

(died)
almost
9 yrs.

2. (BURDICK): Female, aged 29; recurrent inoperable malignant melanoma of lt. thigh, metastases to lt. inguinal nodes and skin of lt. thigh, lt. breast and lt. axilla; onset, 1956; excised 1956, widely re-excised 1 mo. later; steroids administered orally; by March 1958 fist-sized purple recurrent mass present on thigh surrounded by 50 small satellite metastases, also marble size lesion in lt. groin, lt. breast, lt. axilla; February 26, 1959, vaccinia virus injected into largest tumor, *moderately severe generalized toxic reaction, some regression*; methlorethamine hydrochloride (25 mg.) and Thio-TEPA (15 mg.) perfused through femoral artery, March 2 and 5, 1959; *leg metastases steadily decreased in size but new lesions appeared on trunk, jaw, arms, mediastinum*; further vaccinia injections given repeatedly into all but mediastinal lesions at 3 to 6 wk. intervals, with *complete resolution of most of the tumors; inaccessible mediastinal masses also decreased in size; slight dysphagia and cough disappeared*; 1961, bleeding from large necrotic retroperitoneal tumor necessitated extensive surgery; few wks. later thousands of metastases appeared which did not respond to further therapy; disease progressed, death about 1962. (12; 13; 82)

(died)
over
5 yrs.

Series D, Vaccinia Virus Treated Cases, Detailed Histories

CASE 1: Metastatic malignant melanoma primary on the dorsum of the left foot, with metastases to the left groin and left thigh, confirmed by microscopic examinations at Cleveland Clinic Foundation, Cleveland, Ohio.

Previous History: Female, aged 69. The family and early personal history were not recorded. Onset, in the spring of 1957 the patient first noticed a flat, dark macula on the dorsum of the left foot, arising *de novo* and growing steadily with occasional bleeding and ulceration.

Surgery: In the fall of 1958, 18 months after onset, this lesion was excised and reported to be an ulcerating malignant melanoma involving the dermis and epidermis. Several weeks later a lymph node dissection of the left groin was performed.

Clinical Course: Within several months a number of subcutaneous nodules appeared in the left groin.

Further Surgery: The region was again dissected free of gross metastases. These lesions were also reported to be metastatic malignant melanoma.

Clinical Course: In February 1960 a number of new nodular lesions appeared in the left thigh. The patient was admitted to the Cleveland Clinic Foundation in May 1960. Physical examination revealed 17 flesh colored to bluish red nodules clustered about the surgical scar on the left side. The tissue around the left inguinal ligament was thickened, indurated and irregular to palpation, and the edge of the liver was felt two to three cm. below the costal margin, with questionable nodularity. Laboratory findings: the urine was positive for melanin-like pigment. A soft tissue density was noted behind the heart shadow,

which was believed to be evidence of metastasis. Further surgical therapy was believed to be contraindicated and perfusion techniques did not appear feasible in this case.

Vaccinia Virus Therapy: Beginning in May 1960, half a vial of ordinary vaccinia virus (cowpox) was diluted with 0.1 ml. of saline in a tuberculin syringe and injected into one of the nodules. A modified, accelerated type of vaccinia reaction with redness, swelling and induration was seen about this nodule, starting on the fourth day after injection. Slight constitutional symptoms were also present. This reaction was largely dissipated 11 days after the injection. Similar vaccinia injections were continued, at first weekly, then gradually reducing the frequency to three week intervals. The dose was increased to a total of five vials diluted in 0.5 ml. of saline. All the metastatic lesions on the leg were injected. For eight hours after the second and third injections systemic reactions and chills, fever, malaise and vomiting occurred. Thereafter such symptoms were largely obviated by prior injections of phenothiazine. All nodules showed regression, particularly the smaller lesions; the latter had practically disappeared after a year's treatment.

Concurrent Inflammatory Reaction: At this time there appeared an irregular edematous, asymptomatic erythema on large areas of the glabrous skin. In 10 to 14 days the edema and erythema subsided, leaving completely depigmented areas in the previously inflamed regions. Concomitant with this cutaneous reaction, the remaining metastatic nodules of the skin disappeared, and the induration of the left inguinal regions showed remarkable resolution. The liver was no longer palpable.

Further Vaccinia Virus Therapy: The vaccinia injections were then given every three months, and in the next two years the patient remained asymptomatic and apparently free from further evidence of disease. The urine no longer contained melanin-like pigment, and the chest films showed no changes. The case was reported in June 1964. The patient remained well until about February 1965 when some swelling of both lower extremities was noted.

Further Surgery: An exploratory operation revealed metastatic lesions which were removed from the paravertebral region. No other metastases were seen.

Clinical Course: In July 1965 the patient was continuing to do all her own housework (at the age of 77), but her general debility and continuing anemia indicated that further metastases were present. She is said to have died about February 1966, almost nine years after onset.

Comment: This case is a clearcut example of the dramatic effects which may occur following an acute cutaneous inflammatory reaction imitating an erysipelas. If vaccinia virus injections had been continued at more frequent intervals for at least a year after complete regression was observed, it is possible that a permanent result might have been obtained. It is most remarkable that the widespread disease, which was present when vaccinia inoculations were begun, was controlled for nearly six years.

References: 12; 13; 82.

CASE 2: Recurrent inoperable malignant melanoma of the left thigh, with metastases to the left inguinal nodes and to the skin of the thigh, also in the left breast and left axilla, confirmed by microscopic examinations following excision of the primary and some of the metastases.

Previous History: Female, aged 29. The family and previous personal history were not recorded. The patient noticed a brown mole on the sole of her left foot when in high school. A physician was consulted and advised her to

leave the lesion alone. Onset, in 1956 a brown mass appeared on the left thigh above the knee.

Surgery: The lesion was excised and proved to be malignant melanoma. The area was then widely re-excised. A month later the left inguinal lymph nodes were removed.

Steroid Therapy: The only other therapy consisted of steroids given orally.

Clinical Course: The patient was referred to the Cleveland Clinic in March 1958 with a fist-sized, purple, recurrent tumor on the left anterior mid-thigh surrounded by 50 small brown or flesh colored nodules, and firm marble sized masses palpable in the left groin. There was also a mass in the left breast and another in the left axilla.

Vaccinia Virus Therapy: About February 26, 1959 live vaccinia virus was injected into the largest tumor, resulting in a moderately severe generalized toxic reaction and some diminution in the size of the tumor.

Chemotherapy: The patient was hospitalized and 25 mg. of methlorethamine hydrochloride (a nitrogen mustard) and 15 mg. of Thio-TEPA was administered in the femoral artery on March 2 and 5, 1959.

Further Vaccinia Virus Therapy: With the exception of the mediastinal lesions, all the metastases were repeatedly injected with vaccinia at three to six week intervals. The leg metastases steadily decreased in size but new lesions appeared on the trunk, jaw, arms and mediastinum, varying in size from peas to pullet eggs, following the chemotherapy. However complete resolution of most of the tumors finally occurred. The inaccessible mediastinal masses also decreased in size, as seen by x-ray examinations. The slight dysphagia and cough disappeared.

Clinical Course: In 1961 the patient began bleeding from a large necrotic retroperitoneal tumor.

Further Surgery: This necessitated extensive surgery.

Clinical Course: No further vaccinia injections were given. Within a few weeks after this operation thousands of small metastatic nodules appeared. They did not respond to therapy. The disease progressed, causing death about 1962, over five years after onset.

Comment: Note that this patient received steroid hormones following her initial operations in 1956. This may well have hastened the generalization of her disease. Since the response to vaccinia was rather good it might have been well to continue the injections for a year or two, in order to try to gain complete control of the disease. The very widespread metastases which occurred immediately following the final surgery suggests the deleterious effect on host resistance of extensive surgical procedures, and indicates the need for an adjuvant which can stimulate the host before and after operation.

In a personal communication Burdick stated: "In reference to the generalized hypergic reaction to the cowpox, . . . these reactions seem to occur in patients who are progressing most favorably, but by the use of aspirin and Compazine we were able to control the reaction almost completely so that there was little evidence of fever or other toxic reactions. Dr. Hawk, of the Department of Pathology and I then did a series of experiments on hamster melanoma using the transplantable melanoma of Dr. Green. . . . The only two positive findings were that if the vaccinia were mixed with the tumor cells at the time of inoculation, no take occurred; and we could produce necrosis in the primary tumor. This, however, did not seem to influence the rate of metastases or death of these animals. . . ." (82)

References: 12; 13; 53; 82.

INOPERABLE
MALIGNANT MELANOMA TREATED BY RABIES VACCINE

The following patient received rabies vaccine because she had been bitten by a dog believed to be rabid:

Diagnosis: Malignant melanoma, primary in the pretibial region, with cutaneous metastases in the leg and thigh, confirmed by microscopic examinations at Memorial Hospital, following excision of the primary and five cutaneous metastases.

Previous History: Female, aged 32 in 1940. The patient developed a malignant melanoma 3 cm. in diameter in the pretibial region.

Surgery: This was excised at Memorial Hospital in May 1940. An elective groin dissection six weeks later revealed no evidence of metastases.

Clinical Course: In September 1942 three cutaneous metastatic nodules were excised from the same leg and thigh.

Rabies Vaccine: In September 1943, after being bitten by a dog which was believed to be rabid, the patient received 14 injections of rabies vaccine.

Further Surgery: In April 1948, 4½ years later, two additional metastases were excised from the skin on the same side.

Clinical Course: The patient remained well and free from further evidence of disease in 1950, 10 years after onset and seven years after rabies treatment.

Comment: In reporting this case in 1950 Pack stated: "The long latent period of 5½ years intervening between the appearance of multiple metastases was so extraordinarily unusual that it excited considerable speculation among the various members of the clinic staff concerning the cause of this inhibition. In a personal experience of more than a thousand cases of malignant melanoma, we had occasionally noted local recurrence or distant metastases five or more years after removal of the primary, but not such a long interval between the appearance of multiple cutaneous metastases. The only incident in the patient's history which might be of related interest was the . . . immunization against rabies. . . . On the empiric basis of this related coincidence it was decided to give similar series of rabies vaccine to some patients with generalized melanomatosis." (87)

As noted in the introduction, this was done at the suggestion of Dr. J. B. Trunnell, and 30 patients with advanced malignant melanoma received consecutive daily intramuscular injections of the Harris rabies vaccine for 20 days. In some instances the total dose was repeated. In 10 patients no apparent changes were observed and the inevitable course of the disease was uninfluenced. In one patient with innumerable black, elevated, nodular cutaneous metastases involving the face, neck, breasts, trunk, abdomen and thighs, the nodules became macular and flat, with loss of all induration but persistence of pigmentation. With eyes closed the examining physician could no longer palpate the nodules in the skin, and no new lesions were apparent in the course of the next four months. Three of the macular, pigmented spots were excised for microscopic examination. Residual, fully active melanoma cells were seen in each specimen.

Another patient had an eye enucleated for melanoma in 1936. Abdominal exploration at laparotomy for uterine myomectomy in 1949 revealed a spherical black tumor in the right hepatic lobe. This known metastasis in the liver then

grew with great rapidity. In a few months the large firm liver occupied almost the entire right side of the abdomen and extended well below the anterior part of the iliac spine. Two series of rabies vaccine injections were given, consisting of 20 daily doses each, in a period of three months. The regression in size was dramatic, as the liver edge receded to the costal margin, but the nodule, though quite small, could still be palpated. The patient's health improved, and at the end of six months she weighed more than at any time in her life. A laparotomy was then performed and a single, multilobular metastasis was excised from the right lobe of the liver. The tumor was viable, and there were no cellular alterations seen on microscopic study. (87)

In South America, principally in Argentina, approximately 100 patients with malignant melanoma have received rabies vaccine therapy. In 12 of these cases there was apparent significant improvement. (87, Discussion by Rauschkolb)

Perhaps rabies vaccine stimulates the production or release of interferon, as well as non-specific stimulation of the reticuloendothelial and lymphoid tissues, as is the case with bacterial toxin therapy.

SUMMARY AND CONCLUSIONS

In a considerable portion of the cases of spontaneous regression of malignant disease accepted as valid by Everson and Cole and other investigators, fever and infection were implicated.

In the present study the known cases of malignant melanoma with concurrent infection, fever or inflammatory episodes have been reviewed. These cases include a number of spectacular results, not only immediate but in some cases apparently permanent.

While the prognosis in malignant melanoma is notoriously bad, the cases assembled here, both infection and toxin treated patients, suggest that we must adopt a less pessimistic attitude about these highly malignant tumors, and that better results may be obtained in the future by the judicious combination of several modalities. One of these, which until recently has been ignored, is the use of bacterial toxins as a means of enhancing the resistance of the host and potentiating the response to radiation or surgery. The stimulating effect of certain bacterial toxins on the lymphoreticuloendothelial system is believed responsible for much of the salutary effect of concurrent infections or toxin therapy. Increasing the host response to the tumor cells and raising the fibrinolysin titre of the serum in these patients may also contribute to the result. Recent studies indicating that prior administration of bacterial toxins protects animals against the lethal effects of large doses of whole body irradiation, are significant. Other studies indicate that with prior administration of toxins the radiosensitivity of the tumor may be increased without rendering the normal tissues more sensitive to radiation. Thus timing of various therapies becomes of great importance if we are to secure the beneficial effects desired.

The most important factors affecting success or failure with toxin therapy of malignant melanoma include the stage of the disease when toxins are begun, the potency of the preparation used, the duration and intensity of toxin therapy, and the amount of surgery and radiation given prior to beginning such treatment.

Further intensive research is needed to make available a larger number of effective microbial products designed to stimulate host resistance mechanisms in malignant melanoma and other forms of neoplastic disease.

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