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CARCINOGENICITY OF FIBERS AND FILMS: A THEORY

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ABSTRACT

A theory based on frustrated phagocytosis is advanced to explain the carcinogenesis of fibers and films. Exocytosis combined with flexion of a foreign body permits the escape of superoxide radicals which, in a manner similar to that postulated for ionizing radiation, induces somatic mutations. The theory is subject to experimental verification, and offers hope for the development of preventive therapy which can be used to prevent some of the fibrosis and cancer resulting from asbestos inhalation.

Key Words: Carcinogenicity, fibers, films.
Subject Headings: Foreign bodies, phagocytosis, carcinoma, oxygen, carcinogens, environmental.

INTRODUCTION

In spite of excellent experimental work on carcinogenesis by microscopic fibers and by plastic films (1-6), explanatory theories are inadequate (7). In general, most known cancers of men and animals can be explained by the action of chemical carcinogens, ionizing radiation, ultra-violet light or viruses--all of which are known to produce mutagenic changes in the cellular genome (8). The carcinogenic action of microscopic fibers and plastic films appears to be an exception to this generalization: their toxic action is not associated with adsorbed impurities or extractable material (9). Sarcoma can be induced in animals in subcutaneous and pleural spaces by a variety of fibers or films whose chemical content includes no, or only minute traces of, known carcinogens (1-7). Mesothelioma and pulmonary carcinoma in asbestos workers appear to be an analogous finding in man.

Stanton, et al (1-2), have shown that fibers are most carcinogenic when they are durable, long and narrow (over 8μ in length and less than 1.5μ in diameter). Shorter or thicker fibers have less effect. Others agree that fiber dimensions are of great importance in carcinogenesis and fibrosis caused by fibers (6,10). Carcinogenic fibers and films induce a similar reaction in tissues, which differs from that of non-carcinogenic foreign bodies (1-5). There is some evidence that foreign bodies other than films and fibers may induce cancer (7). This action is weak by comparison with that of films (11) and appears to depend on surface smoothness (7).

FLEXIBILITY OF FOREIGN BODIES

Thin films and long thin fibers which are carcinogenic have little in common in the way of chemical composition or physical dimensions, but they do have four things in common: durability in tissues, smoothness, flexibility as a result of their dimensions, and lack of chemical reaction with tissue. Non-carcinogenic foreign bodies share most of these properties. As films get thicker and as fibers get thicker or shorter they become less flexible, and less carcinogenic. The only common factors in which fibers and films differ from non-carcinogenic foreign bodies appears to be their flexibility and smoothness. The similarities noted above and postulated differences in flexibility have not all been established experimentally, but they appear to be generally true.

One of the characteristics of living animal tissue is that it is constantly in motion, even when the animal is at rest. Very thin fibers and very thin films undoubtedly flex with tissue movements. Evidence for the flexion of thin fibers is provided by the work of Kuschner and Wright (10) who noted that many short fibers appeared in lymph nodes after they had put long fibers into the lungs of guinea pigs. No method of breakage other than by flexion seems feasible. How can the repeated flexion of a smooth, durable foreign body that is too large to be phagocytized be responsible for cancer induction? Below is a postulated mechanism which explains the carcinogenesis as a by-product of frustrated phagocytosis.

THEORY

Cells attempting to engulf large foreign bodies use a process known as exocytosis. Both phagocytosis and exocytosis by neutrophils involve enzymes which produce large amounts of the reactive superoxide radical O_2^- (12-13). This radical is quite toxic, damaging membranes, attacking DNA, and killing cells (13-16). Its dismutation products, H_2O_2 and singlet oxygen, are also toxic. Ozone, which also is associated with oxygen radicals, is a mutagen (17-19) and is considered to be radiomimetic (18-20). Much of the damaging effects from ionizing radiation are thought to be a result of its production of oxygen radicals (18-21). It seems probable, therefore, that carcinogenesis by ionizing radiation, films and fibers may be mediated by the same mechanism of oxygen radicals.

When oxygen radicals are produced by biological processes, dismutases, catalases and peroxidases are usually present to quickly detoxify them (13). When normal phagocytosis occurs, this detoxification is usually complete. Some H_2O_2 apparently diffuses out of neutrophils when they are active (22) but the amounts are so small that they injure adjacent cells only under exceptional circumstances (23). When exocytosis takes place there is a danger that substantial amounts of oxygen radicals may leak out around the phagocyte edges. This danger of leakage may be greater with smooth than rough objects, and may be greatly enhanced during the flexion movements of a smooth foreign body. When the oxygen radicals do leak out in substantial amounts, they may diffuse to nearby cells, injuring cell membranes to permit entry, then reacting with DNA components before they can be detoxified. These other cells may not be as well supplied with dismutases, catalases and peroxidases as are blood cells. As a result, some adjacent cells would be killed, but point mutations leading to cancer might be produced in others (8,17,19). Such specific reactions might occur infrequently, requiring durability and frequent flexion of foreign bodies over a prolonged time period to provide a significant probability of inducing cancer.

DISCUSSION

Most observations on fiber and film carcinogenesis are consistent with the above theory. One is that there is probably no direct physical contact between a film and cells at the time of their initial acquisition of neoplastic potential (4). Another is that asbestos fibers are more fibrogenic and carcinogenic than fibrous glass of similar size and shape. Fibrous glass is less durable--it tends to break up with time into short pieces when in tissue (10). Short fibers (less than 8μm) are much less carcinogenic than long ones. The theory gives two reasons for this: short fibers flex less than long ones, and they are subject to engulfment by phagocytes. Thick films, large fibers and other foreign bodies are only slightly carcinogenic, according to the theory, mainly because they do not bend readily when present as a foreign body. Slight carcinogenicity of smooth, thick objects could be attributed to an escape of small amounts of superoxide from phagocytes because they cannot attach themselves to the smooth surface. The observation that asbestos causes chromosome aberrations of hamster cells (24) is also consistent with the theory. Also consistent is the observation that greater amounts of superoxide and its reaction products were present in cultures when alveolar phagocytes were attacking asbestos fibers and coated particles than when attacking rough or smaller particles (25). The observations of Boone, et al (26) may not be consistent with the theory as they reported neoplastic transformation of cultured connective tissue cells by a smooth foreign body. It is not clear whether or not phagocytes were present. Phagocytes, however, do not have a monopoly on superoxide production, so it is possible that fibroblasts, in attempting to anchor themselves to a smooth surface, also liberate sufficient superoxide to cause injury.

A modification of the hypothesis, which applies to fibers, but not to films, is that tissue motion may keep the free ends of fibers in motion, and that fibers of appropriate dimension will keep puncturing cell walls, whereas shorter or thicker fibers will be less likely to do so. Frequent puncturing of cell walls could be accompanied by the introduction into a cell of airborne carcinogens deposited in lungs as well as oxygen radicals from exocytosis. Although such puncturing might kill some cells, others might survive to become malignant. The puncturing might also result in deposition of proteins on fibers in an attempt to protect cells. In this case, one would expect proteinaceous deposits to be greatest near the ends of fibers, rather than about the entire fiber. Observation of coated fibers ("ferruginous" of "asbestos bodies") gives some support to this hypothesis as they are often dumbbell or club shaped, even though proteinaceous deposition is not limited to the ends of fibers (27,28).

A somewhat similar hypothesis was advanced by Kuschner and Wright to explain the fibrotic reaction caused by glass and asbestos fibers (10). They attributed the resulting fibrosis to "frustrated phagocytosis", with leakage of tissue damaging enzymes from phagocytes engaged in exocytosis. It is entirely possible that both pulmonary fibrosis and cancer are caused by the same mechanism. Oxygen radicals could produce both effects, whereas the role of leaked enzymes would probably be limited to fibrosis. Kon proposed a similar role for oxygen radicals in carcinogenesis (29) but proposed uncontrolled ionic iron as being instrumental in its production.

Most of the superoxide dismutases, catalases and peroxidases found in living organisms contain iron, manganese, copper, zinc or selenium (13,30). It is not

clear whether mammals use all of these elements for this purpose or just part of them. Nutritional and metabolic factors are being identified which influence cancer rates. Some of these factors might well be related to tissue concentration of those trace elements which are essential in the formation of enzymes which control oxygen radicals. The theory predicts that a deficiency of these trace elements (or a particular one for any given species) would result in increased carcinogenesis by fibers and films. This is a prediction which is readily subject to experimental verification. If found to be true, the opposite effect might also be true--that an abundance (if not excess) of these trace elements in the diet would inhibit carcinogenesis by fibers and films.

A direct experimental approach is available to check on one aspect of the hypothesis. Techniques are available (22,25) to compare the escape of oxygen radicals into the surrounding medium during phagocytic activity. Flexion of films and of fibers could be achieved mechanically or by piezoelectric methods.

Many substances have been found which give some protection from radiation effects. Some of them may act by enhancing the detoxification of oxygen radicals. If so, they might also protect against the effects of implanted films and fibers. This possibility is also subject to experimental verification.

CONCLUSIONS

It is possible that sufficient reactive oxygen radicals are liberated during repeated attempts to phagocytize some types of foreign bodies that tissue injury would occur, leading to fibrosis and tumors. Smoothness, flexibility, and a size too large to be engulfed by phagocytes are the common characteristics of such foreign bodies. If the theory proves viable, it may lead to three practical results: (1) treatments to reduce asbestos induced cancer (2) simplification of the task of industrial hygienists who could ignore airborne fibers less than 2-5μm in length and (3) development of cell culture containers which would avoid neoplastic transformation.

Note: The theory and opinions expressed above have not been approved or accepted by the Departments of Labor or Health, Education and Welfare.

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