

SPONTANEOUS REGRESSION OF MALIGNANT MELANOMA



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MONOGRAPH #19

CANCER RESEARCH INSTITUTE, INC.
681 FIFTH AVENUE NEW YORK, N.Y. 10022

NEW YORK 1997

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1. INTRODUCTION

Unusual courses of cancer are often observed in clinical oncology. The autonomous regression of primary tumors or metastases represent a phenomenon that has provoked the curiosity of physicians working in clinical and scientific areas. This "spontaneous regression" has retained much interest, since from this knowledge, a therapeutic influence may become possible. Consequently, many authors have dealt with spontaneous regression, especially in cases of metastatic malignant melanoma. Having examined the known case reports and surveys in the literature, it becomes clear that the mystery of spontaneous regression of malignant melanoma remains unsolved. This may indicate that current explanations of this phenomenon are based more on speculation than on known facts [23, 27, 33, 34, 35, 50, 51, 88, 89, 99, 197, 198, 239, 260, 261].

1.1. Historical survey

The first reports of a partial or complete regression of neoplastic tumors without discernible therapeutic manipulation originate in the second half of the 19th century [19, 192, 219]. Until approximately 1920, malignant melanoma was classified in the group of sarcomas as melanosarcoma. At that time, regression of sarcoma was more often documented than carcinoma, possibly explaining why the first documented accounts contain several case reports of partial or complete regression of melanosarcoma [19, 43, 46, 192, 219, 264].

In one of the first reviews by Bennett [19], 17 case reports regarding the unpredictable behavior of benign and malignant tumors are discussed. This report differentiates between histologically or clinically malignant tumors with benign growth and benign tumors with malignant progression. A third group is composed of patients where the author postulates that the patient's psychological frame of mind influenced the course of tumor development. There is a noteworthy division of malignant tumors into one group with dormant tumor activity and a change to a benign condition and in a second group with partial or complete regression. Complete regression was observed only in cases of sarcoma, of which two examples of melanosarcoma are cited. In conclusion, the evidence for spontaneous remission is reinforced, whereby the author suggests that the patient's mental state played an essential role.

Lomer [163] assumes that an increased heat lability exists in neoplastic cells when compared to cells of benign tumors. He postulates an alteration of the blood cells after major increases in temperature, i.e., fever, such as that which can occur in erysipelas, tuberculosis, syphilis, gonorrhea or malaria. The increase in leukocytes seen during the course of these infectious diseases, similar to the situation observed in burns, appears to be an important factor for spontaneous regression. The loss of large amounts of blood followed by cachexia or phthises has also been implicated in the alteration of the blood cells. The possible appearance of specific toxic substances circulating in the blood due to cachexia are also discussed. Furthermore, the author mentions attempted treatment of malignant tumors with substances such as turpentine, arsenic, lysol and cantharidin.

In 1903, Mohr [188] reviewed the current literature citing cases of spontaneous healing processes of cancer. Besides the possible causes mentioned by Lomer [163], the role of lymphocytic infiltrates and tumor cell phagocytosis are discussed. Also, the elimination of a "triggering" carcinogen is taken into consideration as a possible catalyst. The author also reported spontaneous recovery in cases of skin cancer in patients with Xeroderma pigmentosum.

An immunologic relationship between tumor and host was described 18 years later by Boyd [33]. The possibility of a homologous transmission of specific tumor immunity through tissue or blood transmission in mice was recognized at that time. However, heterologous immunization from the mouse to the rat was not successful. The metastatic potential of a tumor was not only attributed to the characteristics of the tumor, but also to the resistance of the host organism. Two melanosarcomas were cited among the three case examples.

Frauchinger [100] takes a more critical view of cases described up to this point in time of spontaneous regression in malignant tumors. The cases documented in the literature as spontaneous recovery were classified in the following categories:

1. scientifically conclusive spontaneous recovery without the slightest therapeutic manipulation
2. uncertain spontaneous recovery without the slightest therapeutic manipulation
3. scientifically conclusive recovery after palliative or incomplete operative procedures
4. uncertain recovery after palliative or incomplete operative procedures
5. regression of primary carcinoma and metastases and stagnation of primary carcinoma
6. spontaneous recovery of skin cancer
7. slow but progressive growth of carcinomas
8. delayed metastasis and delayed recurrence.

Concurring clinical and histologic diagnoses, confirmed clinical course and proven diagnosis through autopsy are prerequisites for the predicate "scientifically conclusive." Interestingly, no example is cited in the first category "scientifically conclusive spontaneous recovery without the slightest intervention."

Dunphy [83] describes unusual courses of tumor progression. He cited examples of spontaneous regression and examples of unusually long life expectancies in spite of obvious tumor progression. Partial and complete operative procedures and hormonal and endocrine effects are taken into consideration as possible catalysts.

In 1952 Stewart [270] reported the spontaneous regression of uterine cancer, neuroblastoma and hepatocellular carcinoma. He also spoke of spontaneous regression in connection with improper or inadequate treatment. Hormonal influences were cited in cases of prostate and ovarian cancer. Possible causes of spontaneous tumor regression due to stem cell differentiation in a benign or malignant cell line are also considered. Examples for spontaneous regression of melanoma were not found. A case of an inoperable myosarcoma is noted in which complete spontaneous regression was accompanied by high fever, a pronounced eosinophilia and a generalized urticaria.

In two major reviews from 1966, Boyd [35] and Everson and Cole [89] report additional cases of spontaneous regression whereby, among the examples documented, regression of a primary tumor or metastasis of the malignant melanoma is frequently described. In the discussion regarding the prognosis, progression and future therapy of malignant melanoma, spontaneous regression is ascribed a permanent position as a fascinating clinical phenomenon [10, 11, 27, 145, 184, 197, 198, 225, 239].

In one of the first reviews relating to the topic "spontaneous regression of malignant melanoma," Nathanson [197] deals with the possible causes and the documented circumstances of spontaneous regression. Reference is made to possible connections between halo naevus with leukoderma development in the regression of the primary tumor as well as metastases and metastatic malignant melanoma of unknown primary tumor exhibiting spontaneous regression.

1.2. Definition of terminology

In the literature, an explanation of the terms "spontaneous" and "regression" was often considered necessary. In 1957, Boyd [34] defines "spontaneous" as "with inadequate therapy" and "regression" as "tumor regression," whereas a differentiation is made between a complete and partial regression and between a permanent and temporary regression. Fauvet et al. [92] present definitions of

the terms "guérison," "rémission," "régression" and "spontané." The term "guérison" is defined as "healing," "rémission" as "transient improvement of symptoms," "régression" as "atrophy, resorption or regression" and "spontané" as "occurring without medical intervention." In this monograph, the clinical phenomenon of an objective regression of a primary tumor or metastasis will also be defined using the term "regression." A regression can be a remission, i.e. freedom from symptoms, but this is not a prerequisite. The term "spontaneous regression" is also disputed in literature and, according to some authors, would be better defined as "biological" or "natural regression" [10, 27, 129, 270]. The terms "biological" and "natural" indirectly encompass the knowledge concerning the factors causing the regression and, in the final analysis, do not allow for "spontaneous regression per se" to arise. In this review, "spontaneous regression" characterizes a process of regression in malignant tumors whose internal mechanism has not (yet) been explained.

In 1966, Everson and Cole [89] defined spontaneous regression as a partial or complete disappearance of a tumor without therapy or during what experience has determined to be inadequate treatment. This conclusion is generally recognized at the present time [10, 27, 36, 197]. However, a critical revision of this definition is obviously required as will become clear in the following monograph.

Fauvet et al. [92] cite 9 cases of spontaneous regression of malignant melanoma amongst 165 cases of spontaneous regression of malignant tumors. Everson and Cole [89] found 176 documented cases since 1900 concerning spontaneous regression of malignant tumors of which 19 are malignant melanoma. They differentiate between six categories. The first group encompasses spontaneous regression of the primary tumor. The spontaneous regression of the primary tumor and metastases are included in the second category with histologic confirmation of malignancy. The third group is characterized by spontaneous regression of the metastatic tumor without histological proof. Presumptive spontaneous regression of metastases on the basis of radiological examination are assigned to the fourth group. In the fifth category, a tumor stasis, which often lasted for many years without clear proof of a tumor regression, is considered to be a balance between progression and regression. In the more recent literature, this is often referred to as "stable disease." Reports can also be found concerning patients described as "long-term survivors," in which regression of metastases is assumed. Everson and Cole [89] define the sixth category as delayed metastasis or recurrence. It appears noteworthy that in 50% of all cases examined, spontaneous regression is documented for four types of tumor (hypernephroma, neuroblastoma, choriocarcinoma and malignant melanoma) even though these tumors represent only a small portion of all malignancies. Depending on the author, malignant

melanoma, which represents only one percent of all malignant tumors in humans, comprises up to 11% of documented examples of spontaneous regression [66, 89, 108, 151].

1.3. Clinical presentation and histology

Spronck [264] observed fatty deposits, necrosis and an infiltration of polymorphonuclear leukocytes in regressed sarcoma. In 1907, Handley [111] noted the connection between histologic evidence of lymphocytic infiltration and "perilymphatic fibrosis" and the clinical presentation of tumor regression in malignant melanoma. In 1965, Smith and Stehlin [258] described examples of spontaneous regression of the primary tumor in malignant melanoma with distinct clinical and histologic criteria. Subsequent evidence of lymphocytic inflammation, presence of melanophages along with pigment incontinuity, neovascularisation and fibrosis are clear indications of spontaneous tumor regression in the face of an appropriate medical history.

Regression zones within the primary tumor were found quite often. However, histologic descriptions of complete spontaneous regression of the primary tumor and/or the metastatic melanoma were seldom found. A connection between vitiligo and halo naevus was also postulated due to an assumed common immunologic process regarding depigmentation with spontaneous regression of the malignant melanoma. In this context, the exclusion criteria formulated by Das Gupta et al. [74] regarding malignant melanoma of unknown primary should be considered (See Chapter 4). The spontaneous regression of the primary tumor is presently seen as the antecedent of metastatic melanoma of unknown primary [14, 36, 59, 74, 108, 145, 151, 183, 184, 211, 214, 232, 258].

1.4. Associated factors

Earlier documentation has shown that in spontaneous regression of malignant melanoma and other tumors, incidental or postoperative infections occurred quite often, especially erysipelas. With the introduction of antibiotics, such as penicillin, concomitant infection gradually decreased in importance as a complication of neoplastic disease. What was at that time thought of as the presumably favorable influence of infection on the course of tumor progression was probably halted by this therapy [1, 2, 31, 43, 46, 67, 73, 100, 163, 188, 192, 194, 219, 224, 225, 228, 235, 239, 248, 264, 296].

Febrile infections are considered to be of great importance during tumor development. Two reviews appeared by Fowler [99] and Nauts [198] that, on

the basis of the documented cases, indicated that febrile infections have a beneficial influence on tumor development.

In addition to sarcoma, Spronck [264] was probably the first to treat malignant melanoma using artificially induced fever. This procedure was described previously by Busch [46], Fehleisen [93] and others. Spronk observed complete tumor regression in sarcoma and melanosarcoma. This method of treatment was expounded upon by other authors and is still used today, along with numerous other therapeutic endeavors, for the treatment of malignant melanoma [67, 141].

Presently, fever is considered an epiphenomenon for as yet unexplained immunologic processes which, along with other factors, have been found to accompany spontaneous regression of malignant melanoma. The other factors implicated include blood transfusions, partial or incomplete surgical intervention, vaccination or intravenous infusion of antibodies and, above all, application of immunostimulating substances. The individual case reports will be discussed later. It appears that greatly varying factors can trigger spontaneous regression of malignant melanoma.

Is, for example, a punch biopsy to obtain histologic proof of malignancy in a suspicious cutaneous lesion a procedure with a therapeutic effect and could this lead to a spontaneous regression of the respective cutaneous lesion? These questions were posed by Nathanson [197]. In spite of the variety of case reports, he contends that four points support evidence of spontaneous regression in malignant melanoma. These points include:

1. direct clinical observation of spontaneous regression,
2. characteristic histopathologic changes in regressed lesions,
3. an immunotherapeutic model in humans of regression of melanoma
4. experimental data on possible mechanisms that could explain the phenomenon of spontaneous regression in melanoma.

Surgical manipulations (from skin biopsy for histologic confirmation of diagnosis to the operative attempt at curative treatment) have to be considered and critically examined for subsequent evidence of spontaneous regression of melanoma. All other accompanying factors which were identified initially by observation and later performed for therapeutic reasons must also be evaluated. As indicated above [10, 27, 89, 197], spontaneous regression is defined as the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy that is considered inadequate. However, it is very seldom that a patient receives no form of treatment, even though - with the exception of excision of the primary tumor - there is presently no standard treatment for metastatic melanoma. An adjuvant treatment with unequivocal improvement of prognosis does not yet exist. Can tumor regression still be defined as "spontaneous" under what experience has

shown is an inadequate treatment, or should regression be considered a singular success of a particular, more or less randomly identified measure? This will be elucidated utilizing a few examples. In a number of documented cases, regression of malignant melanoma during or after radiologic treatment is described as spontaneous. Experience has shown, given the known radiation resistance of melanoma, that this form of treatment is often inadequate. Descriptions can also be found of spontaneous regression following various immunotherapies and, in one case, spontaneous regression of metastatic melanoma was described after multiple operations and Thiotepe therapy [6, 44, 89, 170, 270, 284]. Even though these treatments were considered inadequate at the time, the documented cases of spontaneous regression of melanoma should be re-examined utilizing current knowledge to identify possible therapeutic benefits. This inquiry, however, must include the eventuality that regression of malignant melanoma is indeed spontaneous, even though recovery might have occurred during a particular treatment.

1.5. Importance of spontaneous regression

Experiments on humans and animals were performed in the second half of nineteenth century [67, 163, 264] which were based on observations of spontaneous regression of malignant tumors. Gaylord and Clowes [104] reported spontaneous regression of tumors in mice. They found an increased rate of spontaneous regression in smaller and flatter tumors than in larger and more advanced carcinomas. They also determined that a mouse with a previous spontaneous regression of carcinoma could not be immediately re-inoculated with neoplastic cells and assumed that a temporary "immune force" was protecting the animal from cancer. The theory of host organism immunity towards a malignant tumor was also discussed by Boyd [33], who postulated an inhibiting influence of an organism's immune system towards metastasis. Mohr [188] and Handley [111] noted the importance of the lymphocytic infiltrates. Lomer [163] examined the effect of "epithelial serum" on carcinomas. In patients with halo naevi and vitiligo, detectable antibodies toward melanoma cells were found in the absence of melanoma and led to the presumption of an immunologic relationship between halo naevus, vitiligo and melanoma. Today we know of cellular and humoral immune mechanisms with proven influence on the body's own resistance to melanoma. However, the factors causing their activation and the complex mechanisms involved are only partially understood.

It is conceivable that a more exacting knowledge of the cause and course of spontaneous regression, including an analysis of all associated factors, could result in new directions for treatment or preventive measures.

Summary: There have been reports of spontaneous regression of malignant melanoma for approximately 130 years. The study of this phenomenon is based primarily on the analysis of factors associated with spontaneous regression. Attempts at developing a treatment for malignant melanoma from the accompanying circumstances have not yet been successful. Clinical and histologic correlations may exist between depigmentation processes in halo naevus and vitiligo and spontaneous regression of the primary tumor and/or the metastatic melanoma. The spontaneous regression of the primary tumor is presently seen as the antecedent of metastatic melanoma of unknown primary.

2. LEUKODERMA, HALO NAEVUS, VITILIGO AND MALIGNANT MELANOMA

The appearance of hypo- and depigmentation has been observed in connection with malignant melanoma and its regressive processes. The incidence is thought to be 4 - 20% [5, 49]. Two forms of hypo- and depigmentation have been described that are clinically distinct yet exhibit vague histopathologic differences. Leukoderma is described as a halo-type depigmentation that occurs around and within a primary tumor or metastasis. Bizarrely configured depigmentations, independent from the primary tumor or metastasis and found on the entire integument, are characteristic of vitiligo [148]. Leukoderma and vitiligo are therefore characterized not only by their clinical presentation, but also by their localization (near, within or distant from the tumor) [112, 148].

Contrary to cutaneous malignant melanoma with an incidence of up to 20%, the association of choroidal melanoma with vitiligo is rather infrequent. However, no exact information was found in the literature. Vitiligo occurred in two patients with choroidal melanoma one or even six to eight years after the enucleation of the affected eye [5]. In five patients with cutaneous malignant melanoma, multiple halo naevi were also observed after excision of the primary tumor [86]. A connection between operative treatment of the primary tumor or metastasis, spontaneous tumor regression and the appearance of depigmented cutaneous lesions was confirmed by other authors [89, 148, 173]. The simultaneous appearance of a primary tumor with depigmented areas and vitiligo has also been described [112].

The influence of leukoderma and vitiligo in the prognosis of the disease process is often judged differently. For instance, no influence was found by Happle et al. [112] or by Kraus and Landthaler [148]. In contrast, Bystryń et al. [49] found a prospective 5 year survival rate of 74.8% in melanoma patients with vitiligo and an actual 5 year survival rate of 86.3%. They documented vitiligo in 46 of 1,130 melanoma patients examined (4.1%). Factors considered in calculating the prognosis were the tumor thickness according to Breslow, the depth of invasion according to Clark, the location of the primary tumor and possible metastases [37, 49, 64]. Albert et al. [5] are also of the opinion that melanoma patients who develop leukoderma or vitiligo have a more favorable prognosis. In this context, the unfavorable prognosis of amelanotic melanoma compared to pigmented malignant melanoma should be elucidated. A possible explanation is that an independent cell clone from amelanotic melanoma cells exhibited a greater malignancy than a pigmented cell clone [145].

The histologic examination of a halo naevus and an intratumoral depigmentation shows a mainly lymphocytic inflammation [18, 86]. To

document a partial or complete spontaneous regression of malignant melanoma, modern literature now demands histologic proof of a lymphocytic infiltrations [29, 258]. Many of the reports found in the literature concerning melanoma-specific rejection reactions indicate cellular, i.e. lymphocytic, immune mechanisms [54, 90, 98, 116, 195, 196].

Among other suppositions, an autoimmune mechanism has been postulated in the pathogenesis of vitiligo in patients without malignant melanoma. Histomorphologically, there are no inflammatory changes such as those found in intratumoral regression or halo naevus. However, the frequent occurrence of antibodies, which are also found in Hashimoto-thyroiditis, Addison disease, lupus erythematosus, pernicious anaemia and myasthenia gravis is thought to indicate an immune reaction or immune-modulating humoral mechanism [148, 285]. Humoral antibodies, which are directed against both the cytoplasm as well as against membrane antigens of the melanoma cells, have been detected numerous times [117, 190, 196].

Antibodies directed against melanoma cells were found in patients with halo naevi, who showed no evidence of malignant melanoma [18, 70]. The same phenomenon was observed in patients with vitiligo without evidence of a melanoma [58]. It appears that there is a form of vitiligo associated with malignant melanoma and a form that is not associated with melanoma. There is probably a common pathomechanism for both forms [70]. It is interesting to note that the respective antibodies appear before the melanoma metastasizes and are then no longer detectable in the presence of occult disease. However, a different observation was made in patients with halo naevi in whom the antibodies were no longer detectable after regression of the naevi [70]. The halo naevus has even been described as a "frustrated melanoma" [156], since antibodies directed towards the cytoplasm and membrane antigens of melanoma cells were found in patients with halo naevi, independent of evidence of malignant melanoma. Additionally, lymphocytic infiltrates are considered the histologic correlate to a possible tumor-specific immune reaction. The sensitivity of melanocytes to intermediate products of melanin synthesis can lead to the death of the melanocytes, clinically apparent as vitiligo or the halo of a halo naevus, or lead to cell changes expressed as malignancy. The intracellular components are thereby altered which may trigger the production of immune complexes by specific antibodies. The identification of cross-reactive antibodies against the cytoplasm of melanoma cells in melanoma patients with halo naevi and patients with vitiligo but without evidence of melanoma has underscored the close immunologic relationship between melanoma, vitiligo and halo naevus [18]. Leukoderma and vitiligo in melanoma patients should be given more attention as a possible, clinically apparent epiphenomenon of tumor-specific resistance [112].

Summary: The depigmentation that is pathognomonic for halo naevus and vitiligo has also been found in spontaneous regression of malignant melanoma. Lymphocyte infiltration and antibody production are discussed as possible determinants.

3. REGRESSIVE CHANGES WITHIN THE PRIMARY TUMOR

Regressive areas within the spreading malignant melanoma are a frequent clinical characteristic [10, 176, 285]. Regressive processes in melanoma are also discussed in this context which can lead to lightening, atrophy and occasionally scar formation [115]. The clinical presentation is characterized by white, grey-white, pale-pink-brown or milky-violet portions within the primary tumor [197, 285]. The frequency is given in the literature as 16 - 100% [69, 109, 132, 159, 176, 177, 209, 240, 252, 280].

The tumor thickness according to Breslow [37] and the depth of invasion according to Clark [64] are currently the most important factors in the prognosis and treatment of malignant melanoma [240]. Even though a maximum tumor thickness (TD) of up to 0.76 mm may indicate a favorable prognosis for the patient, the current literature considers regression zones a less favorable prognostic factor, especially for melanoma with a TD of up to 0.76 mm [17, 69, 109, 132, 143, 176, 177, 209, 240, 262, 280, 285].

3.1. Importance of regression zones

Gromet et al. [109] found 23 primary tumors with regression zones in 121 melanomas with a maximum TD up to 0.76 mm (19%). Of these primary tumors, 5 of them (21.7%) metastasized within a follow-up period of 120 months. Two metastases of the primary tumor were found in the remaining 98 melanomas. Regression zones were found in 19% of the melanoma, whereas 71.4% (5 of 7) of the melanoma metastasized. Similar results were reported by Paladugu and Yonemoto [209] with a metastatic rate of 45.5% in melanoma with regression zones and a TD of up to 0.76 mm. Both groups documented a higher risk of metastasis in melanoma with regression zones and a TD up to 0.76 mm. Milton et al. [186] also regarded regression zones as an unfavorable prognostic factor. This view was confirmed in the work by Sondergaard and Hou-Jensen [262], who reported a 10 year survival rate of 79% in a collective of 486 non-metastatic melanoma patients with regression zones. Patients with melanoma without regression had a 10 year survival rate of 95%. All melanomas had a TD up to a maximum of 1 mm. Differences were seen between active and completed regressions. The numbers stated refer to completed, not on-going regression.

Trau et al. [280] found no influence of possible regression zones on the metastatic potential in 549 melanomas with a TD up to 1 mm. Regression zones were evident in 27.1% of superficial spreading melanoma (SSM) and in 17.4% of lentigo-maligna-melanoma (LMM). McGovern [176] found regression zones in

13.8% solely amongst SSM. Other researchers found no connection between metastasis and the presence of regression zones [69, 132, 240].

Regression zones in primary tumors were found more often on the trunk and extremities than in the head or neck area. Kelley et al. [132] described this relationship more frequently in men, and Little [159] more often in woman.

3.2. Clinical presentation

The clinical presentation of melanoma is diverse and includes flattened white, occasionally depressed intratumoral areas, grey to pink colored scar formation as well as complete regression of primary tumor [115, 178, 285]. McGovern [176] summarizes seven clinical and histologic forms. The regression of the primary tumor can present as an infiltrated pigmented or non-pigmented node. Intratumoral scar tissue formation is possible. Multiple residual islands of a melanoma may mimic multicentricity. A pigmented cutaneous lesion with a depigmented halo can occur. Reference is again made to the possible immunologic relationship between melanoma and halo naevus. Additional presentations include scar formation with and without viable melanoma cells after complete regression. Identification of a primary tumor may no longer be possible. In occult metastasis, the melanoma is then classified being of unknown primary.

3.3. Histologic presentation

McGovern et al. [177] reported that two distinct phases of regression could be differentiated histologically amongst 353 melanomas with a regression zone incidence of 58% and a TD up to 0.76 mm. The active phase is characterized by a pronounced lymphocyte infiltration with simultaneous loss of viable neoplastic cells and the appearance of degenerated tumor cells. Completed regression is characterized by vascular fibrosis and the occasional appearance of melanophages. Both phases had no influence on the prognosis.

Shaw et al. [252] divided regression into three temporally distinct stages. The early stage was characterized by lymphocytic infiltration of melanocyte clusters in intradermal or junctional areas and the appearance of isolated degenerative neoplastic cells. In the second stage, the lymphocyte infiltrates were still present, however now proliferating fibroblasts, neovascularization and pigmented melanophages could also be identified. A focal destruction of the rete border and dysplastic melanocytes in the junctional zones were also documented. In the last stage, fibrosis occurred foremost with a

thickened stratum papillare. Neoplastic cells were rare or were only present in small numbers in the junctional zone. Lymphocytes or pigmented melanophages were seldom found. In conclusion, the following histopathologic findings were observed in connection with partial or complete regression of the primary tumor: loss or reduction of neoplastic cells in the junctional zone and dermis, loss of the rete border, loss or distinct reduction of melanin in the epidermis, lymphocytic infiltrates, pigmented macrophages, increased neovascularization and dermal edema [69, 111, 159, 176, 177, 240, 252, 262, 280, 285].

It is interesting to note that regression zones in nodular melanoma (NM) are not described in the literature. McGovern [176] found regression zones exclusively in SSM whereas Trau et al. [280] described regressive changes in SSM and LMM. Kelly et al. [132] documented an incidence of 17.6% for the acral lentiginous form of the melanoma (ALM). In 1969, the clinical and histologic differences and mutualities of NM, SSM and LMM were summarized and depth of invasion was introduced as an important prognostic factor [64]. Additionally, the appearance of regression zones observed only in LMM and SSM were discussed. LMM and SSM, and later ALM, spread initially by superficial horizontal growth. Three phases were described: first, in situ growth, followed by the invasion of the stratum papillare with successive immune stimulation of lymphocytes and macrophages and finally regression [63, 69, 132, 230]. Regression represents the final stage of horizontal growth. It is followed by aggressive infiltration of the lower dermal layers. A description of regression zones in an invasive melanoma could not be found in the literature. Since horizontal growth does not occur in NM, it was not possible to document regressive changes in this type of tumor [63]. For this reason, a revision of the term "nodular melanoma" to "malignant melanoma with no detectable radial growth phase" has been suggested [166].

Ackerman [3] proposes uniform growth for all types of malignant melanoma, beginning with a three dimensional intraepidermal expansion and followed by a vertical extension into the dermis. Melanomas that develop from blue naevi, congenital naevi or from acquired naevi are exceptions to this observation. He found no histologic correlate, in his opinion, for the random clinical classification in LMM, SSM, ALM or NM. The nodular form of melanoma also has an intraepidermal growth phase, albeit a short one.

The inflammatory infiltrate usually appears in the radial, i.e. the intraepidermal growth phase, and is usually associated with fibrosis or neovascularization. This must be differentiated from the lymphocyte infiltrate that has been described in the aggressive vertical growth phase of melanoma. This infiltrate is composed of so-called tumor infiltrating lymphocytes ("TIL") and is not accompanied by fibrosis or vascular modification processes [68].

It appears that melanoma cells in the junctional zone require a specific exposition time (induction phase) to stimulate the lymphohistiocytic infiltrates. This phase is characterized by tumor cell destruction as well as an increased aggressiveness of the neoplastic cells. At this point, the tumor enters into the invasive growth phase [230]. Metastasis during simultaneous spontaneous regression of the primary tumor is also possible. During the invasion of the reticular layer, after destruction of the rete borders, two different mechanisms of metastasis have been described. The growth of neoplastic cells between the individual collagen bundles of the reticular layer is characterized by invasive expansion with successive destruction of the collagen fibers ("infiltrating pattern"). The second mechanism is a uniform spreading of neoplastic cells at the interface between the papillary and the reticular layer with consequent extension of the papillary layer into the reticular layer followed by a compression of the collagen bundles ("pushing pattern"). An invasion level IV has been clearly described for the first mechanism. In the second case, determination of the invasion depth is difficult even though the reticular layer has been compromised.

Shaw et al. [252] found regression zones in primary tumors with a TD of up to 0.76 mm with lymph node metastasis in 100% of melanoma patients. In contrast, the same researchers found regressive changes in primary tumors with a TD of up to 0.76 mm in 67% of the melanoma patients with subsequent metastasis and 61% without metastasis. The authors also discuss a possible immune stimulation resulting from lymph node metastasis with subsequent regression of the primary tumor. An increase in antibody titers was found prior to the clinical appearance of metastases. However, a correlation to regressive changes within the tumor was not proven by the authors. Suppressor cell activity against cytotoxic T-cells, which would favor the growth of lymph node metastases by suppressing the T-cell activity, but should lead to regression of the primary tumor through increased localized cytotoxic activity was also discussed. This emphasizes the complicated relationship between tumor and host [244, 252].

3.4. Influence on the prognosis

The complete spontaneous regression of the primary tumor can not be interpreted as a favorable prognostic indicator for progression or survival [27, 245, 258, 285]. Even in patients with a partial regression, an exophytic lesion with a larger TD and subsequent unfavorable prognosis can develop next to the regressive area. On the other hand, a biopsy from a regressive segment of the lesion can lead to an incorrect diagnosis of a low-risk melanoma with alleged small TD. The unfavorable prognosis in the presence of regression zones has been debated,

especially for melanoma with a TD up to 0.76 mm [17, 69, 72, 109, 132, 143, 176, 177, 178, 186, 209, 240, 244, 252, 262, 280, 285]. A natural selection of highly malignant cell clones due to spontaneous regression processes is conceivable. These cell clones could be responsible for the occasional explosive dissemination, even though the primary tumor can no longer be identified [63, 230, 285].

On the other hand, there are also reports of so-called "long-term survivors," i.e. melanoma patients that were observed to have no primary tumor or metastatic activity. It appears that a growth standstill occurs in the horizontal or intraepidermal phase without evidence of spontaneous regression [59, 95, 174, 244].

Table 1: Data from literature concerning the absolute and relative frequency of regressive changes in malignant melanoma. The maximum tumor thickness (TD) is measured in mm.

Author	max. TD	Total number	Absol. Portion	Rel. Portion
Little [159]		361	57	16%
McGovern [176]		202	28	14%
Gromet et al. [109]	0.76	121	23	19%
McGovern et al. [177]		353	205	58%
Paladugu and Yonemoto [209]	0.76	36	11	31%
Trau et al. [280]	1.00	549	247	45%
Cooper et al. [69]	1.00	48	24	50%
Kelly et al. [132]		844	173	20%
Ronan et al. [240]	0.76	103	30	29%

3.5. Regression zones in choroidal melanoma

Reese et al. [231] reported regressive changes in choroidal melanomas. They differentiate between a diffuse process of "cellular" and "lytic" necrosis, and "infarct" or "coagulation" necrosis characterized by a localized and limited vascular obstruction. Histologically, intracellular changes such as pyknosis, karyorrhexis or karyolysis are mainly found in cellular necrosis. Lytic necrosis is characterized by areas of cystic changes. A lymphocyte infiltrate is seen in all three forms as the correlate of an inflammatory process. No lymphocyte infiltrates are found following therapeutic procedures, such as cauterization, leading the authors to assume that an immunologic process may be involved. After an active inflammatory phase, a chronic inflammatory process is

observed with choroiditis, scleritis, uveitis, secondary glaucoma and retinal detachment. In addition to lymphocytic infiltrates, plasma cells with successive antibody production are found in all forms of necrosis. A reactive change in the vascular endothelium with thrombosis and thrombocyte aggregation was found distinctly in infarct necrosis.

Summary: Regression zones within the primary tumor are frequent. The histologic presentation consists mainly of lymphocytes, melanophages, neovascularization and fibrosis. Atrophy, scar development, depigmentation and complete regression are found clinically. Regression zones within the primary tumor have no influence on the prognosis. Differentiation is made in choroidal melanoma between diffuse regressive changes ("cellular" and "lytic" processes) and localized changes ("infarct necrosis").

4. METASTATIC MELANOMA OF UNKNOWN PRIMARY TUMOR

In malignant melanoma, the appearance of metastases in cases of unknown primary tumor is a recognized phenomenon [10, 14, 36, 42, 59, 74, 85, 108, 131, 151, 183, 184, 185, 197, 207, 211, 214, 232, 244, 258, 267]. Depending on the source, the frequency varies between 1 and 15% [74, 85, 145, 214].

4.1. Clinical presentation

Das Gupta et al. [74] could not identify the primary tumor in 37 of 992 patients (3.7%). In their opinion, metastatic malignant melanoma with unknown primary tumor is defined by the following criteria: Every melanoma patient in whom an eye operation, i.e. enucleation or exenteration of the orbita, was performed should be excluded since it can be assumed that such measures were necessary due to melanoma. Any patient with metastatic melanoma who reported an operative or incidental traumatic removal of a pigmented or non-pigmented lesion in the medical history must also be excluded. A thorough search for the tumor must have been performed, including endoscopic, otoscopic, ophthalmoscopic as well as radiologic examinations. Finally, any cutaneous lesions (especially scars or areas of depigmentation) located in the lymphatic drainage area of the respective metastatic lymph nodes may be considered to be the primary tumor and such patients must be excluded [74, 151]. These patient-selection requirements have been met by a number of studies, whereby the incidence of metastatic melanoma with unknown primary tumor is given as 4 - 8.7% [14, 59, 108, 176, 211, 258].

Baab and McBride [14] found no primary tumor in 98 of 2,446 melanoma patients (4%) and determined a sex distribution of 2.6 :1 (71 men and 27 women). Similar distributions have been documented by other authors [59, 232]. Paul and Müllhofer [214] found no primary tumor in melanoma metastases in 1.7% (24 out of 1,426 patients examined), whereby the gender distribution varied with 20 men and 4 women. Reintgen et al. [232] were able to diagnose 124 patients with "metastatic melanoma of unknown primary tumor" in a collective of 2,612 patients (4.8%). The initial diagnosis was made predominantly on the basis of lymph node metastasis, whereby axillary lymph node involvement in men and inguinal lymph node involvement in women were more prominent. Approximately 30% of the patients examined exhibited visceral metastasis at the time of diagnosis. The metastatic pattern in cases of unknown primary tumor coincide with the pattern seen in melanoma with known primary tumor

location. The age and sex distribution also similar to cases of melanoma with known primary tumor [14, 59, 108, 185, 211, 232].

Milton et al. [185] could not identify a primary tumor in 76 of 1,833 patients examined (4.1%). The prognosis was the same for men and women within this group of patients. In general, no differences in prognosis were found for melanoma patients with known or unknown primary tumor. The manner of the metastasis — lymphogenic or hematogenic — also exhibited no prognostic influence. On the contrary, Reintgen et al. [232] found that patients with unknown primary tumor and hematogenic metastasis have an unfavorable prognosis compared to patients with lymphogenic metastasis. Milton et al. [185] also showed that a medical history indicative of a previous primary tumor did not influence the prognosis for melanoma patients with unknown primary tumor. Medical histories frequently described possible primary tumors [74, 151, 183, 214]. Giuliano et al. [108] found no evidence of a primary tumor in 55 of 980 melanoma patients, yet described five patients with anamnestic or clinical evidence of spontaneous regression of pigmented cutaneous lesions. Similar examples were reported in other studies [14, 74, 151, 183, 184, 185, 211, 214].

Table 2: Data from literature concerning recurrence of metastatic malignant melanoma with unknown primary tumor.

Author	Incidence	Total	Percent
Pack and Miller [207]	29	1190	2.4%
Das Gupta et al. [74]	37	992	3.7%
Smith and Stehlin [258]	40	461	8.7%
Brownstein and Helwig [42]	150	1000	15.0%
Einhorn et al. [85]	65	426	15.0%
Baab and McBride [14]	98	2446	4.0%
McGovern [176]	43	613	7.0%
Milton et al. [185]	76	1833	4.1%
Giuliano et al. [108]	55	980	5.5%
Chang and Knapper [59]	166	3805	4.4%
Panagopoulos and Murray [211]	30	670	4.4%
Reintgen et al. [232]	124	2612	4.8%
Paul and Müllhofer [214]	24	1426	1.7%
Total	937	18454	5.1%

4.2. Possible causes

Various theories have been suggested to explain the phenomenon of "metastatic malignant melanoma of unknown primary tumor." Pack and Miller [207] assumed a "de-novo development" of melanoma cells in the dermal lymph

vessels or lymph nodes. This hypothesis has been discussed by many authors [14, 59, 74, 151, 214]. On one hand it is possible that the primary tumor metastasized from a visceral organ [145, 151, 183, 214]. The following considerations were presented by Milton et al. [183] refuting this argument:

1. In practically all cases of metastatic melanoma with unknown primary tumor, the first metastases are found in lymph nodes draining from the skin. This is in agreement with the usual metastatic pattern for melanoma.
2. If the primary tumor is deeply situated, visceral metastases should draw attention to occult disease more often than is actually the case.
3. Evidence for spontaneous regression of a primary tumor is confirmed by a large number of examples in the literature.

If it can be confirmed that the primary tumor was removed iatrogenically without histologic confirmation and therefore could not be characterized as melanoma, the following explanations of occult disease can be proposed:

1. "De-novo" development in dermal lymph passages or lymph nodes
2. Localization of the primary tumor in visceral organs
3. Destruction of the primary tumor by incidental trauma or inadequate treatment
4. Clinical differentiation from benign lesions is not possible
5. Inadequate diagnostic procedures
6. Complete spontaneous regression of the primary tumor

The spontaneous regression of the primary tumor remains the most probable, currently accepted explanation for metastatic malignant melanoma with unknown primary [10, 14, 36, 59, 74, 108, 145, 151, 176, 183, 184, 185, 211, 214, 232, 258].

Assuming spontaneous regression of the primary tumor, there are no prognostic differences between melanoma patients with known primary and patients with unknown or spontaneously regressed primary tumor [59, 145, 151, 185]. Only Baab and McBride [14] were able to determine a more favorable prognosis for melanoma patients with unknown primary tumor. The therapeutic strategies for unknown primary tumor do not differ from those treatments considered standard for known primary tumor at the same stage of the disease [59, 108, 151, 232].

4.3. Histology

Melanophage accumulation in the upper corium, superficial inflammatory lymphocytic infiltrates and a circumscribed vascular proliferation have all been described as typical histologic indications of spontaneous regression of malignant melanoma [27, 74, 173, 183, 214, 258]. It is also interesting to note that

the histologic examinations of halo nevi in patients with and without melanoma are in accordance with the histopathologic findings of regressed melanoma [18, 74, 86]. According to Voigt and Goos [285], the differential diagnosis of every depigmented cutaneous lesion should be considered with this aspect in mind.

4.4. Case study

The following is an example of an unusual case of malignant melanoma of unknown primary. Sroujeh [267] described a 55 year old patient with histologically confirmed metastatic melanoma on the right side of the neck and occipital region. Both complete and partial excisions of these lesions were performed. Since no primary tumor was found and there was no indication of a primary tumor in the medical history, laparoscopy was performed. The procedure revealed melanoma of the small intestine with multiple metastases of the omentum with mesenterial and paraaortal lymph node involvement. Thirty-five cm of small intestines were resected with no further therapy performed. Three years later, no evidence of a neoplastic process was found during herniotomy. The patient exhibited no further signs of disease eight years after the first operation.

The spontaneous regression of visceral metastatic melanoma of unknown primary or other metastatic process of the small intestine can be assumed from this observation. This case report also fulfills the criteria for metastatic melanoma of unknown primary proposed by Das Gupta et al. [74] and spontaneous remission of the primary tumor by Smith J L and Stehlin [258].

Summary: Varying according to the author, no primary tumor can be found in up to 15% of all cases of metastatic melanoma. There are diverse reasons for this observation. The complete spontaneous regression of the primary tumor is generally recognized as the probable cause today. However, this yields no prognostic or therapeutic consequences.

5. COMPLETE SPONTANEOUS REGRESSION OF THE PRIMARY TUMOR

Regressive changes can lead to the complete remission of the primary tumor. Assuming complete regression of the primary tumor as the most probable cause of malignant melanoma of unknown primary, the incidence of spontaneous regression would be 1.7 - 15%, as cited in Chapter 4. However, the frequency of anamnestic indication of a possible primary tumor obtained through the medical history is much less in comparison to the actual incidence of malignant melanoma of unknown primary. Nevertheless, it can be assumed that the phenomenon of spontaneous regression of the primary tumor occurs more often than previously documented in the literature. Many patients are simply not aware of the appearance or subsequent disappearance of a malignant cutaneous lesion should, with varying latency, no metastases appear. Smith J L and Stehlin [258] were the first to define the clinical and histologic criteria for spontaneous regression of primary tumors, which were later updated and modified by MacDougal et al. [165]. Nathanson [197] distinguished between proven and questionable cases. No further differentiation between cutaneous malignant melanoma and primary tumors of the choroid was attempted. Although Nathanson found a total of 33 cases of spontaneous regression of the primary tumor in the literature, not all documented cases could be accepted in this monograph. Similarly, evidence of possible spontaneous regression in the medical history of suspicious cutaneous lesions and histopathologic results were also lacking in the case reports by Pack and Miller [207] and therefore were also not included. These examples were, however, included in the category "metastatic melanoma of unknown primary." In some of the case studies reported by Milton et al. [183], which were also cited by Nathanson [197], a similar situation was encountered. In the final tally, in addition to 19 of the case reports of spontaneous regression of the primary tumor in cutaneous malignant melanoma cited by Nathanson, an additional 41 documented cases could be included. This yielded a total of 60 anamnestic and, for the most part, histologically confirmed cases of spontaneous regression [12, 13, 32, 41, 74, 91, 95, 133, 151, 153, 165, 170, 171, 183, 197, 205, 210, 213, 214, 215, 228, 237, 245, 258, 263, 273, 279, 285, 291].

Other than the three cases of spontaneous regression of choroidal melanoma cited by Reese et al. [231], two further examples were documented by Nathanson [197] lacking histologic confirmation [247]. Two additional case reports were also found in the literature [130, 150].

5.1. Spontaneous regression of cutaneous primary tumor

An indicative medical history and presence of a clinically suspicious lesion in the lymph drainage area of the primary tumor are important indications of spontaneous regression. This working diagnosis can only be confirmed by histologic examination. Among the 60 cases reported here, 32 (53.3%) were found to have documented medical histories, suspicious lesions and histologic confirmation. In addition, 13 cases (21.6%) were found with only an applicable medical history and suspicious skin lesion. In five other cases (8.3%), the lesions were confirmed histologically yet lacked medical history documentation indicating of possible spontaneous regression. Cutaneous lesions without histologic examination or corresponding medical history were described in five further cases. Medical histories lacking proof of a cutaneous lesion or consecutive histopathologic examination were found in five additional cases.

Table 3: Summary of clinical and histologic criteria according to Smith J L and Stehlin [258] as evidence of spontaneous regression of the primary tumor.

1. Clinical presentation:
1.1. Medical history of a pigmented lesion that initially exhibited changes typical of malignant melanoma followed by regressive changes and located in the lymph drainage area of the metastatic tumor.
1.2. The presence of atypical or depigmented lesions in the skin at the site of the presumed regressive primary tumor or above a subcutaneous metastasis with no further changes indicative of another primary tumor in this area and
1.3. no clinical evidence of any other lesions suggestive of melanoma in this area of skin or elsewhere.
2. Histology:
2.1. Atypical pigmentation in the epidermis and presence of melanophages with
2.2. superficial lymphocytic inflammation, occasional polymorphonuclear leukocytes and eosinophiles as well as
2.3. vascular proliferation with perivascular and interstitial edema and fibrosis.

Those case reports lacking anamnestic confirmation of a suspicious cutaneous lesion and subsequent histologic examination can either be due to complete spontaneous regression of the primary tumor [176] or to possibly inadequate examination of the patient. Lesions without histologic confirmation and lacking a corresponding medical history account for 5 of the 60 cases (8.3%). The deficient medical history may possibly be due to faulty observation by the patient, as may also be the case even where histologic results confirmed

suspicious lesions. In 13 out of 60 descriptions (21.6%), medical history and suspicious skin lesions are documented yet lack histologic confirmation. Obviously, in spite of an applicable medical history or evidence of metastasis, histologic examination of a suspicious lesion is not always performed. The reasons for this are often due to the patients refusal of an operative procedure. In 32 of the 60 cases (53.3%), the criteria proposed by Smith J L and Stehlin [258] with regard to medical history, suspicious cutaneous lesions and histologic examination are met.

Table 4: Distribution of case reports according to the criteria by Smith J L and Stehlin [258] with respect to medical history, cutaneous lesions and histology.

	Number of Reports
Applicable medical history	5 (8.3%)
Suspicious cutaneous lesion	5 (8.3%)
Applicable medical history and suspicious cutaneous lesion	13 (21.6%)
Suspicious cutaneous lesion with histologic confirmation	5 (8.3%)
Applicable medical history, suspicious cutaneous lesion and histologic confirmation	32 (53.3%)

Table 5: Distribution of case reports according to patient age and latency between initial diagnosis of a cutaneous lesion and its spontaneous regression (period of observation).

	Women	Men
Total	24	36
Age at the time of regression (years)	Range 29 - 74	Range 13 - 61
1. 11 - 20	-	1 (2.8%)
2. 21 - 30	3 (12.5%)	4 (11.1%)
3. 31 - 40	10 (41.6%)	9 (25.0%)
4. 41 - 50	5 (20.8%)	13 (36.1%)
5. 51 - 60	2 (8.3%)	7 (19.4%)
6. 61 - 70	2 (8.3%)	2 (5.6%)
7. 71 - 80	2 (8.3%)	-
Average age	44.3	43.9
Period of observation	1 - 55 years	1 - 45 years
Average period of observation	25 years	13 years

In the 60 case reports considered there were 24 women and 36 men. The average age at the time of spontaneous regression of the primary tumor was 44.3 years in women, and 43.9 years in men. The youngest woman was 27 years old and the oldest 74. For men, the youngest patient was 13 years old and the oldest 68. Spontaneous regression was most frequently described in women between 31 and 40 years old (10 cases) and 41 to 50 years (13 cases) in men. The main localization documented in the medical history was on the extremities in women (13 cases) and the trunk in men (15 cases). Suspicious cutaneous lesions were found mainly on the extremities in women (15 cases) and on the trunk in men (18 cases). These findings correlate with the known distribution pattern for malignant melanoma. Reports of ulceration and pruritus were rare. Hemorrhage occurred in 29.1% of women and 19.4% in men. The occurrence of hemorrhage in existing cutaneous lesions appears to be an important anamnestic sign of malignancy in an initially benign cutaneous tumor. The interval between the initial diagnosis of a cutaneous lesion and signs indicative of spontaneous

Table 6: Clinical parameters of spontaneous regression of the primary tumor in malignant melanoma.

	Women 24	Men 36
Medical history:		
1. General	22 (91.7%)	29 (80.6%)
2. Head/Neck	3 (12.5%)	4 (11.1%)
3. Trunk	6 (25.0%)	15 (41.7%)
4. Extremities	13 (54.1%)	10 (27.8%)
Suspicious cutaneous lesion:		
1. General	21 (87.5%)	32 (88.9%)
2. Head/Neck	3 (12.5%)	4 (11.1%)
3. Trunk	3 (12.5%)	18 (50.0%)
4. Extremities	15 (62.5%)	10 (27.8%)
Accompanying factors:		
1. Trauma	2 (8.3%)	3 (8.3%)
2. Infection	1 (4.1%)	2 (5.6%)
3. Manipulation	2 (8.3%)	3 (8.3%)
4. Pregnancy	3 (12.5%)	-
Clinic:		
1. Ulceration	4 (16.7%)	-
2. Pruritus	2 (8.3%)	3 (8.3%)
3. Hemorrhage	7 (29.1%)	7 (19.4%)
Prognosis:		
1. Complete remission	6 (25.0%)	7 (19.4%)
2. Metastasis	6 (25.0%)	9 (25.0%)
3. Deceased	7 (29.1%)	12 (33.3%)

regression (period of observation) was between 1 to 55 years in women and 1 to 45 years in men. The average period of observation was 25 years in women and 13 years in men. Frequently, the remark "spot present since birth" was documented. Complete spontaneous regression was not found to have a favorable influence on prognosis.

Table 7: Cases of spontaneous regression of the primary tumor (PT). The age and prognosis are given at the time of regression.

No.	Sex	Age	Author	Location	Prognosis
1	f	27	Sumner [273]	l. inner malleolus	no relapse
2	m	35	Das Gupta et al.	r. shoulder	deceased
3	m	49	[74]	r. shoulder	no relapse
4	m	40	Smith and Stehlin	back	deceased
5	m	45	[258]	r. knee	no relapse
6	f	29		l. 5. finger	deceased
7	m	27		r. arm	deceased
8	m	33		l. cheek	deceased
9	f	31		r. foot	deceased
10	f	34		r. axilla	deceased
11	f	49		r. arm	no relapse
12	m	44		back	no relapse
13	m	60	Olsen	back	no
14	f	68	[205]	leg	information
15	m	31	Todd et al. [279]	back	no information
16	m	29	Milton et al.	l. calf	no
17	m	50	[183]	back	information
18	m	30		r. hand	
19	m	49	Parache and Chardot [213]	chest	deceased
20	m	37	Brincker and Andersen [41]	r. arm	no information
21	f	45	Farnsworth [91]	back	no information
22	f	72	MacDougal et al. [165]	l. cheek	no information
23	m	49	Nathanson [197]	back	deceased
24	f	47	Manelis et al. [170]	r. inner malleolus	deceased
25	f	33	Palmer and Poulgrain [210]	back	deceased
26	f	31	Lerner et al. [153]	back	no information
27	f	50	Pellegrini [215]	l. leg	no information

Table 7 (Continued)

No.	Sex	Age	Author	Location	Prognosis
28	f	53	Whicker et al. [291]	r. cheek	deceased
29	f	42	Landthaler and Braun-Falco [151]	r. leg	no information
30	m	23		back	
31	f	39		r. leg	
32	m	41		r. calf	
33	f	63		l. knee	
34	f	34	Riberti et al. [237]	r. arm	no information
35	f	39	Fernandez et al. [95]	l. leg	no information
36	f	40	Kessler et al. [133]	l. knee	no information
37	f	29	Martinelli et al. [171]	l. arm	no information
38	m	42	Saida and Tsuchiya [245]	back	deceased
39	m	37	Rampen and Meijer [228]	occiput	deceased
40	m	43	Voigt and Goos [285]	neck	deceased
41	f	57	Azón-Masoliver et al. [13]	forehead	deceased
42	m	60	Soong et al. [263]	l. flank	deceased
43	m	48	Paul and Müllhofer [214]	l. arm	no information
44	m	50		chest	
45	m	50		back	
46	m	56		back	
47	m	37		back	
48	m	36		l. calf	
49	f	74		r. groin	
50	m	13		r. leg	
51	m	61		back	
52	m	52		l. arm	
53	f	40	Avril et al. [12]	l. leg	no relapse
54	m	57		l. flank	deceased
55	m	42		l. shoulder	no relapse
56	m	68		r. arm	deceased
57	m	52		r. arm	no relapse
58	f	33		back	no relapse
59	m	63		back	no relapse
60	m	40	Bottger et al. [32]	forehead	no relapse

Six women and 9 men developed metastasis during or after spontaneous regression of the primary tumor and 7 women and 12 men died. The role that accompanying factors may have played in the spontaneous regression of the metastatic melanoma raises many questions. In five patients trauma to the

primary tumor, in three patients an infection and in five patients inadequate therapy or manipulation (squeezing, cauterization, etc.) were documented. Three cases of spontaneous regression were described during pregnancy. Byrd and McGanity [47] found evidence of a possible hormonal influence on spontaneous regression of malignant melanoma in humans. They observed regressive tendencies in a primary tumor after each of five pregnancies in one patient. The patient noted an enlargement of the tumor during each of the pregnancies.

A case report by Olsen [205] shows how varied the possible influence of particular factors on the spontaneous regression of the primary tumor can be from the patient's point of view. The author described a 60 year old man that refused all treatment. The patient ascribed the spontaneous regression of the primary tumor to the consumption of garlic, raw vegetables, fruit and herbal tea.

Immunologic analyses during spontaneous regression of the primary tumor were conducted in only one case [245]. The researchers found a normal cellular immune response with a normal sensitivity reaction to dinitrochlorbenzol (DNCB). The lymphocyte cytotoxicity was not increased. No antibodies were found directed against homologous or autologous melanoma cells. The patient died from the metastases during the period of observation.

Farnsworth [91] reported a metastatic melanoma that mutated in the brain to an oligodendroglioma. The mutation of a malignant tumor to a histologically benign form was discussed previously in one of the first publications concerning spontaneous regression of malignant tumors [19].

5.2. Spontaneous regression of choroidal melanoma

According to Reese et al. [231], three different histologic forms of regressive changes in choroidal melanoma can be differentiated:

1. cellular necrosis,
2. lytic necrosis
3. infarct- or coagulation necrosis.

The occurrence of extensive chorioretinal fibrosis, retinal detachment and a dense mononuclear infiltrate surrounding the choroidal scar tissue are typical for the spontaneous regression of choroidal melanoma according to Lambert et al. [150]. After treatment with, for example, a laser, no lymphocyte infiltration occurred [231]. This observation is considered to be evidence of an immunologic process. The spontaneous regression of choroidal melanoma can only be confirmed through observation and pathohistology of the enucleated eye. This is analogous to spontaneous regression of cutaneous malignant melanoma. Differential diagnostical considerations in choroidal melanoma

allow clarification only through enucleation and histological examination of the eye in question. Jensen and Andersen [130] reported an observation of a 65 year old male with a 12 year old lesion in the upper temporal quadrant of the right eye. During this period, no radiation treatment, hormone- or chemotherapy was applied. Various differential diagnoses were discussed, including atypical choroidal melanoma, exsudative retinitis, retinal adenoma and hematoma. The eye was enucleated after the patient complained of an increase in pain. Histologically, large polymorphic cells ("balloon cells"), fibrosis, isolated melanophages and calcification were found. Inflammatory cells and signs of neovascularization could not be identified. The authors therefore consider this phenomenon to be spontaneous regression of a choroidal melanoma.

Noteworthy is the long period of observation whereby similar periods of 7 or 8 years [231] and 15 years [150] have also been described by other authors. Scheffer and Binkhorst [247] have assumed spontaneous regression of choroidal melanoma based on clinical examinations in two patients.

Lambert et al. [150] described a 34 year old male seen due to blurred vision in his right eye. A 2 x 2 mm pigmented mass was seen in the right fundus with fluorescein leakage around the mass in the angiogram. Systemic treatment with 32 mg/day triamcinolone was given for presumed chorioretinitis. One and a half years later, the visual acuity deteriorated further. The enucleation of the right eye was performed after a 15 year period of observation. Histopathologic examination revealed lymphocyte infiltration, fibrosis and calcification consistent with partial regression of choroidal melanoma. No evidence of metastasis was found.

The enucleation of the affected eye was performed due to vitreous hemorrhage [231], pain [130] and deterioration of vision [150]. Enucleation was not performed in two patients where the diagnosis was made based on clinical findings [231]. Accompanying factors regarding spontaneous regression were not found in the cases documented.

Metastases were not described in any of the cases during the lengthy periods of observation. Only seven cases of spontaneous regression of choroidal melanoma in the known literature underscore the infrequent occurrence of this phenomenon.

Summary: The spontaneous regression of the primary tumor in malignant melanoma is an event seldom documented in the literature. It is closely related to metastatic melanoma of unknown primary tumor. Neither a more favorable prognosis nor therapeutic strategy is influenced by spontaneous regression. The location of the primary tumor in cases of spontaneous regression based on

patient observation as well as the actual location of the primary tumor determined by the presence of a suspicious cutaneous lesion are both in agreement with the known pattern of melanoma distribution. In a few cases, ulceration or pruritus were present clinically. Hemorrhage from clinically suspicious cutaneous lesions is an important indication in the medical history of a possible malignant process. Trauma, inflammation, inadequate treatment and pregnancy were documented as accompanying factors. However, none of these events are causative but rather epiphenomena of a suspected immunologic process. Cellular and humoral immunity, however, remain unchanged during spontaneous regression of the primary tumor [245].

Regressive changes in choroidal melanoma are classified into localized (cellular and lytic necrosis) or diffuse (infarct- or coagulation necrosis) processes. The differential diagnosis includes an exudative retinitis, retinal adenoma or hematoma as well as spontaneous regression of the choroidal melanoma. Histologically, lymphocyte infiltrates, plasma cells, melanophages, fibrosis, proliferation of vascular endothelium, thrombocyte aggregation and calcification were evident and did not influence the prognosis. Associated factors are not documented in any of the case reports.

6. SPONTANEOUS REGRESSION OF METASTATIC MELANOMA

Regardless of the difficulty involved in defining the term "spontaneous regression" and the difficulty of presenting objective evidence, all available reports, documentation and case reports on the subject of "spontaneous regression of metastatic malignant melanoma" are included in this monograph. In comparison to the spontaneous regression of the primary tumor, evidence of metastasis in melanoma and subsequent independent regression - without therapy or after what experience has shown as an inadequate method of treatment - is difficult to obtain. Everson and Cole [89] refer to regression of metastases that were not confirmed histologically or to regression of presumed metastases on the basis of radiologic examination. Today there are other diagnostic methods available, such as sonography, computer tomography, scintigraphy and magnetic resonance tomography. Biopsies taken from ascites, pleural effusions, suspicious lymph nodes, suspicious foci in the lungs or brain or even a diagnostic laparotomy can assist in the diagnosis. In this respect, the question of a possible influence on the tumor/host relationship due to diagnostic measures resulting in spontaneous regression must be elucidated.

Spontaneous regression is often considered as a possible explanation in the literature for unexpectedly lengthy courses of metastatic melanoma. On one hand, there are reports of unusually long survival times usually in connection with various, most often operative treatment, or without any therapy. The clinically visible phenomenon of tumor regression, however, is less important than a balanced relationship between tumor progression and tumor regression. This equilibrium allows some patients to maintain a satisfactory quality of life for years in spite of a sometimes slow, yet steady growth of the tumor. On the other hand, there are also reports of delayed or late appearance of localized recurrence or metastasis. This is especially true in choroidal melanoma. Freedom from recurrent disease lasting for years could be classified as either successful therapy or as a spontaneous regression of the tumor. The phase of interrupted tumor growth is also described as "stable disease." Long survival time and the late appearance of metastases, under the aspect of a possible spontaneous regression, have similar origins and are combined in the same chapter.

Reported cases concerning independent regression of melanoma metastases are dependent on the judgement of the examining physician. The histologic confirmation of diagnosis in visceral metastases was present in very few case reports. Cutaneous and subcutaneous nodules, as well as suspicious lymph nodes were usually examined. The examination of the factors and constellations

associated with spontaneous regression is more interesting than scrutiny of the individual cases in respect to complete medical histories or diagnostic confirmation. Here is a wide spectrum of accompanying circumstances which may assist in the development of new forms of treatment. The individual circumstances and correlations of the case reports will be discussed and noteworthy observations covered in detail.

6.1. Delayed metastasis, delayed recurrence and "long-term survivors"

Frauchinger [100] and later Everson and Cole [89] believe that unusually long survival times and the late appearance of metastases are evidence of a possible influence of tumor progression through spontaneous regression processes.

6.1.1. *Late metastasis in choroidal melanoma*

One of the first reports of extended survival time and late appearance of metastasis comes from Dobbertin [81] who reported the case of a 46 year old patient who developed melanomasarcoma of the cerebellum and spinal cord 10 years after enucleation of the left eye due to an "angioma behind the eye." The connection of this tumor with the enucleated eye is mentioned here because, according to the author, the 10 year latency and freedom from recurrence invalidates a possible metastasis of a choroidal melanoma. A similar case is described by Lilley [158]. A histologically confirmed choroidal melanoma metastasized to the liver after a 10 year remission. Cairns [52] described a patient in whom the first metastasis appeared on the shoulder eighteen years after excision of a choroidal melanoma. Another unusual feature of this case was the presence of metastases in the muscles, tendons and bones of the shoulder. Further examples of latent tumor growth following enucleation of choroidal melanoma are documented by Wilbur and Hartmann [294] and Hall [110]. The latter described a 29 year old patient with melanoma of the left eye, where following trauma and subsequent infection, the affected eye was enucleated due to an increase in pain. The patient remained in remission for 27 years. According to the author, this observation could have been due to the subsequent infection which may have triggered regression. The patient then died from wide spread metastases of the choroidal melanoma, as did all of the other above-mentioned patients. Further examples can be found by Morton and Morton [191], who observed remission intervals of six to eight year duration following enucleation of the affected eye. Extended periods of remission are also documented in other case reports of spontaneous regression of choroidal melanoma [130, 150, 231].

6.1.2. *Long-term survival in cerebral metastasis*

Melanoma patients who develop cerebral metastasis during the course of the disease generally have a poor prognosis. However, reports appear time and again of unusually long periods of survival following the initial operation or multiple operations. The spontaneous regression of cerebral metastasis has often been discussed and can not be ignored. A survival time of more than ten years was observed by McCann et al. [174] in a melanoma patient with a metastasis near the lateral ventricle. The patient received two months of post-operative radiation treatment. In a different patient, two craniotomies were performed due to a melanoma metastasis in the rear parietal region with documentation of a fourteen year survival time. It is interesting to note that the metastasis was not removed completely during the first operation. Radiation treatment and an incomplete operative procedure are discussed as possible triggering factors for spontaneous regression of metastases. A report by McNeel and Leavens [180] describes a melanoma patient with three surgical procedures to the left frontal lobe due to recurrent metastases and a survival time of five and one half years. Further examples of unusually long survival times are reported by Reyes and Horrax [236], Fell et al. [94] and Fernandez et al. [95]. The latter also reported spontaneous regression of the primary tumor during development of leukoderma three and one half years prior to the appearance of cerebral metastases.

6.1.3. *Delayed metastasis of cutaneous melanoma*

Seven cases of delayed metastasis after excision of a cutaneous primary melanoma were described by Wilbur and Hartmann [294]. They found latencies of five to thirteen years between removal of the primary tumor and subsequent metastasis. In another example, eleven years passed between excision of the primary tumor and the appearance of pulmonary metastases and a further nine years between the first pulmonary metastasis and the death of the patient. In this case, bronchopneumonia, pleural effusion as well as radiation treatment with a total of 4700 r were integral factors in the clinical course [103]. Presuming spontaneous regression, it can be assumed that there may exist correlation to accompanying infection and radiation therapy. Further case reports of metastases of cutaneous malignant melanoma appearing with a latency of more than ten years after excision of the primary tumor can be found by Ariel [9], Briele et al. [39], Koh et al. [144], Raderman et al. [222] and Briggs and Ibrahim [40].

Ward and Acquarelli [288] described a 51 year old patient with malignant melanoma on the left ear that, according to the patient, was present for over 10 years. Following neck-dissection due to submaxillary lymph

node metastases, an infection with fistula development in the operative site which was treated with penicillin. At the time of the report, the patient had been in remission for nineteen years following restitution of the fistula. A correlation between infection and a possible spontaneous regression can also be construed.

6.1.4. *Long-term survival despite tumor progression*

Boyd [33] described a 70 year old melanoma patient with metastases to the groin, chest and nose with a survival time of seven years and, in spite of slow tumor progression, reported no reduction in the quality of life. Enlarged lymph nodes in the axilla were found in another patient where, seven years previously, a tumor of unknown histology had been removed from the back. Cutaneous metastases developed in the chest and abdomen and, eight months later, the intestinal lymph nodes were surgically removed. The patient survived a further three years and died of unknown cause. Boyd assumed host tissue resistance directed against the tumor. Two examples were also reported by Morton and Morton [191] with long-term survival following cutaneous metastatic melanoma. In one case (No. 11) of this report, a correlation between possible spontaneous regression and radiation treatment or recurrent infection can be postulated. Six patients with metastatic melanoma and survival times ranging from five to eighteen years were documented by Bagley et al. [15]. The cause of death in all of these patients evidenced no known reference to the tumor.

6.1.5. *Summary*

Unusually long-term survival and delayed metastasis are probably correlated to spontaneous regression processes of tumors. Successful treatment cannot be excluded in some individual cases. On the basis of current knowledge, radiation treatment, for example, should be relegated a more important role than has previously been the case due to a greater therapeutic effectiveness [114]. The influence of infection must also be examined in greater detail. No generally valid conclusions can be construed from the case reports presented at this time. It is not possible to claim complete documentation in all cases with unusually long-term survival or delayed appearance of metastasis.

6.2. Spontaneous regression lacking detailed documentation

In the current world literature, there are numerous examples of spontaneous regression of metastatic cutaneous melanoma and choroidal melanoma lacking detailed case information. Reference to possible spontaneous regression was

found, among other points, in tables, in notes in the margin or in methodic descriptions of particular cell cultures. However, spontaneous regression of metastatic melanoma remains a rare event and it is therefore unfortunate that these cases are not fully documented.

Fauvet et al. [92] make passing reference to a report from Biédert (1866) whereby spontaneous regression and healing of a melanosarcoma was observed following erysipelas.

In conjunction with a detailed case description, Bennett W H [19] indicates a "similar case," differing from the first case only in the location of the primary tumor. Further information concerning the patient or diagnostic and therapeutic procedures were not included.

Handley [111] mentions two examples of possible spontaneous regression which were related to him by other colleagues. One case (from Pearce Gould) was presented in great detail whereas the other case (from Jocelyn Swan) is described only as a "similar case" without any further information.

Coley [67] cites a colleague named Dr. Greenwood who is said to have observed complete spontaneous regression of a metastatic malignant melanoma in a seven year old boy in connection with the appearance of erysipelas. Further information concerning regarding this case is not given. In retrospect, the diagnosis must be doubted, since the appearance of a malignant melanoma in childhood is itself a rarity [121, 218, 234].

In Stidolph [272] two case reports of complete spontaneous regression of metastatic melanoma are cited yet lack further information regarding the patient or diagnostic and therapeutic procedures (cases from Eastcott and Qvist). Bodenham [26] reported seven cases of spontaneous regression in metastatic melanoma that were all observed in women. Exact data regarding the patients are not available. In two women, spontaneous regression of metastases occurred after excision of the primary tumor, whereas the primary tumor was still present in two other women. According to the author, the remaining three patients received inadequate treatment, also with subsequent observation of spontaneous regression of the metastases. No information is supplied concerning the type and extent of the metastases. One of the patients was in remission for three and one half years following spontaneous regression.

Morton et al. [190] observed complete regression of subcutaneous nodules in two patients during immunotherapy with the BCG vaccine. The authors assume a spontaneous regression of the nodules since the BCG was not applied directly into the lesion. In one patient, complete regression occurred with a remission interval of two years following BCG therapy. Additionally, a clear increase of antibodies directed against melanoma cells was documented after the treatment. Further evidence of spontaneous regression can be seen in the tables

or in the text by Eilber and Morton [84], Moore and Gerner [189] and Falk et al. [90]. A total of eighteen literary references lacking detailed documentation of spontaneous regression in cutaneous metastatic melanoma are listed. It is not possible to completely substantiate all of the information cited. The references to independent regressive processes which have been presented in the literature must be considered uncertain since complete information concerning patient data, diagnostic procedures, treatment prior to the presumed spontaneous regression and additional accompanying factors are not included.

Detailed case reports with questionable histologic results are also classified as uncertain. Beswick and Qvist [22] report a patient with lymph node metastases in both axillae. Scrutiny revealed a scar on the patient's back thought to be the primary tumor site where previously, according to the patient, a skin tumor had been excised. Histologic examination of this tumor was not available, whereas the histologic examination of the lymph nodes was described as "undifferentiated carcinoma." Complete regression occurred following a second operative procedure to remove a lymph node metastasis followed by radiation treatment. There is no clear histologic evidence of melanoma in this case and such can only be assumed on the basis of the clinical presentation.

6.3. Case reports

A total of 68 case reports of spontaneous regression of metastatic malignant melanoma were examined with respect to accompanying factors influencing tumor regression. Only those reports where documentation regarding the patient (age and sex), extent of the tumor, probable therapy prior to the presumed spontaneous regression and adequate follow-up observation were included. Cases reported by Müllleder [194] and Cade [51] are exceptions since patient information is lacking, however, both documentations were considered due to the extent of their observations. In the first cases [46, 219], the period of follow-up observation was 9 1/2 years.

The histologic confirmation of malignancy in cutaneous and subcutaneous nodules and in lymph node metastases is documented in most cases. Histologic confirmation of visceral metastases is found in only some cases. The histologic confirmation of malignancy in a presumed melanoma metastasis is examined in relation to a possible correlation to spontaneous regression. Everson and Cole [89] do not exclude the possibility of a complete operative excision of the tumor with spontaneous restitution following a residual infection as the presumed cause of "spontaneous regression."

It would have been desirable to examine a portion of the spontaneously regressed tumor utilizing the pathohistologic criteria outlined in the literature [10, 27, 133, 214, 258]. These criteria are in accordance with the lesions found in the regression of the primary tumor (see page 23, Table 3). According to various authors, the incidence of spontaneous regression in metastatic melanoma is roughly 0.23%. One case of spontaneous regression occurs in approximately 400 cases of metastatic melanoma. This is summarized in Table 8.

Table 8: Incidence of spontaneous regression in metastatic malignant melanoma.

Author	Incidence	Total number	Percent
Daland and Holmes [73]	1	174	0.58
Vogler et al. [284]	1	253	0.40
Block and Hartwell [25]	1	236	0.42
Cade [51]	1	226	0.44
Pack and Miller [207]	1	1190	0.08
Peterson et al. [217]	2	621	0.32
Moore and Gerner [189]	2	1700	0.12
Bodurtha et al. [28]	1	226	0.44
Nathanson et al. [197]	1	141	0.71
Total	11	4767	0.23

Table 9: Age distribution of patients with spontaneous regression.

	Women	Men
Total	32	35
Age at the time of regression (years)	Range	Range
1. 0 - 10	2	-
2. 11 - 20	-	1
3. 21 - 30	3	9
4. 31 - 40	7	6
5. 41 - 50	9	6
6. 51 - 60	7	4
7. 61 - 70	6	2
8. 71 - 80	2	2
Average age	42.6	43.9

With the increasing incidence of melanoma, the number of cases reported should also increase. However, the cases presented here are spread equally over a period of 130 years. The variety of treatment attempted has lead to a somewhat confusing interaction, making the definition of the event to be reported, specifically spontaneous tumor regression, more difficult.

Spontaneous regression was described in 32 women and 35 men in 68 case reports. Cade [51] did not include the age or sex of one patient. The average age at the time of tumor regression was 42.6 in women and 43.9 in men. The youngest female patient was a two and one half month old infant, whereby a transplacental tumor transmission due to disseminated melanoma in the mother exhibited spontaneous regression and complete remission during a two year observation period [57]. The oldest female patient was eighty years old. The youngest male patient was twenty and the oldest was 78. Spontaneous regression was observed most often in women in the 41 to 50 age group (9 cases) and in men in the 21 to 30 age group (9 cases). The relatively equal distribution in women between 31 and 70 and in men between 21 and 50 is especially interesting. A significant grouping could not be determined and the age distribution in women does not appear to support the theory of a hormonal dependence in melanoma. Examples of spontaneous regression are present in all age groups. A total of three cases for both sexes were described up to the age of twenty. The small number can be attributed to the rarity of malignant melanoma at a young age. The reduction in cases of spontaneous regression with increasing age may be explained by the decline in the number of patients in

these age groups. There has been some speculation regarding reduced function of the immune system with increasing age.

6.3.1. *Accompanying illnesses and medication*

Conditions diagnosed and treated prior to spontaneous regression include, for example, arterial hypertension, gastric and duodenal ulcer and nephrolithiasis (2 cases). In one female patient, a biopsy due to fibrocystic mastopathy and a complete thyroidectomy due to Hürthle-cell carcinoma were performed during the presumed regression of the tumor. Post-operatively, calcium lactate and vitamin D had to be substituted [44]. Milton et al. [183] describe a patient with prostate cancer and subsequent treatment with estrogen. In another female patient, an estrogen and progesterone substitution was necessary due to a Turner-syndrome [154]. There was evidence of diabetes mellitus in two reports [154, 183]. Pain medication was administered in two cases [41, 219].

Table 10: Accompanying diseases in spontaneous regression of metastatic melanoma.

Accompanying diseases	Number of cases
Xeroderma pigmentosum	4
Diabetes mellitus	2
Nephrolithiasis	2
Prostate cancer	1
Benign hyperplasia of the prostate	1
Ulcerative disease	1
Myoma of the uterus	1
Hypertension	1
Turner syndrome	1
Hemorrhoids	1
Eczema	1
Cervical carcinoma in situ	1
Hürthle-cell adenoma	1
Fibrocystic mastopathy	1

Table 11: Accompanying medication in spontaneous regression of metastatic melanoma.

Accompanying medication	Number of cases
Estrogen	3
Analgesics	2
Calcium lactate	1
Vitamin D	1
Progesterone	1
Topical hydrocortisone	1
Insulin s.c.	1

The fact that spontaneous regression occurred in four patients with Xeroderma pigmentosum [8, 164, 241] is amazing and remains to be explained. Tables 10 and 11 provide a summary of other accompanying factors, whereby multiple entries are made for one patient. Among the cases of spontaneous regression of metastatic malignant melanoma, an unusually large number of cases are found in the available literature in patients with Xeroderma pigmentosum. Other diseases, including dermatologic conditions, were not represented to such a great degree. A relationship to a particular medication could not be demonstrated.

6.3.2. Complete and partial regression

Amongst the 68 cases, there were 52 examples of complete regression and 16 examples of regression in some cutaneous nodules or partial lymph node metastases (partial regression). Complete spontaneous regression was documented exclusively in 14 cases of cutaneous and/or subcutaneous nodules and in 19 cases of metastatic lymph nodes, while possible regression of cutaneous metastases was not considered. The probable simultaneous regression of cutaneous and lymph node metastases are not reported among the 19 cases of complete regression of visceral metastases. Case reports of spontaneous regression of visceral metastases without histologic confirmation of malignancy were also analyzed. Partial regression was described in 14 cases of cutaneous metastases and in 2 cases of lymph node metastases.

Spontaneous regression of cutaneous metastases was found twenty-eight times and twenty-one times in lymph node metastases. No reports of partial regression of visceral metastases were found.

Table 12: Summary of complete and partial regression.

Complete regression	Cases	Partial regression	Cases
Total	52	Total	16
cutaneous and subcutaneous nodules	14	cutaneous and subcutaneous nodules	14
lymph node metastases	19	lymph node metastases	2
visceral metastases	19	visceral metastases	-

6.3.3. Spontaneous regression of visceral metastases

Nine reports of spontaneous regression of pulmonary metastases, mainly diagnosed using X-rays, were available [25, 57, 89, 96, 134, 155, 181, 277]. In one case, a lesion was excised to confirm the diagnosis [277]. Evidence of cerebral metastases was found in seven cases [89, 170, 192, 224, 241, 277]. None of the reports documented spontaneous regression of cerebral metastases histologically. The spontaneous regression of liver or intestinal metastases was confirmed on the basis of biopsy and clinical findings during re-laparotomy [44, 51, 175, 224, 256]. Spontaneous regression of bone metastases was documented in three cases [134, 170, 202]. Boyd [33, 34] reported regression of liver and spleen enlargements which were considered indicative of metastatic disease. Manifestation of spontaneous regression appears possible in all affected organs. The prevalence of pulmonary metastases is probably due to a predilection of malignant melanoma for that organ.

Table 13: Spontaneous regression of visceral metastases. Multiple entries from one patient are possible.

Visceral metastases	Cases 19
Pulmonary	9
Cerebral	7
Enlarged liver (clinical)	4
Hepatic metastases (histologic)	3
Skeletal	3
Intestinal	3
Enlarged spleen (clinical)	1

6.3.4. *Special accompanying circumstances*

The fact that Xeroderma pigmentosum was found four times amongst 68 cases of spontaneous regression is rather unusual. In one case, spontaneous tumor regression of a cutaneous melanoma occurred in twins (brother and sister) [164]. A further peculiarity is the association of spontaneous regression in metastatic melanoma with Turner-syndrome [154]. The report by Wormald and Harper [298] is worthy of note. A patient with histologic confirmation of malignant melanoma with generalized cutaneous and subcutaneous metastases developed a black hypopyon in both eyes. The patient described a black spot on his back that had been expanding for more than 20 years. Simultaneously to the development of the hypopyons which, according to the author, were due to pigment deposits in the anterior chamber of the eyes, spontaneous regression of cutaneous and subcutaneous nodules was observed. The patient refused all treatment. The authors proposed either a primary cutaneous melanoma with metastases to both eyes or a choroidal melanoma with secondary involvement of the skin. The simultaneous appearance of choroidal melanoma and cutaneous malignant melanoma was also discussed. The authors assume a possible connection on an immunologic basis between the spontaneous regression of the cutaneous nodules and the appearance of the black hypopyons. Spontaneous regression of metastases of choroidal melanoma are reported by Levison [155], Malleson [169] and Olsen [205]. A survival time of up to 40 years despite recurrent metastases and simultaneous regression of cutaneous nodules was described by Anstey et al. [8].

Table 14: Factors accompanying spontaneous regression. Multiple entries from one patient are possible.

Associated Factors	Number of cases
Operations	68
Infection	21
Radiation or Telecobalt therapy	11
Pregnancy	4
Administration of antibodies with I ¹³¹	3
Chemotherapy	2
Blood transfusions	2
Administration of irradiated autologous tumor cells	2
Blood transfusion from "long-term-survivors"	2
BCG	1
Rabies vaccination	1
Extremity perfusion	1

6.3.5. *Accompanying factors*

Operative or incomplete procedures were described in all cases. Post-operative infection or spontaneous occurrence of a systemic inflammation is found in 21 cases. Erysipelas was observed in most of these instances. Radiation treatment before or during spontaneous regression was described eleven times. A distinction was made between X-ray therapy (9 cases) and telecobalt application (2 cases). Accompanying immunologic factors such as blood transfusions or intravenous treatment with tagged antibodies directed against melanoma cells is documented in 13 cases. The transfusion of blood from a patient in remission with a long survival time ("long-term survivor") following complete spontaneous regression of metastatic melanoma or a rabies vaccination are considered accompanying immunologic factors.

Hormonal factors were presumed during pregnancy (4 cases) or in the application of hormones (3 cases). The spontaneous regression of metastatic melanoma is broadly related to and, according to the reported cases available, frequently associated with operations, hormonal factors, infection, radiation treatment or immunologic factors.

6.4. Five detailed case reports

In five detailed case reports, five different accompanying circumstances and factors are introduced as examples of those most frequently found in humans to be associated with spontaneous regression of malignant melanoma. The selection of these cases is random. However, an attempt was made to cite the first reported description whenever possible. A short commentary follows each of the documentations.

6.4.1. *Bruns [43]*

Case report: A 47 year old female patient was seen in 1880 due to a tumor in the left breast. One and one half years previous, the patient had noticed a nodule the size of a cherry and within one year the nodule had grown to the size of a hen's egg. In the course of a few months there had been intermittent pain in the breast that radiated to the left axilla. Physical examination revealed a fist-sized tumor in the left breast and two enlarged lymph nodes in the left axilla. The breast was removed and dissection of the axillary lymph nodes was performed. A histologic diagnosis of melanoma to the breast with metastases of the axillary lymph nodes was made. Four weeks after an otherwise unremarkable post-operative course, erysipelas developed that, according to the author, spread over almost the entire body. After an additional three weeks, the continuous fever, which at times was over 40° C, disappeared. The patient received no further treatment for the erysipelas. During this time, the lesion recurred in the original operative field. After the clinical signs of the erysipelas had abated, the recurrent lesion regressed without external manipulation. A few weeks later, the patient was completely free of symptoms.

Note: The first singular reports of spontaneous regression of malignant melanoma primarily contain information regarding infections that most often occur post-operatively and that are mainly manifested on the skin (erysipelas). It appears that the duration of inflammation and the degree of fever are also important. The initial diagnosis was made histologically and no follow-up histologic confirmation of the recurrent lesion was performed. No medication (i.e. analgesics or antipyretics) was given. The complete regression is apparently directly associated with the operation and febrile infection. The remission survival time was eight years.

6.4.2. Mathews [172]

Case report: A 45 year old patient was seen for a pigmentated naevus on the shoulder blade. According to the patient, the naevus had been there for as long as he could remember but had recently started to increase in size. The clinical examination revealed a tumor above the clavicle and a lymph node conglomerate in the ipsilateral axilla. The naevus was removed and a portion of the lymph node conglomerate was excised. The tumor above the clavicle and some of the axillary lymph nodes were left intact. Histologically, diagnosis of a primary melanoepithelioma with metastases to the axillary lymph nodes was made. Due to the expected quick progression, no further treatment was considered. The supraclavicular tumor disappeared completely whereas a hazelnut sized lymph node could still be palpated. The remission survival time was two years.

Note: In every case report of spontaneous regression of metastatic malignant melanoma, there is evidence of an operative procedure. The incomplete surgical removal of metastases is documented less often. The diagnosis was also confirmed histologically in this case.

6.4.3. Allen [6]

Case report: In July, 1942, a spot was removed from the extensor side of the right forearm in a 38 year old female patient which, according to the patient, had become darker after trauma. The histologic examination showed no evidence of a malignant process at that time. Two months later, the lesion recurred in the scar. In May, 1943, a broad excision to the fascia was performed. Melanoma was confirmed histologically. Follow-up radiation to the area with a total of 4700 r was performed. In November, 1943, the patient exhibited no signs of recurrence and was 10 weeks pregnant. In March, 1944, (seventh month of the pregnancy) multiple subcutaneous nodules appeared on the right flank, the right upper arm and in the left lower abdomen. The presumed diagnosis of cutaneous metastases was confirmed histologically. Fourteen days after the birth in May, 1944, additional tumors on the right scapula and in the right groin were diagnosed. During a physical examination in July 1944, all nodules, with the exception of one small lymph node in the right groin, were no longer evident. The remission survival time was 11 years.

Note: In addition to the operative measures and radiation treatment, pregnancy was considered an additional accompanying factor of the spontaneous regression. The connection between spontaneous regression of metastatic melanoma and pregnancy remains controversial.

6.4.4. Block and Hartwell [25]

Case report: A brown spot was excised from the left upper thigh of a 63 year old patient in March, 1950. In December, 1950, metastatic melanoma was confirmed by biopsy from the left groin. In October, 1951, an intravenous therapy with antibodies labelled with I^{131} was performed. In December, 1951, pulmonary metastases were diagnosed. In February, 1954, a decision to excise the groin metastases was made and, according to the author, performed incompletely. Complete regression occurred. In February, 1958, the patient died from myocardial infarction. Autopsy revealed no evidence of tumor. The remission survival time was four years.

Note: There is no histologic confirmation of the suspected primary tumor. Also, the pulmonary metastases were not confirmed histologically. The question also arises why the operative procedure to remove the lymph node metastases from the groin was performed with a four year latency. We have already discussed the possible connection between incomplete operative procedures and spontaneous regression. The intravenous treatment with labelled antibodies as a form of immunotherapy is of interest. Assumptions regarding a possible connection between the immunotherapy in October, 1951, and regression of the pulmonary metastases first diagnosed in December, 1951, should be allowed.

6.4.5. O'Connell et al. [202]

Case report: A pigmented cutaneous lesion on the left upper arm was excised in a 40 year old patient. According to the patient, the spot had been present for five years with enlargement, darkening and hemorrhage appearing within the last 6 months. A nodular malignant melanoma was diagnosed histologically with a maximum tumor diameter of 1.3 mm and Clark level III with a low mitotic index. A thorough examination for metastases was negative. A second excision was performed which also showed no histologic evidence of a tumor. Within three months (November, 1985), a subcutaneous metastasis developed in the area of the primary tumor and was subsequently excised. Another subcutaneous nodule was excised two months later from the left forearm. After a new nodule was discovered one month later, it was decided to perform an extremity perfusion of the left arm with melphalan. Dissection of the axilla was performed simultaneously. At that time no further evidence of metastases was found. In June, 1986, the patient complained of back pain. Metastases of the vertebrae, pelvis and multiple ribs were found. Additionally, pathologic fractures of the first lumbar vertebral body and the third, sixth and seventh rib on the left side were identified. Multiple palliative telecobalt treatments to a

9 x 6 cm area from the twelfth thoracic vertebrae to the second lumbar vertebrae were performed. The patient was free of symptoms after January, 1987. All fractures healed completely and the pain disappeared. Further metastases did not occur. The remission survival time was two years.

Note: There is no evidence of histologic confirmation of the bone metastases. However, diagnosis utilizing computer tomography and, especially, scintigraphy is sufficient. The alkaline phosphatase values were high and returned to normal values during regression. The telecobalt treatment was carried out as a strictly palliative measure. In this context, the factor "radiation treatment" and reference to spontaneous tumor regression is mentioned. A total of eleven reports of radiation treatment could be found in the current literature [6, 89, 96, 99, 205, 217, 224, 241, 272, 284]. However, all authors emphasize that either no therapeutic effect (tumor progression or local recurrence) could be achieved through radiation treatment (X-ray or telecobalt treatment) or that spontaneous regression occurred in those parts of the tumor that were not treated with radiation. Radiation therapy is indicated in brain- and/or bone metastases [114, 120]. Assuming this observation is based on an immunologic process due to the effects of a localized radiation treatment, this factor must then be taken into consideration as a possible triggering factor of spontaneous regression. No research regarding this supposition could be found in the current literature. However, this conclusion can not be derived from the case reports available. Radiation treatment as a factor associated with spontaneous regression can be discounted.

Additionally, O'Connell et al. [202] reported numerous operative procedures and one example of an extremity perfusion yielding a questionable influence on the regression of bone metastases. The question remains whether spontaneous regression of bone metastases has occurred that was not influenced by external factors.

Summary: The incidence of spontaneous regression of metastatic melanoma is roughly 0.23%. Spontaneous regression processes were observed in cutaneous and subcutaneous nodules, in lymph node and visceral metastases. Spontaneous regression of visceral metastases can occur in all organs. Accompanying circumstances mentioned in the literature that were most frequently associated with spontaneous regression of metastatic melanoma include: febrile infection, operative procedures, hormones, immunologic factors or no apparent triggering factor. An increase in therapeutic possibilities also increases the number of accompanying circumstances that could influence spontaneous regression.

Besides, the effectiveness of the individual treatments is dependent on the judgement of the author and must be taken into consideration. This judgement is dependent on the general opinion that prevails at the point in time when the case report was first documented.

Other than the unusually frequent association with Xeroderma pigmentosum, no relation between spontaneous regression and other diseases or particular medications could be determined. No definite conclusions can be construed from the age and sex distribution of patients with spontaneous regression of metastatic melanoma.

The spontaneous regression of metastatic melanoma has been proposed as a possible explanation for unexpectedly prolonged courses of disease and the delayed occurrence of metastases. The clinical and histologic criteria of spontaneous regression of primary tumors originate from Smith J L and Stehlin [258]. Uniform guidelines for the documentation of spontaneous regression in metastatic melanoma do not yet exist.

The outline contains the information necessary for a comprehensive documentation of spontaneous regression.

A Comprehensive Documentation of Spontaneous Regression

1. Patient information
 - 1.1. Age
 - 1.2. Sex
 - 1.3. Previous illnesses
 - 1.4. Previous medication
 - 1.5. Medical history (Autonomic symptoms)
2. Information regarding the primary tumor
 - 2.1. Localization
 - 2.2. In the case of operative excision
 - 2.2.1. Maximum vertical tumor diameter
 - 2.2.2. Depth of invasion according to Clark
 - 2.2.3. UICC classification (1987)
 - 2.2.4. Evidence of regression zones
 - 2.2.5. Margin of safety
 - 2.3. Incidental or traumatic removal
 - 2.4. Spontaneous regression without external influence

3. Information regarding metastases
 - 3.1. Diagnostic procedures
 - 3.1.1. Diagnostic imaging techniques
 - 3.1.2. Bioptic techniques
 - 3.2. UICC classification (1987)
4. Information regarding spontaneous regression of metastases
 - 4.1. Diagnostic procedures
 - 4.1.1. Diagnostic imaging techniques
 - 4.1.2. Bioptic techniques
 - 4.2. UICC classification (1987)
5. Information regarding accompanying factors during the regression interval
 - 5.1. Patient observations
 - 5.2. Medical examiner observations
6. Follow-up period

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
1	43	f	Busch [46]	cutaneous and subcutaneous tumors, enlarged cervical lymph nodes TNM: M1a St. IV	complete regression	numerous operations, facial erysipelas	traced well - 3 years
2	50	f	Mosengeil [192]	cutaneous and subcutaneous tumors left-sided visual impairment TNM: M1b St. IV	complete regression	numerous operations, facial erysipelas	no follow-up
3	22	f	Plenio [219]	right inguinal lymph node metastases TNM: N2c St. III	complete regression	numerous operations, post-op. erysipelas, on the right hip, pneumonia, oral analgesics	traced well - 4 years
4	47	f	Bruns [43]	Tumor of the left breast, recurrent lymph node metastases in the l. axilla TNM: N2a St. III	regression of the recurrent tumor	excision of primary and axillary metastases, erysipelas of the entire integument	traced well - 8 years
5	52	f	Bennett [19]	cutaneous tumors, inguinal lymph node metastases TNM: N2c St. III	complete regression	numerous operations incl. foot amputation	3 years remission
6	80	f	Northrop [cited by 99]	3 times recurrent inoperable primary, right nasal cavity. Cervical and supraclavicular lymph node metastases TNM: N2a St. III	complete regression	numerous operations, erysipelas of the face and neck	no follow-up
7	38	m	Gould [cited by 111]	disseminated cutaneous tumors, lymph node metastases TNM: N2c St. III	complete regression	excision of the primary tumor	8 months remission death due to generalized metastases
8	45	m	Mathews [172]	supraclavicular and axillary lymph node metastases TNM: N2a St. III	complete regression	excision of the primary tumor and incomplete excision of the lymph nodes	2 years remission

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
9	7	f	Coley [67]	submaxillary, cervical and supraclavicular lymph node metastases TNM: N2a St. III	complete regression	numerous operations, facial erysipelas, lanced abscess	3.25 years remission
10	?	m	Müllerer [194]	left inguinal lymph node metastases TNM: N2a St. III	partial regression of the lymph- nodes	numerous operations, erysipelas of the left leg and groin	1.5 years remission
11	43	m	Daland and Holmes [73]	cutaneous tumors, inguinal lymph node metastases TNM: N2c St. III	complete regression	numerous operations, erysipelas of the lower thigh	6 years remission, death due to cerebral metastases
12	32	f	Pack [206]	cutaneous tumors TNM: N2b St. III	complete regression	numerous operations, rabies vaccination	10 years remission
13	43	f	Levi and Lewison [154]	cutaneous tumors, lymph node metastases TNM: N2c St. III	partial regression of cutaneous tumors and lymph node metastases	numerous operations, hormone treatment of Turner-Syndrome, Diabetes mellitus (insulin dependent)	2 years remission, death due to generalized metastases
14	30	f	Sumner [273]	disseminated cutaneous and subcutaneous tumors TNM: N2c St. III	complete regression	numerous operations, erythema infectiosum, pregnancy	traced well - 21.5 years, depigmentation of all regressed tumors
15	38	f	Allen [6]	subcutaneous tumors TNM: N2b St. III	complete regression	numerous operations, radiation treatment, pregnancy	traced well - 11 years
16	70	f	Blocker [cited by 88]	cutaneous tumors TNM: N2b St. III	regression of tumors during recur- rence of primary tumor	numerous operations	7 years remission

*(UICC 1987)

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
17	60	m	Levison [155]	lesion in chest X-ray, melanuria TNM: M1b St. IV	complete regression	enucleation of the right eye due to choroid melanoma	1 year remission
18	22	m	Malleson [169]	enlarged lymph nodes in chest X-ray, lymph node metastases TNM: M1a St. IV	complete regression	possible choroid melanoma of the left eye	2 years remission
19	36	f	Meyer [cited by 89]	lymph node metastases in the l. axilla TNM: N2a St. III	complete regression	incomplete lymph node excision with abscess development	traced well - 20 years
20	63	m	Vial and Coller [cited by 89]	5 lesions in chest X-ray, cutaneous tumors, inguinal lymph node metastases TNM: M1b St. IV	regression of pulmonary lesions	numerous operations, radiation treatment, i.v. injection of I ¹³¹ antibodies	2 years remission followed by recurrence in the groin
21	33	f	Boyd [34]	lymph node metastases, enlarged liver TNM: M1b St. IV	complete regression	numerous operations	5 years remission, death due to generalized metastases
22	23	f	Boyd [34]	cutaneous tumors enlarged liver TNM: M1b St. IV	complete regression	numerous operations, pregnancy	7 years remission, death due to generalized metastases
23	52	f	Vogler et al. [284]	cutaneous tumors, inguinal lymph node metastases TNM: N2c St. III	regression of tumors, that were not irradiated	numerous operations, radiation treatment	3 years remission
24	26	m	Sumner and Foraker [274]	disseminated cutaneous tumors TNM: N2c St. III	complete regression	numerous operations, transfusion of 250 ml blood from patient # 14	5 years remission
25	63	m	Block and Hartwell [25]	inguinal lymph node metastases, pulmonary metastases TNM: M1b St. IV	complete regression	incomplete excision of inguinal lymph nodes, i.v. injection of I ¹³¹ antibodies	4 years remission, death due to myocardial infarction

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
26	?	?	Cade [51]	subcutaneous tumors, inguinal lymph node metastases intestinal metastases TNM: M1b St. IV	complete regression	numerous operations, including intestinal resection	4 years remission
27	20	m	Ellis [cited by 89]	cutaneous and subcutaneous tumors, inguinal lymph node metastases, lesions in chest X-ray, possible cerebral metastases TNM: M1b St. IV	complete regression	numerous operations	6 years remission
28	54	f	Petersen [217]	cutaneous tumors TNM: N2b St. III	complete regression	numerous operations	6 years remission
29	38	f	Petersen [217]	preauricular lymph node metastases TNM: N2a St. III	complete regression	numerous operations, radiation treatment	traced well - 13 years
30	29	m	Teimou- rian and McCune [277]	pulmonary metastases, possible cerebral metastases TNM: M1b St. IV	complete regression	excision of pulmonary metastases, blood transfusion from a melanoma patient with 10 year remission	10 years remission, death due to cerebral metastases
31	46	m	Baker [16]	primary on ear, cervical lymph node metastases TNM: N2a St. III	complete regression	numerous operations, tumor mass grossly infected	traced well - 33 years (Feb.1992)
32	2.5 mo.	f	Cavell [57]	transplacental cutaneous metastases, lesions in chest X-ray TNM: M1b St. IV	complete regression	numerous operations	2 years remission
33	32	m	McCredie [cited by 89]	disseminated cutaneous tumors, enlarged liver, possible cerebral metastases TNM: M1b St. IV	complete regression	numerous operations, Cobalt- radiation, blood transfusions	4 years remission

* (UICC 1987)

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
34	22	m	Boyd [35]	disseminated cutaneous tumors, inguinal lymph node metastases liver and spleen enlargement TNM: M1b St. IV	complete regression	numerous operations, blood transfusions	6 years remission
35	56	m	Olsen [205]	disseminated cutaneous tumors TNM: M1a St. IV	complete regression	exenteration of the right eye due choroid melanoma	8 years remission
36	48	f	Ronchese [241]	disseminated cutaneous and subcutaneous tumors, cerebral metastases TNM: M1b St. IV	partial regression of subcutaneous tumors	numerous operations, radiation treatment, Xeroderma pigmentosum	traced well - 25 years time in spite of frequent cutaneous recurrence
37	78	m	Milton et al. [183]	submandibular and preauricular lymph node metastases TNM: N2c St. III	regression of lymph nodes during recurrence of primary tumor	excision of the primary tumor, radiation treatment, estrogen treatment of prostate cancer, Diabetes mellitus	4 years remission, death due to diabetic coma
38	23	m	Stidolph [272]	lymph node metastases in the I. axilla TNM: N2a St. III	complete regression	numerous operations, radiation treatment	3.5 years remission
39	21	m	Fowler [99]	inguinal lymph node metastases TNM: N2a St. III	complete regression	numerous operations, suppurative infection, lymphadenitis	no further metastases after infection. Traced well - 39 years. Death due to prostate cancer
40	58	f	Fowler [99]	inguinal lymph node metastases TNM: N2a St. III	complete regression	numerous operations, erysipelas of the groin, infection and necrosis	10 years remission
41	27	m	Fowler [99]	lymph node metastases in the I. axilla TNM: N2a St. III	complete regression	incomplete excision of lymph nodes, Staphylococcus infection	traced well - 37 years (1983)
42	40	m	Fowler [99]	disseminated cutaneous tumors TNM: M1a St. IV	complete regression	numerous operations, radiation treatment, infection, abscess, fever	in excellent health. He died 1976 at 86. 45 years after regression

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
43	42	f	Savel [246]	disseminated subcutaneous tumors, inguinal lymph node metastases TNM: M1a St. IV	partial regression of subcutaneous tumors	numerous operations	1 year remission
44	38	f	Foley and Coon [96]	cutaneous tumors TNM: N2b St. III	partial regression	numerous operations	5 years remission, death due to generalized metastases
45	62	m	Foley and Coon [96]	inguinal lymph node metastases, lesions in chest X-ray TNM: M1b St. IV	complete regression	numerous operations, radiation treatment, i.v. injection of I ¹³¹ antibodies	6 years remission, death due to myocardial infarction
46	43	m	Krementz [149]	cutaneous and subcutaneous tumors TNM: M1a St. IV	complete regression	numerous operations, including amputation, i.c. injection of the patient's own tumor cells, after destruction by radiation	1 year remission
47	42	f	Moore and Gerner [189]	cutaneous tumors TNM: M1a St. IV	partial regression of the tumors	numerous operations	4 years remission
48	57	m	Brincker and Andersen [41]	disseminated cutaneous tumors TNM: M1a St. IV	complete regression	numerous operations, oral analgesics, external hydrocortisone	4 months remission, death due to generalized metastases
49	46	m	The et al. [278]	disseminated cutaneous tumors TNM: M1a St. IV	complete regression	numerous operations	2 years remission, death due to generalized metastases
50	65	m	Doyle et al. [82]	cutaneous tumors TNM: N2b St. III	complete regression	excision of the primary tumor	5.5 years remission
51	70	m	Maurer et al. [173]	disseminated cutaneous and subcutaneous tumors TNM: M1a St. IV	partial regression of the tumors	numerous operations	8 years remission, death due to generalized metastases

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
52	58	f	Bulkley et al. [44]	cutaneous and subcutaneous tumors, liver metastases TNM: M1b St. IV	complete regression	numerous operations, including liver biopsy, chemotherapy (Thiotepa), post-op. infection, pregnancy	traced well - 12 years, cystic mastopathy surgery and Hürthle cell carcinoma
53	74	m	Bodurtha et al. [29]	cutaneous tumors TNM: M1a St. IV	complete regression	excision of the primary tumor	19 months remission
54	58	f	Nathanson [197]	cutaneous tumors TNM: N2b St. III	partial regression	numerous operations	2 months remission of the tumor
55	49	f	Sindelar and Ketcham [256]	cutaneous and subcutaneous tumors, inguinal lymph node metastases, liver metastases TNM: M1b St. IV	complete regression	numerous operations including diagnostic laparotomy, post-op. infection	traced well - 12 years
56	33	f	Lynch et al. [164]	cutaneous tumors TNM: M1a St. IV	partial regression of the tumors	numerous operations Xeroderma pigmentosum	9 years remission, 3 normal pregnancies
57	28	m	Lynch et al. [164]	cutaneous tumors TNM: N2c St. III	complete regression	numerous operations Xeroderma pigmentosum (brother of pat. #56)	traced well - 12 years
58	47	f	Manelis et al. [170]	disseminated subcutaneous tumors, inguinal lymph node metastases, bone metastases, possible cerebral metastases TNM: M1b St. IV	partial regression of tumors, possible regression of cerebral metastases	numerous operations, treatment with BCG, infusion of autologous tumor cells killed by radiation treatment	spontaneous restitution of the neurological symptoms for 5 weeks, death within 2 years due to generalized metastases
59	41	m	McCarthy et al. [175]	cutaneous tumors, intest. metastases TNM: M1b St. IV	partial regression of the tumors	numerous operations, including intestinal resection because of ileus, numerous postoperative infections, pulmonary embolus, pleural effusion	traced well - 11 years

Table 15: Spontaneous regression of metastatic malignant melanoma: 68 cases

No.	Age	Sex	Author	Site of Primary or Metastatic Tumors*	Regression	Associated Factors	Course
60	62	f	McCarthy et al. [175]	inguinal lymph node metastases TNM: N2c St. III	complete regression	numerous operations, postoperative infection	8.5 years remission
61	32	m	Rampen [224]	intestinal metastases, cutaneous tumors, possible cerebral metastases TNM: M1b St. IV	complete regression	numerous operations, including intestinal resection by ileus, radiation treatment, postoperative infection	traced well - 18 years
62	26	m	Hori et al. [124]	cutaneous tumors TNM: N2b St. III	partial regression of the tumors	chemotherapy (hydroxy-urea, vincristin, cyclophosphamid, methotrexat and 5-FU)	10 months remission, death due to generalized metastases
63	56	m	Wormald and Harper [298]	disseminated cutaneous tumors TNM: M1a St. IV	partial regression of the tumors	appearance of bilateral black hypopyon	1 year remission, death due to myocardial infarction
64	77	f	Mikhail and Gorsulovsky [181]	cutaneous tumors, lesions in chest X-ray TNM: M1b St. IV	complete regression	numerous operations	1 year remission
65	40	m	O'Connell et al. [202]	subcutane tumors, bone metastases TNM: M1b St. IV	complete regression	numerous operations, including extremity perfusion, Cobalt radiation treatment	2 years remission
66	67	m	Anstey et al. [8]	disseminated cutaneous tumors TNM: M1a St. IV	partial regression	numerous operations, Xeroderma pigmentosum	traced well - 40 years time in spite of frequent cutaneous recurrence
67	51	f	Hurwitz [128]	inguinal lymph node metastases TNM: N2c St. III	complete regression	tumor biopsy	6 years remission
68	31	m	Kleeberg [134]	pulmonary, liver and bone metastases TNM: M1b St. IV	complete regression	numerous operations, incl. excision of cerebral metastases, bronchopneumonia, pleuritis, high fever	15 months remission, then cerebral metastases

7. ASSOCIATED FACTORS

It is not possible to judge all of the factors with a possible influence on tumor regression that are described in the literature in connection with spontaneous regression of metastatic malignant melanoma. Nathanson [197] had already arrived at this conclusion. Besides those factors observed during spontaneous regression, other possible influences and causes can be found in the literature.

In a review of spontaneous regression of malignant tumors by Fauvet et al. [92], the following "determining factors of the regression" (p. 2360) are mentioned:

1. infection, or prolonged high fever
2. shock (mostly hemorrhagic) and cachexia
3. operations to remove chronic irritation (i.e., gastroenterostomy, preternatural anus or ureterosigmoidostomy)
4. incomplete operations
5. diagnostic laparotomies
6. biopsy
7. pregnancy
8. immunologic factors.

These circumstances are still valid today whereby, according to the authors, gammaglobulins play an important immunologic role.

Everson and Cole [89] found "possible causes of spontaneous regression of cancer" (p. 6):

1. endocrine influences
2. fever and infection
3. allergic or immunologic reactions
4. influences on tumor nutrition
5. elimination of carcinogens
6. unusual response to an uncommon therapy
7. complete operative removal of the entire tumor
8. incorrect diagnosis.

Cole [66] was also able to add the influence of enzymes, interferon and viruses to the factors mentioned above. Medicinal therapy or the combination of operation, radiation treatment and chemotherapy were also listed as causes for a regression. Cole also went on to mention the possible effect that excision of the primary could have on the development of metastases, which was also later described by Shaw et al. [252].

In conclusion, the "possible mechanisms of spontaneous regression of malignant melanoma" (p. 70) enumerated by Nathanson [197] should also be mentioned:

1. immunologic factors
2. endocrine factors
3. direct cytotoxicity of pigment metabolites
4. inhibitory effect of intracellular factors
5. influences on tumor nutrition
6. elimination of carcinogens
7. genetic factors.

A number of these items have been confirmed by other authors [10, 27, 87, 145, 184, 225].

The multiplicity of related terms should also be noted. Fauvet et al. [92] mention "accompanying circumstances," Everson and Cole [89] cite "possible causes," and Nathanson [197] specifies "possible mechanisms" for spontaneous regression. If spontaneous regression refers to the regression of a tumor, whose cause is not, or has not yet been explained, then only those factors can be evaluated that stand in probable direct connection with tumor regression. Stephenson et al. [269] and Stephenson [268] performed a computerized analysis of 224 reported cases regarding "spontaneous regression of malignant tumors." They were able to determine a stimulation of the reticuloendothelial system (immunostimulation) in 77 cases, an infection or prolonged fever in 62 cases and an influence on the endocrine system in 45 cases. Considering the reported cases available, five major accompanying circumstances could be identified: febrile infection, operative procedures, hormonal influences, immunologic factors or no objective cause. The first factor to be examined in detail are febrile infections.

7.1. Spontaneous regression and febrile infection

The first reports concerning spontaneous tumor regression of malignant melanoma are exclusively connected with febrile infections of the skin (erysipelas). The infection usually occurred post-operatively, could not be treated properly due to a lack of antibiotics and was usually of one week duration. Reports connecting febrile infection and spontaneous regression are also found at the present time. A total of twenty case reports of spontaneous regression of metastatic melanoma and four instances of spontaneous regression

of the primary tumor have been documented in connection with febrile infections [16, 43, 44, 46, 67, 73, 89, 99, 134, 170, 175, 192, 194, 198, 219, 224, 228, 256, 273, 279].

Huth [129] connects spontaneous regression with erysipelas, abscess development, phlegmona, sepsis, pneumonia and other suppurating processes. He believed that an acute infection of short duration was not effective, since prolonged fever resulted in a continual lysis of the pathogen followed by the development of pus. Fever alone was not enough, but rather the lysis of the microorganism. The type of microorganism was also not important. The bacterial toxins alone were also not important for tumor regression, but rather the immune process triggered by the toxins. After the infection has abated, recurrent tumor development becomes possible since a continual supply of infectious substances is necessary to propagate the immune process. "The application of healthy, normal cell constituents or enzyme systems of particular microorganisms may initiate regression of the malignant tumor in persons afflicted with tumors" [129] (p. 550).

Papachristou and Fortner [212] examined melanoma patients with lymph node metastases and post-operative infections and found that these patients had less local recurrence than the control group who exhibited similarly affected lymph nodes and were free of infection. Long term prognosis and remission interval were not influenced. The authors list the following immunologic factors which are supposedly connected with the management of tumors through infection:

1. active migration of neutrophilic granulocytes and monocytes from the blood stream towards the tumor
2. lymphocyte adherence to tumor cells
3. production of a macrophage inhibition factor
4. cytotoxic factors
5. the production of specific antibodies.

In addition to specific immunologic mechanisms, Papachristou and Fortner believe that other unspecific processes (i.e. cytotoxicity that is non-antibody dependent) also take part in possible spontaneous regression.

Due to the frequently observed association of spontaneous regression with febrile infection, experimental treatments with bacterial lysates commenced after the second half of the nineteenth century and are still being attempted to date [67, 199, 264]. In Kölmel et al. [141], reference is found concerning physiological changes in serum parameters measured after intravenous doses of

toxins. At the peak temperature, increased values for interleukin-1, interleukin-2, interferon-gamma and the tumor-necrosis-factor, and after 48 hours, an increased value for monocytes, natural killer cells, and B- and T-lymphocytes are found. These findings correlate with observations made by Huth [129] and Papachristou and Fortner [212].

The Cancer Research Institute in New York has made a special study of febrile infections and their effects in cancer patients. Here reference is made to early monographs by Fowler [99] and Nauts [198]. The incidence of the inhibitory effects caused by febrile infections on tumors has been documented numerous times in case-control studies [1, 2, 142, 235, 248].

Reports were made by Rampen [224, 225] and Rampen and Meijer [228] concerning spontaneous regressions in metastases, as well as in the primary tumor, that were connected to infections. They postulate that random, incidental trauma to the tumor, which is often followed by local infection, is responsible for the spontaneous regression of the primary tumor.

Febrile infection can be seen as the trigger of immunologic processes which can possibly lead to tumor regression. A positive definitive connection has not yet been proven to date. However, a protective effect is probable. The connection of febrile infection and tumor regression is the most frequent association found in the literature.

Table 16: Febrile infections associated with spontaneous regression of metastatic melanoma.

Febrile infections	21
erysipelas	9
post-operative abscess development	8
staphylococcus infection	1
bronchopneumonia	1
suppurative lymphadenitis	1
infectious erythema	1

7.2. Spontaneous regression and surgical procedures

In every case report, reference can be found regarding operations performed for diagnostic or therapeutic purposes. In a review of 302 cases of spontaneous regression of malignant tumors, Rohdenburg [239] found that the most frequent

association with spontaneous tumor regression was incomplete operations. He assumed an influence on the tumor by interruption of the blood supply. Sindelar and Ketcham [256] speak of "ischemic regression" which is described in more detail in cases of choroidal melanoma [197, 231]. Folkman et al. [97] identified a tumor-specific "angiogenic" factor they believe to be responsible for endothelial proliferation and neovascularization, both of which are necessary for the growth and blood supply of the tumor. Analogous to uncompleted operations, reduction in tumor size was also discussed which ostensibly assists the natural immune system to induce the regression of the remaining tumor.

Diagnostic operative procedures, from biopsy to laparotomy, were mentioned by Fauvet et al. [92] as accompanying circumstances for spontaneous regression. The possible influence on the tumor-host relationship due to diagnostic operations was mentioned previously [197]. Besides Fauvet et al., Sindelar and Ketcham also indicate the importance of the elimination of possible carcinogens by operative methods (i.e. preternatural anus or ureterosigmoidostomy). They contend that influences on the endocrine system by psychological events such as trauma, stress and post-operative febrile infections are further decisive factors with a possible connection between spontaneous tumor regression and operative measures. Medicinal influences (i.e. anesthetics or antibiotics) or post-operative intravenous feeding of the patient must be taken into consideration, including plasma or blood transfusions.

A causative connection between operative procedures and spontaneous regression processes in metastatic malignant melanoma appears questionable. However, the case cited by Mathews [172] should be mentioned which describes spontaneous regression after an incomplete operation. Since all of the melanoma patients included here were subject to operative procedures, the incidence of spontaneous regression of metastatic malignant melanoma would be more than approximately 1 : 400. Immune processes were possibly generated by factors connected with the operation or were caused by the operation itself though definitive proof has not yet been found.

7.3. Spontaneous regression and hormones

A hormone dependency of malignant melanoma is still being discussed today. Advocates list case reports in which clear progression of the tumor during

pregnancy and spontaneous regression after delivery are described. Corresponding reports of metastatic malignant melanoma are available from Sumner [273], Allen [6], Boyd [34] and Bulkley [44]. Cases in which a tendency toward spontaneous regression of the primary tumor after birth were made by Byrd and McGanity [47], Stewart H [271], Smith J L and Stehlin [258], Lerner et al. [153] and Riberti et al. [237]. Reports concerning an activation or stimulation of melanomas during pregnancy or the possible malignant transformation of existing naevi by hormonal influences were found, among others, by Wilbur and Hartmann [294], Pack and Scharnagel [208], Cawley [58], Miller and Pack [182], Whicker et al. [291] and Pennington [216]. Levi and Lewison [154] describe a case of spontaneous regression of metastatic melanoma in a patient undergoing estrogen substitution due to Turner syndrome. Milton et al. [183] reported spontaneous regression of metastatic melanoma in connection with estrogen treatment of prostate cancer.

The possible effects on the course of tumor growth in melanoma due to pregnancy or hormones (contraception or hormone substitution) have not been clarified. The following clinical observations and results indicate a hormonal influence on malignant melanoma:

1. melanoma occurs more often in women
2. melanoma before puberty is rare
3. women have a better prognosis than men
4. post-menopausal women have an unfavorable prognosis
5. the prognosis for multipara is better than for nullipara women
6. there are reports of post partum regression of melanoma
7. hormone receptors have been found in melanoma

[10, 27, 66, 87, 122, 152, 260, 299].

The effects of pregnancy were judged differently in clinical studies: George et al. [105], White et al. [293], Smith R S and Randall [259], Houghton et al. [126], McManamny et al. [179], Wong et al. [297] and McKie et al. [167, 168] all reported that there were no differences regarding tumor behavior in pregnant women when compared to non-pregnant women. Pack and Scharnagel [208], Reintgen et al. [233] and Slingluff et al. [257] assume an influence on the malignant transformation of existing naevi and the remission interval after excision of the primary tumor.

Women have a better prognosis than men [152, 227, 229, 250, 251, 292, 299]. This is possibly due to the location of the primary tumor. The primary tumor is more frequently found on the extremities in women and on the trunk in men.

Supposedly men have a more unfavorable prognosis due to the path then taken by metastases. In addition, a greater tumor thickness is usually found in men at the time of diagnosis. According to Shaw et al. [250], this is not due to a delay in diagnosis generated by the patient ("patient delay"), but rather due to a faster tumor growth in men, since the medical histories revealed equal intervals for both sexes.

Post-menopausal women have a more unfavorable prognosis than women prior to menopause [250] and multipara have a better prognosis than nullipara women [119, 250]. Hersey et al. [119] discussed an immunization against known fetal antigens on melanoma cells during pregnancy as a possible protective factor resulting in a more favorable prognosis. This could explain why melanoma patients with multiple pregnancies did not have different prognoses when compared to women who had not been pregnant [233, 275]. In contrary, Shiu et al. [253] found an unfavorable prognosis in pregnant or multiparous women with same-stage lymph node metastasis than for women who had never been pregnant.

Beral et al. [20], Adam et al. [4], Beral et al. [21], Holly [122] and Colbourn et al. [65] were not able to identify a clear connection between oral contraceptives and a possible influence on tumor progression in malignant melanoma.

Neifeld and Lippman [200] found receptors for steroids in the cytoplasma of melanoma cells. Chaudhuri et al. [61] clearly identified a higher incidence of cytoplasmatic steroid receptors in melanoma cells and in naevi from melanoma patients than in naevi from healthy individuals. On the contrary, Creagan et al. [71] found no increased amounts of estrogen receptors in the cytoplasma of melanoma cells.

Sadoff et al. [243] discussed a possible estrogen-dependency of malignant melanoma. According to the authors, the following points underscore their assumption:

1. the rare appearance of melanoma in sexually immature individuals
2. the important role of estrogen in melanogenesis
3. the activation of melanoma due to pregnancy
4. the remission due to anti-estrogen therapy
5. extended remission of melanoma, as found in other hormone-dependent tumors.

Rampen and Mulder [229] and Rampen [226, 227] found no differences in patients with existing metastases regarding the course of tumor progression

between pre-menopausal and post-menopausal women and between multiparous and nulliparous women. They proposed an androgen dependency of melanoma. The following observations could be explained with this hypothesis: the faster tumor growth and the resulting unfavorable prognosis in men and activation of the melanoma during pregnancy and spontaneous regression after delivery, since increased androgen levels are also found during pregnancy. However, no androgen receptors have been found in melanoma cells to date.

Börner and Goder [30], Frenkel and Klein [101] as well as Seddon et al. [249] reported cases of choroidal melanoma during pregnancy. A connection with hormones (MSH, ACTH or steroids) is considered questionable. For Hartge et al. [113], hormonal influences play a secondary role regarding the course of the tumor in choroidal melanoma. Holly et al. [123] found no influence by contraceptives or other hormone substitutes. Seddon et al. [249] could not find proof of steroid receptors.

Hormonal influences on tumor growth in malignant melanoma are still being discussed to date. A causative connection has not been proven. However, a possible association between endocrine and immunologic factors can be construed, since, for example, the number of T-helper cells is reduced during pregnancy [265].

7.4. Spontaneous regression and immunologic factors

The multiplicity of immunologic factors discussed associated with spontaneous regression of tumors is remarkable. The term "immunologic factors," using the reports available, includes the following circumstances accompanying spontaneous regression of metastatic melanoma: rabies vaccination [206], blood transfusion from a patient with prolonged remission after complete spontaneous regression [274, 277], intravenous injection of I^{131} labelled antibodies directed against melanoma cells [25, 89, 96], blood transfusion [35, 89], intralesional application of Bacillus-Calmette-Guérin (BCG) [190] or intracutaneous injection of irradiated autologous tumor cells [149, 170].

In nine of the 68 cases described immunohistologic or experimental animal examinations were performed with no firm conclusions [8, 29, 44, 124, 170, 173, 246, 274, 278]. In other reports on the topic "spontaneous regression in malignant tumors," major importance was ascribed to humoral and cellular immune mechanisms [35, 55, 66, 89, 92, 195, 196].

7.4.1. Humoral immune responses

The discovery of tumor specific transplantation antigens in animal tumor models [135, 136, 203, 220] has stimulated the search for cancer specific antigens in humans [204]. The most conclusive evidence, for the existence of a specific humoral immune response in melanoma patients was presented by Lloyd Old and colleagues in the 1970s [56, 125, 254, 255, 289]. Their approach of typing tumor cells in tissue culture with autologous serum antibodies by exhaustive absorption procedures added a new dimension to cancer serology. In melanoma and other tumor systems, as well, three classes of human cancer cell surface antigens were identified:

1. unique or individually distinct tumor antigens (class I),
2. shared tumor antigens within a specific group of tumors (class II), and
3. tumor antigens with a broader tissue distribution (class III).

Since serum antibodies identified this way generally were found to have rather low titers, an approach was developed to try to augment humoral immune responses to autologous cancer cells by autologous cancer cell vaccines or allogeneic tumor cell vaccines with a defined serologic phenotype (shared tumor antigens, class II). The molecular nature of some of these antigens identified by autologous typing has been further studied and glycoprotein antigens as well as glycolipid antigens were identified. Watanabe et al. studied a differentiation antigen, the ganglioside GD2, as one of the class II antigens identified by 'autologous typing' [290]. GD2 is found in malignant and normal cells of neuroectodermal origin. The quantitative cell surface expression in some melanomas may be increased over the levels found in normal melanocytes. The natural tolerance to this differentiation antigen may be incomplete in some patients, allowing a humoral immune response in vivo. The clinical courses of some melanoma patients in whom class I or II antigens were identified, was remarkably favorable. The pathophysiologic significance of these findings for the clinical outcome, however, remains speculative.

With the introduction of the hybridoma technology [140, 146] to the study of cancer antigens an important step forward was made in cancer serology [78]. However, the hope to identify cancer specific antigens by monoclonal antibodies has not materialized, yet. With murine and human monoclonal antibodies, as well, numerous antigen systems were identified and characterized, most of which were classified as differentiation antigens rather than tumor specific antigens, i.e. antigens unique for the individual tumor. In some instances, quantitative expression of differentiation antigens on tumor

cells was found to be remarkably different from normal cells [78, 80, 162, 221]. The disialoganglioside GD3, identified by a monoclonal antibody R24 [78, 221], for example, is highly expressed on the cell surface of many melanomas, but also detectable on melanocytes or other tissues of neuroectodermal origin [80]. The difference in quantitative expression on melanoma cells versus normal melanocytes has given a basis for the first clinical application of this GD3-specific monoclonal antibody R24 in metastatic melanoma [79, 127, 138]. Particular interest was focussed on human monoclonal antibodies as they provide direct evidence for a humoral immune response *in vivo* [300]. However, so far none of the antigen systems identified by human monoclonal antibodies were proven to be cancer specific.

In melanoma many different glycolipid and glycoprotein antigens, or epitopes on these antigens were identified over the past two decades. Much attention was focussed on glycolipid antigens as targets for immune intervention strategies with antibodies for therapy or vaccines to stimulate the immune system [60, 62, 160, 161, 238]. It is conceivable that some of the antigens identified by monoclonal antibodies are target structures *in vivo*, eliciting an immune response inducing a favorable clinical course or regression of melanoma.

7.4.2 Cellular immunity

Cell surface antigens for long were thought to be the only structures accessible to immune recognition. More recently it has become clear how intracellular antigens may be recognized as targets for an immune response. The discovery of intracellular antigen processing and presentation of antigenic peptides at the cell surface by molecules of the major histocompatibility complex family (MHC) to T lymphocytes has given a new focus to tumor immunology. Extrapolated from the study of autologous systems in cancer serology, autologous combinations of tumor and cytolytic T cells (CTL) were established by different groups over the past decades in melanoma and studied *in vitro* for antigen recognition by CTL at the clonal level [7, 118, 137, 139, 193, 281, 295]. Much of this work only became feasible with the discovery of growth factors to support the *in vitro* propagation of specific T cell clones [107].

As in patients studied by autologous typing for tumor reactive antibodies, patients were identified with strong T cell responses to autologous tumor cells *in vitro*. Some of these patients had remarkably favorable courses of disease despite metastatic spread of melanoma and surgically incomplete resection of metastases. From two patients vaccinated over extended periods of time with

autologous tumor cells, cultured in vitro and irradiated before vaccination, stable CTL clones were established [118, 137, 193]. By immunoselection studies multiple antigens were identified on autologous tumor cell clones [75, 139, 281, 295].

From two of these melanoma systems, MZ-MEL-2 and SK-MEL-29 (AV), Van der Bruggen and colleagues recently cloned two genes coding for antigens recognized by cytolytic T cell (CTL) clones in association with MHC class I products. The first gene, MAGE-1, codes for one of these antigens, MZ2-E, recognized on melanoma cells in association with HLA-A1 [282]. The other gene coding for a CTL defined antigen was recently identified by Brichard and colleagues as the tyrosinase gene [38].

While MAGE-1 directs the expression of an antigen MZ2-E which is recognized by CTL in association with HLA-A1, the tyrosinase gene product is recognized by CTL in association with HLA-A2. Since MAGE-1 is not expressed in most normal tissues tested, the antigen MZ2-E may become a target for immunotherapy in melanoma patients expressing MAGE-1 in association with HLA-A1. The differentiation antigen tyrosinase apparently may be recognized by the immune system in vivo due to incomplete tolerance to this antigen. It is conceivable that further studies of how to augment an immune response to these antigens in selected patients will open new perspectives for cancer immunotherapy. The identification of MAGE-1 and the tyrosinase gene coding for CTL defined antigens in melanoma constitutes a new molecular basis for the understanding of immune responses to cancer cells including spontaneous regression of melanoma.

It may well be that heat shock proteins are identified in the near future as another molecular system to present cancer antigens to the human immune system, and in particular to CTL [102, 266]. On the other hand, triggering of a tumor directed T cell repertoire mediated by bacterial 'superantigens' may constitute a new basis for the understanding of 'spontaneous' melanoma regression in association with septic episodes secondary to bacterial infections.

7.4.3. Non-specific immunity

The et al. [278] found phagocytized melanoma cells in smears of spontaneously regressed cutaneous metastases. Falk et al. [90] observed no increased cellular immunity during treatment with BCG and also assumed a non-specific immune mechanism mediated by macrophages. Cameron et al. [53] documented cytotoxic

macrophages directed against autologous and allogenic tumor cells in carcinoma patients. Anstey et al. [8] found increased values for natural killer cells.

Summary: Immunologic processes at humoral and cellular levels are the most important factors for spontaneous regression of metastatic malignant melanoma as described already by Boyd [35]. The destruction of individual malignant cells prior to development of the tumor and tumor resistance through non-specific and immunologic mechanisms were also discussed. These two concepts are presently termed "immunosurveillance" and "tumor protective immunity" [48]. Hellström et al. [116] and Hellström and Hellström [117] were able to identify a humoral and cellular response to melanoma cells. Lymphocyte infiltrates in regression zones were considered a correlate to cellular immunity [252].

Lewis et al. [157] found increased activity in the lymph follicle with a concomitant increase in B-lymphocytes and antibodies against cytoplasmic antigens during tumor progression. Simultaneously, a decrease of histiocytes and monocytes, as well as antibodies against membrane antigens, was observed. A decrease of anti-membrane-antibodies was described parallel to an increase of anti-antibodies, antigen-antibody complexes and free antigen. The non-specific and specific immune mechanisms could be stimulated through external and internal stimuli. Boyd [35] assumed an improved immune response through the surgical elimination of "antigen." A correlation between immunostimulation by the above listed factors and resulting spontaneous regression of metastatic melanoma can only be postulated.

Halo naevus, vitiligo, metastatic melanoma with unknown primary tumor or also dermatomyositis were given as examples of conditions with immunologic antecedents in connection with malignant melanoma [89, 197, 288].

7.5. Spontaneous regression of unknown etiology

Disregarding surgical procedures or radiation treatment, 35 cases were found in which no apparent cause of spontaneous regression of metastatic malignant melanoma could be identified [8, 19, 29, 34, 41, 51, 57, 82, 89, 96, 111, 128, 154, 155, 164, 169, 172, 173, 181, 183, 189, 197, 202, 205, 217, 241, 246, 272, 278, 284, 298].

In addition to the possible triggering factors listed above, an influence by inhibition of tyrosinase-catalyzed metabolism was postulated. An inhibition of melanoma growth could be achieved by reducing the amounts of tyrosin or phenylalanine in the diet, as well as oral doses of penicillamine, which as an inhibitor of the copper-dependent protein tyrosinase, reduces the vital oxidative tyrosinase-dependent processes necessary for the survival of the melanoma cell [76, 77]. Ramirez-Bosca et al. [223] were able to document an *in vitro* increase in tyrosinase activity of melanoma cells through the application of L-DOPA and L-Tyrosine. The tyrosinase activity in progressing growth increased by a factor of 34 in partial tumor regression and by a factor of 400 in complete tumor regression. These results were obtained in animal experiments however [147]. Wagner et al. [287] delineated further presumed connections to melanoma growth which include lipids, proteins, vitamins or trace elements.

An inhibition of melanoma cells by intracellular factors such as lysosomes, enzymes (i.e. lysozyme) or chalone have also been discussed [24, 45, 66, 187]. Ghadially [106] observed spontaneous regression of induced carcinoma in hamsters following chronic trauma. Further possible triggering factors of spontaneous regression could exist in connection with a genetic predisposition or the elimination of applicable melanoma-specific carcinogens which have yet to be fully explained [197].

Everson and Cole [89] also raised the possibility of a faulty diagnosis regarding malignancy. Presently, diagnosis of melanoma has been greatly improved utilizing, for example, monoclonal antibodies. Regrettably, according to the reports included in this monograph, samples were rarely taken to substantiate the diagnosis of spontaneous regression. Van der Esch et al. [283] were able to prove, however, that the increasing incidence of malignant melanoma is not due to improved or more reliable diagnostic techniques.

8. SUMMARY

The designation as "the most incalculable of all tumors" is due to the unpredictable biological variety of malignant melanoma, which includes phases of spontaneous regression to fulminate aggression. Eleven percent of all the complete spontaneous regressions of malignant tumors were observed in melanoma, which represent only one percent of all carcinomas. Cases of spontaneous regression of malignant melanoma have been described for approximately 130 years. The study of this phenomenon is based primarily on the analysis of factors associated with spontaneous regression.

The depigmentation that is pathognomic for halo naevi and vitiligo is also found in cases of spontaneous regression of malignant melanoma. Lymphocyte infiltrations and antibody development have been implicated as possible causes. Antibodies directed against melanoma cells have been described in patients with halo nevi or vitiligo without proof of melanoma. The appearance of vitiligo and/or halo naevi during the course of melanoma supposedly indicates a more favorable prognosis.

Metastatic malignant melanoma of unknown primary tumor is, depending on the author, found in up to 15% of all metastatic melanoma. Possible causes include "de-novo" development of the primary tumor in intestinal lymph vessels or lymph nodes, localization of the primary tumor in visceral organs, destruction of the primary tumor through incidental trauma or inadequate treatment, absence of differential characteristics of benign lesions, inadequate diagnostic procedures and complete regression of the primary tumor. The complete spontaneous regression of the primary tumor is presently considered the probable cause of metastatic melanoma of unknown primary. The histologic presentation of regression includes lymphocytic infiltrates, reactive vascular proliferation and fibrosis. The prognosis and treatment of metastatic malignant melanoma with unknown primary does not differ from those for melanoma with known primary tumor.

Depending on the author, regression zones within the primary tumor were found in 20 - 100%. Clinical presentation includes, atrophy, scarring, depigmentation and complete regression. Histologic findings evince mainly lymphocytes, melanophages, neovascularization and fibrosis. Lymphocyte infiltrates were found in the radial growth phase of the primary tumor and in the vertical spread zone ("tumor infiltrating lymphocytes-TIL"). The factors responsible for the differentiation and role of both inflammation zones have

not yet been clarified. Complete regression of the primary tumor during simultaneous progression of lymph node metastases is possible. This may be due to altered antigen characteristics of the individual melanoma cells as well as the development of new melanoma cell clones with altered antigen spectrums. Regression zones within the primary tumor have no influence on the prognosis.

Regressive changes in choroidal melanoma were divided into localized (cellular and lytic necrosis) and diffuse (infarct- or coagulation necrosis) processes. Differential diagnostic considerations include, other than the spontaneous regression of choroidal melanoma, exudative retinitis, adenoma of the retina or hematoma. Histologically, lymphocyte infiltration, plasma cells, melanophages, fibrosis, proliferation of the vascular endothelium, thrombocyte aggregation and calcification were observed whose presence did not influence the prognosis. In the analysis of seven reported cases, no associated factors were identified.

Sixty reports of complete spontaneous regression of the primary tumor were found and the possible accompanying factors examined. Prior trauma was observed five times, infection three times and inadequate treatment five times. Pregnancy was associated with three cases. Previous hemorrhage of the primary tumor was found in approximately 25% of the cases involving women, and in approximately 20% of the cases involving men. The complete spontaneous regression of the primary tumor had no influence on the prognosis. The possible connection between complete spontaneous regression of the primary tumor and metastatic melanoma with unknown primary tumor was noted. The medical history must specify a changing skin lesion and proof of a suspicious skin lesion in order to document cases of spontaneous regression of the primary tumor. The location of suspicious cutaneous lesions and transforming skin lesion follow the known distribution pattern. Specific pathohistologic findings have not yet been irrevocably identified. Lymphocyte infiltration, melanophages, neovascularization and fibrosis provide only indications, but not proof of occult disease.

In connection with a possible spontaneous regression of the metastatic melanoma, proof of a distinct malignancy of the respective lesion must be documented. The spontaneous regression of pulmonary metastases, which are solely supported by X-rays, are questionable. The histologic criteria for regressed lesions are the same as those for spontaneous regression of the primary tumor.

A total of 68 case reports were analyzed. Spontaneous regression of skin metastases was found in 28 cases and of lymph node metastases in 21 cases. Spontaneous regression of visceral metastases occurred 19 times, and multiple organs were often affected. Pulmonary metastases regressed in nine cases, cerebral metastases in seven, liver metastases in seven, skeletal metastases in three, intestinal metastases in three cases and splenic metastases in one case. Histologic proof of regressed tumors was documented four times (three times for intestinal metastases and once for liver metastases). The frequency of factors found to be associated with spontaneous regression include operative procedures 100% (68 cases), febrile infections in approximately 30% (21 cases), radiation treatment in approximately 16% (11 cases), general immunologic factors in approximately 19% (13 cases) and, with the exception of operative measures, no accompanying factors were found in approximately 53% (35 cases). Pregnancy was discussed as a possible cause in four reports. A relationship between spontaneous regression and other conditions or medications could not be determined with the exception of Xeroderma pigmentosum. This condition was found four times in conjunction with spontaneous regression of metastatic melanoma.

Current beliefs assume an immunologic etiology of spontaneous tumor regression whereby the triggering factors remain obscure and unexplained. Many authors regard cytotoxic macrophages and melanophages evidence of non-specific, lymphocyte infiltrates evidence of cellular and plasma cells evidence of a humoral immune processes. The presence of lymphocyte infiltrates or plasma cells is not melanoma-specific and can be observed in any malignant tumor or inflammatory reaction. The trigger for possible host resistance based on an immune reaction can be construed from many factors connected with spontaneous regression.

The spontaneous regression of the primary tumor during simultaneous progression of metastases is considered to be evidence of the development of different melanoma cell clones with altered antigen spectrums [276]. Local regression zones, such as those often found in primary tumors, are probably due to phagocytosis of immature melanocytes. The mature melanocytes are not affected and the tumor presents histologically as a "melanoma with local regression zones" with no recognizable vertical growth phase [242].

In this review an attempt has been made to describe the problems in defining "spontaneous regression" and the varying descriptions found in world literature as well as the difficulties in supplying histologic proof of complete

spontaneous regression. The factors associated with spontaneous regression can only allude to the possible mechanisms involved. The variability of the antigen spectrum of an individual melanoma cell must also be considered. Further concepts for the prevention and treatment of malignant melanoma can be conceived through an improved understanding of the phenomenon of spontaneous regression [201].

9. LITERATURE

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The authors gratefully acknowledge the help of Helen Coley Nauts, D. Sc., Hon., for proof-reading and constructive suggestions, as well as Alex Knuth, M.D., Eberhard Günther, M.D., for revising the immunological part of the manuscript, and John Buzanoski, M.D., for the skillful translation.

Many thanks go to the Cancer Research Institute, New York, for making this publication possible.

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