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# Some Effects of Mechanical Trauma on the Development of Primary Cancers and Their Metastases

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**ABSTRACT:** Posttraumatic inflammation and, much less commonly, mechanical trauma itself may affect the clinical course of cancer. There is no evidence that a single incident of trauma can cause cancer, although posttraumatic chronic inflammation may be associated with carcinogenesis. In patients with cancer at the time of trauma, inflammation and repair processes may inhibit or enhance cancer growth, and trauma and its sequelae may increase the *rates* of invasion and dissemination.

**KEYWORDS:** pathology and biology, cancer, injuries, carcinogenesis, invasion, mechanical trauma, metastasis

The effect of mechanical trauma on the cancer process is a matter of considerable medicolegal and forensic science interest. Recent advances in cancer research not only provide new data on these effects and their underlying mechanisms, but also permit a critical examination of older studies. At present, some questions about the relationships between trauma and cancer permit definitive answers; other questions do not, and can be answered only in terms of feasibility as distinct from probability. In these cases, it is mandatory for the reviewer to provide an outline of the background on which the assessments of feasibility are based.

The clinical course of cancer is governed both by the biology of the primary lesion and the development of metastases. With advances in surgical and parasurgical techniques, which permit the successful resection of many different primary cancers, metastasis has become a dominant factor in the treatment and prognosis of malignant disease. Therefore, in discussing the influence of mechanical trauma on the cancer process as a whole, attention must be given to people with or without cancer at the time and, in the former, the effects on both the development of primary lesions, and the interrelated processes of invasion and metastasis. An adequate bibliography is given to document this wide clinico-pathologic spectrum and to provide a meaningful guide to the vast multidisciplinary literature.

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**Mechanical Trauma and Carcinogenesis**

Until now, the major focus in the forensic science literature has been on the role of mechanical injury in *causing* cancer [*1–11*].

Although physical trauma caused by radiation and many chemical agents is causally related to carcinogenesis, mechanical trauma appears not to be directly related. This view was very well summarized by Stewart [*3*]: "Attempts to rely on single trauma to explain cancer depend on the exercise of primitive forms of reasoning. . . . The normal wear and tear of life induces a multiplicity of traumas which are rarely noted or quickly forgotten until the time arises to make something out of them." Although much current emphasis is on the medicolegal implications of "to make something," it should be remembered that anecdotal associations are common among patients with cancer and with no legal plans.

Many physicians will recall, for example, women who were quite convinced that their breast cancers were caused by antecedent trauma, regardless of the precise temporal and spatial relationships of the trauma and cancer sites. Severe mechanical trauma to the breast may result in traumatic fat necrosis with hematoma, affecting the superficial subcutaneous tissues rather than the parenchyma itself. After 7 to 14 days a local induration develops, which together with skin-tethering, may clinically resemble carcinoma. However, the short elapsed time between the injury and the appearance of the lesion exclude a carcinogenic process, and the benign nature of the lesion, may be verified by histologic examination if necessary. Rare benign tumors have also been associated with antecedent trauma [*12*].

It is often difficult to isolate the effects of mechanical trauma from other factors in relation to carcinogenesis. For example, the high incidence of melanomas on the soles of barefooted, Bantu Africans was attributed to mechanical trauma [*13*]; however, later analysis revealed that the incidence of this cancer was approximately equally high among shoe-wearing, urbanized Bantus [*14*].

Although mechanical trauma is not considered to be direct initiator of cancer, there has been the suggestion that it may act as a promoter [*15*]. This hypothetical role of trauma as a promoter in *"at-risk"* tissues is supported by the rare development of tumors at wound sites [*16–21*]; however, there is no unequivocal evidence for cancer being caused by a single traumatic event [*22*], and only rarely have cancers been induced in animals by repetitive wounding [*23*]. In contrast to these (negative) direct effects of trauma, there are many observations starting with Margolin in 1828, indicating that cancer can occur rarely in scars, ulcers, and sinuses [*24*]. Where chronic inflammation or its sequelae occur as a result of mechanical trauma, then trauma can be said to play a role in carcinogenesis. However, it must be emphasized that when cancers, particularly squamous cell carcinomas, do develop, it is only after decades, and that the rarity of the event suggests a multifactorial process. In addition, the incidence of chronic inflammation associated with persistent infection has become progressively infrequent with advances in therapy.

It is also of interest that the process of wound-healing is associated with the release of growth factors, one of which, so-called platelet-derived growth factor is homologous to the c-sis protooncogene product [*25*]; wounding also activates the arachidonate cascade [*26*], generates oxygen-derived radicals [*27*], and activates protein kinase C. All of these factors *may* play a role in the carcinogenic process. The oxygen-derived radicals have been shown to cause cytogenetic damage analogous to both initiation [*28*] and promotion [*29*], and as leukocytes are a major source of the oxygen metabolites, there is the possibility, as yet unproven, that this is the mechanism underlying a causal relationship between chronic inflammation and cancer. In all of these cases, the etiologic factor is chronic inflammation consequent upon trauma, not the mechanical trauma itself. Furthermore, although it is difficult to document numerically and on an acceptable time

base, the vast majority of people with episodic chronic inflammatory lesions do not appear to develop cancer, unless additional factors are operative.

## Mechanical Trauma and Preexisting Cancer

It is generally accepted that mechanical trauma may serve to draw attention to a preexisting, undiagnosed cancer at the same or a nearby site. This doubtless accounts for many of the anecdotal accounts of the association between trauma and cancer, which were confused with causal relationships.

The inflammatory and reparative sequelae of mechanical trauma may act directly on established cancers, to either (a) inhibit or (b) enhance growth.

### *Growth Inhibition*

It has been known for over 100 years that bacterial infection may be associated with tumor regression. It is now appreciated that this effect is not due to a direct action of the bacteria on the cancer cells, but is an indirect action, mediated by host cells as part of a nonspecific inflammatory response [*30*].

Examples of the effects of inflammation on cancer growth inhibition are provided by intravesical or intralesional *bacillus Calmette-Guérin* (BCG) therapy for superficial bladder tumors and cutaneous malignant melanomas, respectively. Preliminary data suggested that over the short term, BCG prolonged the disease-free interval over transurethral resection, without significantly altering the long-term natural history of the disease. Although six weeks of postoperative intravesical BCG reduced tumor recurrence and disease progression, in a group of patients in which all were expected to have recurrent tumors and more than 50% progression rates, the long-term results showed that 50% of patients relapsed and 30% progressed [*31*]. Local regression of cutaneous melanomas has also been reported following intralesional injections of BCG [*32*]. Regardless of the therapeutic use of "inflammo-therapy," these and other results [*33*] demonstrate that a local inflammatory response may cause complete or partial regression of a cancer. By extrapolation, a severe inflammatory response following mechanical trauma could well do the same.

### *Growth Enhancement*

The inflammation which follows mechanical trauma is itself followed by regeneration and repair and involves cell proliferation. In addition to acting on normal tissues, the various inflammatory agents and products might also act on cancer cells. The enhancement of tumor growth in acutely inflamed tissues in rats [*34*], and by abscesses in mice [*35*] is in accord with this suggestion. In addition, substances normally regarded as inducers of inflammation-associated tumor inhibition, including Corynebacterium parvum [*36*], BCG [*37*], and endotoxin [*38*], may also stimulate tumor growth.

Assuming that generalizations can be made about posttraumatic inflammation, the evidence indicates that a localized response is more likely to inhibit than enhance growth of a preexisting primary tumor. However, if local infection follows the trauma, and this may be the case in patients immunocompromised by their disease or its treatment or both, enhancement of tumor growth may occur. Thus, in individual cases it is impossible to make ab initio predictions of the direction of the response to trauma and extremely difficult to measure its degree without stringent controls, which are not usually available. Taken separately, both trauma and cancer may decrease the quality of life and survival, at present, it is not possible to generalize on the effects of trauma/cancer interactions on these parameters.

Stahl and Mathe [*30*] have pointed out that the stage of tumor development at which cancer cells meet with an inflammatory process may well be critical in determining whether the resulting interactions favor growth inhibition or enhancement. However, they consider that, in general, the inflammatory response will only favor the host/tumor equilibrium in the direction to which it already points.

## The Metastatic Process

Metastasis has been reviewed in depth elsewhere [*39*] and will be covered here only to identify potential trauma-sensitive steps, as summarized in Fig. 1.

The first steps in metastasis culminate with the entry of cancer cells into various dissemination routes, which may be the bloodstream, the lymphatic system, or various body cavities. On the one hand, entry may involve breaching basement membranes as part of an invasive process. On the other hand, cancer cells, particularly but not exclusively in sarcomas, may be shed directly into vascular clefts which they line. Between these two extremes, the point of entry may be via the imperfect, fenestrated neovasculature of the tumor itself or through venules containing little or no basement membranes. Because the lymphatic saccules and smaller lymphatic vessels also do not possess basement membrane, their degradation or breaching or both is not a prerequisite for (lymphatic) intravasation.

The next steps involve the arrest of metastasizing cells in various target organs or sites; arrest culminates in the death of most cells delivered by rapid or slow processes [*40*]. Surviving cancer cells within the microvasculature eventually extravasate and, if they are to grow beyond micrometastatic diameter (>2 mm), acquire a neovasculature. The metastases may then metastasize, thereby repeating the whole process, but from a different anatomic site.

## Mechanical Trauma and Metastasis

The entry of cancer cells into lymphatic and blood vessels may be enhanced by mechanical trauma, which may occur from natural causes associated with increasing intra-

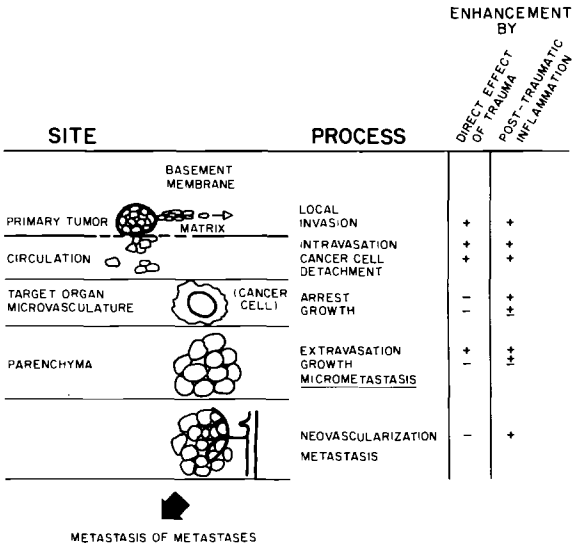


FIG. 1—*Summary of effects of trauma and posttraumatic inflammation on steps of the metastatic process.*

tumoral pressures, from accidents, or as a consequent of traumatic diagnostic and surgical procedures [*41*].

*Surgical Trauma and Metastasis*

There has been a long-standing realization that surgical trauma can promote the dissemination of cancer [*42–44*], and it was demonstrated in tumor-bearing mice that massage of their cancers could enhance metastasis [*45,46*]. The recognition of surgical trauma as a dissemination-promoting agent has of course led to improvements in surgical techniques [*41,47,48*]. Following accidental mechanical trauma, fragments of normal tissues may also be embolized, including the liver [*49*], cerebral cortex [*50*], and fat [*51*], and trauma to tumors has been directly associated with their dissemination [*52,53*].

Healing surgical wounds may provide a favorable environment for the growth of metastatic tumors. Thus, an increased incidence of tumors was seen in organs subjected to laser and conventional surgical procedures in both tumor-bearing mice, and in those receiving postsurgical, intravenous injections of cancer cells [*54*]. The former could be partially due to accelerated growth of previously seeded micrometastases, and the latter to enhanced seeding of circulating cancer cells or their accelerated growth or to both.

Other evidence indicating enhancement of metastasis by surgical trauma comes from studies of the effects of colonic anastomoses on the localization and growth of MC 28 sarcoma cells injected via the left ventricle, in the rat [*55*]. Enhancement of cancer cell arrest and survival occurred maximally from two to eight days after forming an anastomosis, with a calculated, approximate 1000-fold increase in the chances of an arriving MC 28 cancer cell giving rise to a tumor. This observation may be relevant not only to metastasis, but also to recurrence as a result of cancer cells "spilled" during surgery [*56,57*].

*Biopsies and Metastasis*

Indirect evidence of the effects of mechanical trauma on invasion and metastasis comes from studies of incisional and excisional biopsies. In the former, small pieces of tissue are removed from a tumor, whereas in excisional biopsies, the whole apparent tumor is removed, often with little margin of "normal" tissue.

It is reasonably expected that when large lesions are removed by excisional biopsy, there is the risk that new tissue planes may be opened up, leading to contamination of new sites with cancer fragments. In addition, the presence of large hematomas as a consequence of biopsy is considered to lead to local spread of disease [*41,58*]. Similar considerations apply to other traumatic surgical procedures, particularly curettage. Although attempts have been made to assess the effects of biopsy on dissemination, the results require comment. Thus, in 1961, Cole wrote, "It is difficult to find any conclusive evidence concerning dangers of biopsy in human beings, but it is our impression that biopsies in certain tumors are harmless, whereas in many types of tumors they may result in dissemination of the tumor. There is one tumor in which there appears to be complete agreement that biopsy is harmful; this is the malignant melanoma. So many surgeons and pathologists have observed wide and vicious dissemination of a melanoma following an incisional biopsy or cauterization that there can scarcely be any doubt about this danger."

In *apparent* contradiction of Cole, others [*59,60*] observed no statistically significant, deleterious effects of biopsy on the survival of patients with melanomas. However, the major purpose of these two studies was to determine in cases in which the diagnosis was in doubt as to whether or not biopsy, followed after a few days by surgical excision where indicated, put patients at increased risk compared with those on whom definitive surgery

was performed immediately. Thus, in the present context of mechanical trauma which is not followed by immediate cancer resection, increased risk of dissemination is implied by such generally accepted statements as "the surgeon should avoid cutting directly into suspected tumor if it is not necessary to do so" [*58*].

*Additional Data*

In quantitative experiments [*61*], a variety of B16 melanoma cells with different invasive and metastatic potentials were injected intramuscularly into the thighs of mice. They were reproducibly traumatized by drawing a miniature wheelbarrow back and forth over the tumor five times on each of eight days, beginning seven days after implantation. After another fourteen days, the mice were killed and autopsied. Wheelbarrow treatment of tumors from two poorly metastatic cell lines produced no change in metastasis and no changes in the numbers of cancer cells in the blood, as detected by bioassay. In contrast, massage increased metastasis from tumors derived from more invasive and metastatic melanoma sublines, and in one of these sublines, an increase in the number of circulating cancer cells. Experiments in which different cancer cells were injected directly into systemic veins revealed that the differential effects of massage were related to cancer cell intravasation, not subsequent events. Taken together, the results of these experiments indicate that mechanical trauma increases the *rate* at which cancer cells gain access to the bloodstream, but if entry would not have occurred "naturally," it would not be enhanced by trauma. These results seem in accord with most of the clinical data. From a medicolegal viewpoint, it is exceptionally difficult to estimate acceleration of a process when its natural rate of progression is not known in individual cases.

**Posttraumatic Inflammation and Metastasis**

Inflammation is the normal tissue response to injury, regardless of its type. Therefore, in assessing the role of mechanical trauma on metastasis, one must take into account the effects of inflammation.

Immediately following trauma, there is vasoconstriction. Next, there is local adhesion to the endothelium of leukocytes, which, when activated, produce endothelial injury and matrix degradation, resulting in increased vascular permeability manifest as edema [*62*] and extravasation of blood cells. Initially, neutrophil polymorphs are the predominant leukocytes, but after several days, in the absence of further inflammatory stimuli, the proportions of monocytoid cells gradually increase.

The underlying mechanisms of leukocyte-induced injury are the release of granule-associated enzymes [*63*] and probably the generation of oxygen radicals [*64,65*], although radical-independent pathways also operate [*66*].

*Invasion*

Basement membranes and the interstitial stroma serve to compartmentalise tumors from normal tissues. The first step in invasion by carcinomas is the penetration of basement membrane, which characterizes progression from in situ to invasive carcinomas. To gain access to lymphatic and blood vessels, cancer cells may first have to invade the interstitium, and to enter and leave blood vessels, they may have to penetrate subendothelial basement membrane [*67*]. The relationship between penetration and matrix degradation may be obscured by resynthesis of matrix components by both cancer and noncancer cells. All of these processes may be initiated or promoted or both by mechanical trauma.

The various mechanisms underlying invasion include breaching of the various barriers

to cancer cell and tissue expansion by indirect mechanical trauma, by enzymatic degradation [*67,68*], by interstitial edema [*69*], combined in some cases with active locomotion of cancer cells [*70–72*] and in some cases with active expansion of tumors along a pathway of diminished resistance [*73*].

*Inflammation and Invasion*

Although cancer cells themselves produce enzymes which degrade the various barriers to invasion, it is important in the present context that cells associated with the inflammatory response can also produce enzymes and other agents, including oxygen-derived radicals, which promote and enhance barrier breakdown. The most dramatic examples of enzymatic degradation are seen in the rheumatic diseases [*74*], and the production of relevant enzymes has been documented in neutrophil polymorphs [*75–77*] and macrophages [*78*], and by interactions involving macrophages [*79*] and lymphocytes and fibroblasts [*74*]. Proteinases having a role in invasion have been described in a variety of noncancer cells during inflammatory and reparative processes [*80*]; the invasive capacities of neutrophil polymorphs have long been recognized [*81*], and cancer cells have been observed passing through defects in vessel walls, previously caused by migrating leukocytes [*82*].

It is noteworthy that although cartilage is particularly resistant to invasion by cancer cells [*83*], it may occur in the presence of inflammation, associated with the cartilage-degrading enzymes of leukocytes [*74,84*]. This is particularly relevant to cancers in sites commonly subject to chronic inflammation, such as the nasal mucosa, where involvement and destruction of cartilage by advanced carcinomas is not uncommon. Osteosarcomas may penetrate epiphyseal cartilage as part of their natural history [*85*], and this also appears to be enhanced by inflammation. Invasion of human lung carcinoma into bronchial cartilage, which may occur in as many as 25% of cases, is nonetheless extremely limited. In these cases, immunohistologic studies revealed no apparent "participation of inflammatory cells in tumorous degradation of cartilage" [*86*]. However, in the present context, it would be more relevant to compare the extent of invasion/degradation of cartilage in the presence and absence of inflammatory cells.

*Cancer Cell Arrest*

Most of the cancer cells arrested within the microcirculation of target organs are killed by a variety of rapid and slow processes [*40*], and the same appears true for cells delivered via the lymphatic system to lymph nodes [*87,88*]. When comparing *different* organs, there is no simple direct mathematical relationship between cancer cell delivery and arrest, and metastasis, as a result of "seed-and-soil" effects [*89–92*]. However, regardless of the mechanisms underlying differential organ-specific degrees of *"metastatic inefficiency"* [*93*], the fact remains that the greater the number of cancer cells delivered to an organ, the greater the chance of metastasis in that organ. Against this background, the effects of mechanical trauma on cancer cell arrest-related events can be examined.

*Arrest and Trauma*

There are many reports that trauma is associated with enhanced metastasis in a number of animal experiments (for example, Refs *94–100*). In most of these, trauma-enhanced metastasis has been attributed to increased adhesion and retention of cancer cells because of disturbed microcirculation and associated blood coagulation. Broadly speaking, the involvement of coagulation is implicated by abrogation of the trauma-induced increases in metastasis by anticoagulants and thrombocytopenia. However, in untraumatized animals, a variety of anticoagulants produced no change in the arrest patterns of intrave-

nously injected cancer cells [*101*]. Trauma to an organ may be followed by hemorrhage and inflammatory change, the hallmark of which is increased vascular permeability with local mobilization of platelets. However, while it is *feasible* that these factors play a part in increasing the arrest of circulating cancer cells both locally and at distant sites as a result of mechanical trauma, there is no direct evidence in support of this and similar hypotheses.

### *Arrest and Inflammation*

In mice with acute inflammation of the lungs, more circulating cancer cells were arrested and more pulmonary tumors developed than in controls. In mice with chronic inflammation, the results were not so clear cut; depending on the agent used to induce inflammation, there was either reduced arrest or no change, with either fewer or greatly increased numbers of pulmonary tumors, respectively [*102*]. That these metastasis-related changes were inflammation-induced, was indicated by their abrogation by a synthetic, anti-inflammatory glucocorticoid [*103*]. Other experiments have shown that damage to pulmonary endothelial cells caused by leukocyte activation enhances cancer cell arrest and tumor development [*104,105*] and that this enhancement was lost after endothelial repair.

### *Cancer Cell Migration*

In addition to the general enhancement of metastasis by systemic inflammatory processes [*34,102*], local enhancement of metastasis may result from the stimulated migration of cancer cells to sites of inflammation [*106,107*], in peritonitis [*108*] and in pneumonitis [*109*]. The chemattractants appear to be, at least in part, breakdown products of the C5a component of complement by leukocyte-derived lysosomal enzymes [*107*].

Breakdown products from leukocyte-degraded collagen are also chemotactic for cancer cells [*110,111*], and exposure to collagenase may directly enhance cancer cell motility [*112*].

### *Angiogenesis*

A small primary or metastatic tumor derives its nutrition by diffusion; further growth is dependent on the tumor acquiring its own blood supply or neovasculature, by proliferation or angiogenesis from the microvasculature of the host [*113–116*]. Without neovascularization, it seems likely that small tumors will remain in a clinically dormant state, and, conversely, events enhancing angiogenesis will promote or accelerate their development, or both. In addition to growth promotion, the tumor neovasculature provides a convenient portal of entry into the circulation for metastasizing cancer cells.

During angiogenesis, endothelial cells from nearby capillaries or venules form sprouts directed toward the source of angiogenic stimulus. By a process of fusion, matrix dissolution and remodeling, the neovascular elements envelope and invade the tumor [*117*]. At first, it was proposed that angiogenesis was stimulated by a *tumor* angiogenesis factor, but it has subsequently been shown that, in addition to tumors, angiogenesis may be stimulated by inflammation, wound repair and the chronic inflammatory response [*118*]. Cells providing angiogenic stimuli include neutrophils [*119*], lymphocytes [*120*], macrophages [*121*], and mast cells [*122*]. Factors affecting tissue degradation and endothelial cell migration will coincidently promote angiogenesis.

As cancer cells themselves secrete angiogenic factors, the inflammatory and reparatory sequelae of trauma are expected to enhance the process of tumor neovascularization, and, once again, acceleration rather than initiation is expected.

## Conclusions

### *General*

Trauma may have direct effects on the clinical course of cancer, but effects that do occur are most likely to be indirect and due to posttraumatic inflammation. Direct or indirect effects on invasion and metastasis are probably not all or none, but rather indicate acceleration of processes that would have taken place without trauma. The assessment of the degree of acceleration is often difficult or impossible and can doubtless form the basis for medicolegal argument.

### *Specific*

1. There is no evidence that a single incident of mechanical trauma can directly cause cancer. Among other considerations, such evidence would require an appropriately long latent period (10+ years) for carcinogenesis.
2. A chronic inflammatory process occurring at the site of previous trauma may rarely be one of a number of factors associated with carcinogenesis.
3. Posttraumatic inflammation and repair may on the one hand inhibit and on the other hand enhance the growth of all or part of a preexisting lesion.
4. Trauma and posttraumatic inflammation may directly enhance the invasion and dissemination of cancer. In general, although the inflammatory response kills many cancer cells, it may also promote invasion and metastasis among the survivors.
5. The posttraumatic inflammatory response may promote the growth of micrometastases by enhancing their neovascularization.

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