

CRITERIA REQUIRED TO PROVE CAUSATION OF OCCUPATIONAL OR TRAUMATIC TUMORS

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THE diagnosis of a tumor¹ should not be accepted without incontrovertible proof of its nature obtained either by pathologic examination of the entire specimen when removed,² or by biopsy.³ So many possibilities for error exist in the diagnosis of a tumor by clinical means, even when supported by radiologic evidence, that pathologic proof should be insisted upon in addition. Not only is accurate diagnosis and classification of a tumor impossible without microscopic examination of a section obtained from the substance of the tumor, but also microscopic examination gives important information as to probable rate of growth.

Since the causation of tumors is not yet clearly understood, it is inevitable that a great mass of speculation should have been built up on this subject. In general, it can be said that there is no one cause for cancer, any more than there is one cause for inflammatory diseases, but rather there are a number of causes, some known, some unknown, which produce different types of tumor. Some tumors are clearly congenital, and some are related to endocrine disturbances;⁴ others are due to the action of specific chemical or physical agents on the body tissues,⁵ while others are of unknown origin.⁶ We have learned from observation of cases in human

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¹ The term tumor as generally used indicates a new growth of cells which is independent of the normal restraint exerted by the body on its tissues, but it may also be used very broadly to indicate any swelling regardless of its nature. However, in the medical sense, usually a new growth or neoplasm is meant. In general, tumors are classified according to the type of cell which they tend to reproduce.

² That is, removed from the body by surgical excision.

³ Biopsy implies the sampling of an organ or tissue, usually the site of some disease process, and its examination by suitable means, such as microscopic study, to permit the establishment of an accurate diagnosis.

⁴ For example, breast tumors may be associated with disorders of the ovaries. Endocrine disturbances are abnormalities of secretion of one or more of the ductless glands, such as the thyroid, the pituitary, or the adrenal, which lead to abnormal conditions of the body.

⁵ For example, cancer may be produced by the action of radium. By body tissues are meant the various cellular components of the body substances which they form, and the fluids which bathe them.

⁶ No clue exists as to the reason for development of certain tumors. Among those tumors which arise from unknown causes are cancer of the large intestine and cancer of the kidney.

beings and from experiments in animals that the response to a given agent acting in a given degree is not necessarily uniform, that there are individual variations, that even in the case of highly purified hydrocarbons which have been shown to produce cancer in experimental animals, a dose that will produce a cancer in one animal may not produce it in another.⁷

OCCUPATIONAL TUMORS

Occupational tumors are those neoplasms that arise as a result of contact with some exogenous agent,⁸ physical or chemical, brought about by some phase of the regular work of the individual concerned, that leads to an independent proliferation of cells.

The soundest criterion for the occupational character of a neoplasm is the proof of its occurrence among the workers of a given industry significantly more frequently than in the general population of comparable age and sex.

As secondary proof of the occupational character of a tumor, the production of tumors in experimental animals by the suspected agent is of great value, but it is not a prime requisite. It must be remembered that the susceptibility to various carcinogenic agents⁹ of different animal species and even of individuals within the same species is not at all uniform, and it is quite possible that a concentration of a given substance which is carcinogenic for man may be incapable of producing a tumor in the experimental animal. However, at times the statistical evidence relating to the incidence of a certain type of tumor in a certain occupation may be inconclusive, and here the experimental reproduction of the tumor is of great value. In addition, of course, successful production of the tumors in animals greatly facilitates the development of preventive measures.

So far, much of the information as to the incidence of cancer in the general population is derived from mortality statistics, which not only leave something to be desired from the standpoint of accuracy of diagnosis, on the one hand, but give rather indefinite information as to the morbidity of the disease, on the other hand. From the occupational standpoint, one is concerned primarily with cancer morbidity rather than with cancer mortality. It is to be hoped that with the passage of time an adequate mass of data as to the number of cancer cases in the general population may become available.

⁷ Hartwell, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*. U.S. Public Health Service (1941).

⁸ An agent produced outside the body.

⁹ A substance known to produce cancer in experimental animals.

Sometimes it is not enough to know that an individual works in a certain general field. Thus, an oil worker may come in contact with Scotch shale oil, which has a marked tendency to produce occupational skin cancer;¹⁰ with paraffin base petroleum oils, which are rarely associated with cutaneous malignancy;¹¹ or with asphaltic American crude oils, which have almost never produced a skin cancer. It is therefore important to know the exact nature of the occupational exposure.

Occupational tumors must be sharply distinguished from tumors which arise spontaneously in employed individuals and have no relationship to their work. At times a court's decision that a tumor is or is not occupational is determined more by the vigor and keenness of counsel's arguments than by a scientific analysis of the actual facts. Unfortunately, the compensation laws in different states and also in different countries, relating to occupational tumors, vary a good deal and hence are often inequitable.

The determination of whether a given tumor is occupational is often made particularly difficult by the long time interval which may elapse between the onset of symptoms of the tumor and the exposure that occurs. This latent period may be only a matter of a few months or it may be many years. The existence of this latent period has not been adequately recognized by the framers of many industrial compensation laws, some of which contain time clauses of one or two years only. Legislation of this type is obviously unfair, as individuals who are exposed to radioactive materials or beta-naphthylamine at the present time may not show evidence of significant change for several years.

Another complicating aspect of the problem is that during the latent period the worker may change his occupation, and the individual who develops leukemia¹² following exposure to benzol,¹³ or osteogenic sarcoma¹⁴ following the inhalation of radioactive material,¹⁵ may have changed occupation before the symptoms of the disease have become apparent and may be employed in other occupations, such as building or office work, when the signs and symptoms of the disease become apparent.

¹⁰ Leitch, Mule-Spinners' Cancer and Mineral Oils, 2 Brit. Med. J. 941, 942 (1924).

¹¹ Twort and Twort, Suggested Methods for the Standardization of the Carcinogenic Activity of Different Agents for the Skin of Mice, 17 Am. J. Cancer 293 (1933); Wood, The Noncarcinogenic Nature of Purified Mineral Oils, 94 J.A.M.A. 1641 (1930); Heller, Occupational Cancers, 12 J. Indus. Hyg. 169, 182 et seq. (1930).

¹² Leukemia is a cancerous disease in which too many white blood cells are formed.

¹³ Benzol is a solvent frequently used for resinous substances.

¹⁴ This is a malignant tumor arising in bone.

¹⁵ By a radioactive material is meant radium or some of its derivatives. These radioactive materials are commonly used in the preparation of luminous paints.

Still another problem in some of the compensation laws is that specific chemicals are mentioned by name as recognized sources of occupational tumors, whereas closely allied chemical substances which may also give rise to these tumors are not named. It is wise to avoid overly specific cataloging of possible carcinogenic chemicals when framing or revising compensation laws.

The tumors formed as a result of agents encountered in the course of occupation affect a wide variety of tissues, and unfortunately the majority of these tumors are malignant. A useful classification of occupational tumors is that given by Hueper,¹⁶ a modification of which follows:

1. Direct contact tumors.

- a) Cutaneous neoplasms caused by direct local action of mineral oil, crude paraffin, creosote, anthracene, solar rays, ultraviolet rays, roentgen rays, rays from radioactive substances upon the cellular components of the skin.
- b) Pulmonary tumors¹⁷ resulting from the inhalation of radioactive material, chromates, asbestos, nickel carbonyl, tarry substances.
- c) Tumors of the nasal passages and sinuses following upon the exposure to radioactive substances, chromates, nickel carbonyl.
- d) Neoplasms resulting from impingement of roentgen or other radiation on the deeper tissues.

2. Excretory contact tumors.

- a) Tumors of the urinary tract resulting from an exposure to certain aromatic amines¹⁸ excreted in the urine.

3. Depository contact tumors.

- a) Cancers of the skin associated with the deposition of arsenicals¹⁹ in the cells of this organ.
- b) Sarcomas of bone, leukemia, and leukemoid reactions following the storage of radioactive material in the bones.

4. Tumors in tissues as a result of parasitic infestation.²⁰

- a) Cancer of the bladder following bilharziasis.²¹

The skin is by far the most frequent site of occupational neoplasms. This is to be expected in view of the very wide range of agents to which the skin is exposed, as contrasted with other of the tissues of the body. An important factor in the development of certain skin cancers is the

¹⁶ Hueper, *Occupational Tumors and Allied Diseases* (1942).

¹⁷ These are usually cancerous growths arising in the lung or the bronchial tubes.

¹⁸ Aromatic amines are aromatic chemical substances containing both nitrogen and one or more benzene rings.

¹⁹ Substances containing arsenic, such as might be encountered in mining or smelting arsenic or ores contaminated with arsenic, or encountered in the use of plant or orchard sprays containing arsenic.

²⁰ By this is meant infestation by parasites such as the various parasitic worms.

²¹ The disease produced by infestation with a particular kind of fluke worm.

amount of pigmentation that the skin contains. In general, the most heavily pigmented skins are those which are least susceptible to damage from sunlight or other forms of radiant energy.

Several types of occupational cancer deserve special mention. The cancers of the bladder developing in those working with aniline²² and certain of its derivatives became established as an occupational disease in 1883.²³ These carcinomas of the bladder develop as a result of the excretion of the inspired material through the kidneys and the prolonged persistence of the injurious agents in the urine held in contact with the bladder wall.

One of the best publicized occupational tumors is the radiation carcinoma of the skin from which so many of the pioneer workers with radium and X-ray died.²⁴ Fortunately we now know enough about the character of the disease to afford protection.

Certain tumors may arise in greater frequency among certain occupational groups but are not properly considered occupational because not peculiar to that particular group of workers. Thus the farmers in the South apparently have a higher incidence rate of skin cancer than is to be expected for a corresponding age and sex group of the entire population. However, since exposure to sunshine and weather is a factor common to all, varying only in degree, it is hardly proper to consider these skin cancers as truly of occupational origin.

Another disease, perhaps not properly occupational, is bilharziasis²⁵ of the human bladder. It has been known for thousands of years that the schistosomes are peculiarly apt to involve agricultural workers when exposed to infected mud and water, in those regions where the parasitic infestation is prevalent.

In general, the mesenchymal²⁶ tissues are relatively well protected against the access of the various chemical factors. As a result, none of the numerous chemical substances which may induce epithelial tumors in human beings produce either sarcomas or benign tumors of mesenchymal origin. However, it must be remembered that this apparent immunity

²² This is an oily substance derived from coal tar, the starting point for many of the complex, synthetic, chemical substances.

²³ W. Grandhomme, cited in Hueper, *op. cit.* supra note 16.

²⁴ Haagensen, Occupational Neoplastic Disease, 15 *Am. J. Cancer* 641, 660-70 (1931); Saunders and Montgomery, Chronic Roentgen and Radium Dermatitis, 110 *J.A.M.A.* 23 (1938).

²⁵ See note 21.

²⁶ These are the supporting structures of the body, such as muscle, tendons, bone, and cartilage.

probably rests not so much on the characteristics of the connective tissue cells²⁷ themselves as on their protection from prolonged exposure.

Since Diesel engines have come into more common use, the forcing of oil deep into connective tissue and muscles by the high-pressure spray is not unusual, and it will be intensely interesting to see whether with the passing of years some of these lesions develop neoplastic tendencies.²⁸

Undoubtedly, if we can judge fairly from our past experience, there are at present in use in industry compounds which will prove in later years to have been carcinogenic. It is of the utmost importance that every precaution be taken to protect workers from appreciable contact with substances other than those proved to be innocuous. Those workers in particularly hazardous fields, such as radium-dial painters,²⁹ should be carefully followed by all means of protection possible, and, in addition, frequent checks should be made of the actual conditions existing in the plant, both as to the hazards which exist under normal circumstances and the hazards which may exist through some fortuitous chain of events.

TUMORS DUE TO MECHANICAL TRAUMA

While trauma in the broad sense is any damage to the body, as ordinarily meant medically it implies the application of mechanical force to the body with sufficient violence to produce a break in the continuity of one or more of the body tissues. Repeated minor traumas may be spoken of as chronic irritation. As ordinarily used, the term traumatic cancer implies a malignant tumor which has arisen following a single mechanical injury. While there is much legal and scientific evidence that certain types of substances acting on the body over a period of time may produce certain types of benign or malignant tumor, so far as a single mechanical injury producing trauma is concerned, the evidence rests chiefly on reasoning from *post hoc ergo propter hoc*, all too often fallacious.

The minimal criteria necessary are: first, the integrity of the tumor site prior to injury must be established; second, the injury must be sufficiently severe to disrupt the continuity of the tissue at the site and so initiate reparative proliferation of cells; third, the tumor must follow the injury by a reasonable length of time; fourth, the tumor must be of a type which might reasonably develop as a result of the regeneration and repair

²⁷ Tissue cells are those cells that form the fibrous tissue of muscle and scars.

²⁸ That is, show evidence of cancerous change.

²⁹ Martland and Humphries, 7 Arch. Path. 406 (1929).

of those tissues which received the injury. These criteria have been evolved gradually³⁰ and appear sound in the light of our present knowledge.

The mere coincidence of two rare events, such as an injury in an unusual part and the subsequent development of a tumor in that part does not necessarily establish a causal relationship.

One requisite, sometimes mentioned in the literature, for the implication of a single trauma as a causative factor in tumor production is the presence of so-called bridging symptoms, i.e., symptoms that continue to give evidence of the continuance of disability from the time the injury is sustained to the time the tumor makes its appearance. Among these are continuity of pain, persistence of swelling, persistence of induration or of ulceration. However, this group of symptoms is of little practical importance in establishing causal relationship with the trauma and has no bearing from either the negative or the positive standpoint. Even in instances where a tumor is incited by the subcutaneous injection of carcinogenic substances in experimental animals, such as methyl cholanthrene, there may be no continuity of signs from the time of injection to the time of the appearance of the induced sarcoma.³¹ On the other hand, merely because inflammation, ulceration, or swelling has been present in a region, there is no certainty that the subsequently diagnosed tumor is in any way due to the conditions associated with the persisting signs and symptoms. Indeed, such signs and symptoms may actually be due to a tumor already present before the injury and masked for a time by the inflammatory and reparative processes following the trauma.

The previous integrity of the part may be assumed if its appearance and function have been normal. Only rarely is a thorough medical or X-ray examination available for reference in this regard. In many instances local trauma only calls attention to a tumor already present but unnoticed.

The adequacy of trauma is usually not difficult to determine. The injured person usually has had a careful medical examination soon after the event, and there is often observation of the injured part at frequent intervals for an extended period of time. These observations may be made

³⁰ Thiem, *Handbuch der Unfallkrankungen* 589 (2d ed. 1909); Graef, 17 *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.* 603 (1913); Ewing, *The Relation of Trauma to Malignant Tumors*, 40 *Am. J. Surg.* 30 (1926); Knox, 7 *Arch. Path.* 274 (1929).

³¹ An induced sarcoma is a malignant tumor of fibrous tissue developing in an experimental animal as the result of the purposeful application of a cancer-producing agent.

by the simple means of inspection³² and palpation,³³ or they may be supplemented by various types of radiographic and laboratory examinations. It may be fairly stated that trauma which fails to produce either an extravasation of blood into the tissues or a break in continuity of some of the tissues in the part affected is incapable of initiating a tumor.

The time interval that may intervene between a trauma and the development of the tumor at the site is very difficult to determine. Any evidence bearing on the rate of growth of the tumor, from either clinical observation or pathologic study, is most helpful. In general, four weeks may be regarded as the minimal time for the appearance of a rapidly growing tumor following the receipt of an adequate injury. A maximal limit is difficult to set, but probably should not be over three years after the injury.

The type of tumor developing at the site of injury is important. Obviously, any dermoid³⁴ or teratoid tumor,³⁵ other than in the testicle, would be automatically ruled out. Any tumor of cell type foreign to the part would be considered metastatic³⁶ rather than primary.

Curiously enough, although sarcomas of bone are among the tumors most often considered as of traumatic origin, they practically never appear after the thousands of fractures that annually provide adequate trauma for tumor development.

Much consideration has been given to tumors developing in scar tissue, thus indirectly relating the genesis of tumors to a previous trauma. Traumatic epithelial cysts³⁷ are known to occur as a result of trauma driving epithelium down into the deeper tissues, but have little clinical significance.³⁸ It has been clearly established that the epithelium overlying

³² Inspection, in the medical sense, implies visual examination with the naked eye.

³³ Palpation implies the determination of size, contour, consistency, mobility, and temperature of a given object, in this instance a suspected tumor, by means of examination with the hands.

³⁴ A dermoid tumor is one derived from embryonic germ cells and containing tissues representing two out of the three primitive germ layers.

³⁵ A teratoid tumor is one that contains within itself representatives of all three of the primitive germ layers. Tumors of this type can originate only from the primitive class cells or from groups of cells misplaced during the development of the embryo.

³⁶ Metastasis implies the secondary deposit of a malignant tumor at some point in the body distinct from that at which the tumor originated.

³⁷ By traumatic epithelial cysts are meant the small masses which sometimes appear in the hand or the fingers, among other places, as a result of the forcing deep into the tissues of bits of skin by injury of one or another type. Instead of dying, these sometimes continue to grow and form a cystic mass.

³⁸ Warvi and Gates, *Am. J. Path.* (in press.)

the scars of burns is peculiarly likely to become malignant. If there is a chronic persisting ulcer in the area of the scar, this is even more likely to bring about development of malignancy. The latent period before scars become cancerous may be extremely long, instances of fifty years or more having been reported.

Certain types of cancer may develop following chronic irritation³⁹ where repeated trauma activates degenerative and attempted reparative changes over a long period of time. While the great majority of chronic ulcers⁴⁰ never become malignant, in a few the attempted reparative processes may ultimately lead to neoplastic proliferation.⁴¹ In instances where this type of origin of tumor is alleged, the contributory negligence of the employee in permitting the chronic irritation to continue without adequate medical treatment should be carefully weighed.

One of the most difficult points to decide is whether or not trauma can change a benign tumor⁴² into a malignant one⁴³ or can increase the malignancy of a cancer already present. It is, of course, obvious that if the malignant tumor is of a different cell type from the pre-existing benign tumor, there can be no relationship. On the other hand, if it is a malignant variant of the same cell type the question remains open. Here, no general rule can be laid down, but in coming to a decision, it must be remembered that benign tumors may take on malignant characteristics entirely without the intervention of trauma.⁴⁴

I have never seen an instance in which there has been satisfactory evidence of a single mechanical trauma converting a benign tumor into a malignant tumor. Many times, however, evidence appears sound that benign pigmented nevi⁴⁵ may be converted into malignant melanomas⁴⁶ by single or repeated injuries of various sorts. To prove aggravation of a pre-existing tumor by injury, it is necessary to establish that the tumor

³⁹ Hueper, *op. cit.* supra note 16.

⁴⁰ For example, varicose ulcers of the leg.

⁴¹ Neoplastic proliferation is the uncontrolled growth and multiplication of cells.

⁴² An example of benign tumor is the common fatty tumor, or lipoma.

⁴³ As, for example, a pigmented mole, present since birth, benign and harmless, is traumatized and, as rarely happens, takes on the power of uncontrolled growth, changing into a malignant melanoma.

⁴⁴ Benign tumor of the breast—the so-called adenofibroma—may change spontaneously into the malignant form—the adenofibrosarcoma—without application of any known type of stimulus.

⁴⁵ This is the ordinary pigmented mole.

⁴⁶ That is, the so-called black cancer which may develop from pigmented moles which have apparently been harmless for years.

existed prior to the injury, that perceptible damage was done to it by the injury, and that the tumor's subsequent course was accelerated over that which would be ordinarily expected.⁴⁷ These factors can be evaluated only by detailed clinical and pathologic study of each case. Some evidence exists that mechanical trauma to a malignant tumor will facilitate its invasion of adjacent structures and the escape of cells to establish metastases elsewhere.

To summarize, a single trauma rarely, if ever, causes a cancer, in spite of many case histories purporting to establish that fact. Repeated trauma may rarely produce a cancer, as may trauma to a scar. Trauma may aggravate a pre-existing tumor.

⁴⁷ Behan, *Relation of Trauma to New Growths* (1939).