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Perspectives in Cancer Research

Increased Cell Division as a Cause of Human Cancer[1]

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Abstract

Carcinogenesis research is increasingly focused on chemicals that are not genotoxic and yet, at high doses, can induce cancer, apparently by increasing cell proliferation. We hypothesize that increased cell division *per se* stimulated by external or internal factors is also associated with the development of many human cancers. Although this hypothesis is well substantiated in the experimental literature, it has not been generalized as an important mechanism for carcinogenesis in human populations. Under this increased cell division model, the pathogenesis of cancer may result from molecular genetic errors induced during the process of cell division and from altered growth control of malignant or premalignant cells. Molecular genetic analysis of human cancers has shown that tumor cells contain multiple genetic defects including mutations, translocations, and amplifications of oncogenes and are reduced to homozygosity for putative tumor suppressor genes; these phenomena all require cell division for their occurrence and fixation. Increased cell division increases the risk of such events occurring. An accumulation of a combination of such genetic errors leads to a neoplastic phenotype. Examples are discussed of human cancers in which increased cell division, which drives the accumulation of genetic errors and can lead to neoplastic transformation, is caused by hormones, drugs, infectious agents, chemicals, physical or mechanical trauma, and other chronic irritation.

Introduction

Carcinogenesis research is increasingly concerned with chemicals that are not genotoxic and yet can induce cancer at high dose. Whereas genotoxic agents directly alter DNA, these nongenotoxic agents appear to have their effect by increasing cell proliferation (1). Terms commonly used to describe chemical carcinogens such as initiator, promoter, complete carcinogen, etc. describe their role in an experimental protocol but fail to describe the mechanism of their effect as genotoxic and/or as one of increasing cell proliferation. Chemicals administered at the maximum tolerated dose commonly cause cell proliferation, presumably because this cytotoxic dose causes cell death which stimulates proliferation of surviving cells as well as stimulating phagocytosis and its associated production of oxygen radicals and inflammation (2). To complement the considerable effort being devoted to studying nongenotoxic carcinogens, we offer a number of epidemiological observations which also suggest that cancer risk is increased when cell division *per se* is increased. Many such human carcinogens are hormones, infectious and other agents that increase cell division in a particular tissue and therefore increase the risk of cancer developing in that tissue, apparently in the absence of exposure to a specific genotoxic agent. Other human carcinogens such as tobacco increase cell proliferation and have genotoxic effects as well.

Recent advances in the field of the molecular genetics of cancer have provided a molecular basis for the concept that cell division is essential in the complex process of the genesis of human cancer. Cell division *per se* increases the risk of genetic errors of various kinds (3, 4). Cell division is necessary for conversion of adducts or other single-stranded DNA damage to gaps or mutations. Cell division also allows for mitotic recombination (*e.g.*, nondisjunction, gene conversion) which results in more profound changes than those from a single mutation (5). The development of a fully malignant tumor appears to involve the activation or altered expression of protooncogenes to oncogenes and the loss or inactivation of tumor suppressor genes the function of which is to control normal cellular activity (6–8). The activation of oncogenes whether by mutation, translocation, or amplification requires cell division. One model explaining the inactivation of a tumor suppressor gene suggests that the first "hit" is the inactivation by a mutational event of one of its two alleles followed by a reduction during mitosis to homozygosity for the faulty chromosome (9). The fixation of the initial mutagenic event and the loss of the wild-type allele of the tumor suppressor gene both require cell division.

Epidemiological evidence indicates that increased cell division induced by external or internal stimulation is indeed a common denominator in the pathogenesis of many human cancers. "Increased" may imply increased mitotic activity above the baseline rate or division of a subset of cells that would ordinarily not be dividing. In the face of a constant DNA damage rate, the amount of irreparable DNA damage is a function of the level of cell division, because division must occur for a DNA error to be propagated before it can be repaired. Nondividing cells in adults, such as nerve cells and cardiomyocytes, never develop tumors. Other cells that would ordinarily not be replicating, such as the Schwann cells in the nerve sheath, can, at times, be stimulated to divide, and when this happens tumors may develop (see below).

Agents that can lead to increased cell division and eventual neoplastic transformation include a wide variety of physical, infectious, and chemical agents (Tables 1 and 2). Factors causing increased cell division listed in Table 1 are those for which the evidence suggests that their primary carcinogenic action is to stimulate cell division. Factors listed in Table 2 also seem likely to contribute to neoplasia by stimulating cell division, but the evidence supporting this mechanism as the one critical to carcinogenesis is less strong. Other agents, including established carcinogens such as tobacco, may operate at least partly through increasing cell division. We will present in some detail various examples of human cancers in which increased cell division and hence increased cancer risk are caused by the following agents: (*a*) hormones; (*b*) drugs; (*c*) other chemical agents; (*d*) infectious agents; (*e*) physical or mechanical trauma; and (*f*) chronic irritation.

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Table 1 *Established risk factors for human cancers, the major action of which is to induce increased cell division*

Factor causing cell proliferation	Cancer site
Hormones	
Estrogen	Endometrium
Estrogen and progesterone	Breast
Ovulation	Ovary
Drugs	
Oral contraceptives, anabolic steroids	Liver
Analgesics	Renal pelvis
Infectious agents	
Hepatitis B virus	Liver
S. haematobium	Bladder
S. japonicum	Colon
C. sinensis, O. viverrini	Biliary tract
Epstein-Barr virus	Burkitt's lymphoma
Chemical agent	
Betel nut, lime	Oral cavity
Physical or mechanical trauma	
Asbestos	Mesothelium, lung
Gallstones	Gallbladder
Other chronic irritation	
Tropical ulcers	Skin
Chronic ulcerative colitis	Colon

Table 2 *Other suggested risk factors for human cancers, the major action of which is to induce increased cell division*

Factor causing cell proliferation	Cancer site
Hormones	
Testosterone	Prostate
Drugs	
Diuretics	Kidney
Infectious agents	
Epstein-barr virus	Acquired immunodeficiency syndrome lymphoma
Tuberculosis	Lung
Chemical agents	
Bile and pancreatic juice	Small intestine
Saturated fat	Colon
Salt	Stomach
Tobacco[a]	Oral cavity, lung, larynx, esophagus
Physical or mechanical trauma	
Hard foods (*e.g.*, coarsely ground corn)	Stomach
Asbestos	Gastrointestinal tract lymphomas
Loud noise	Acoustic nerve sheath
Head injury	Intracranial meninges
Other chronic irritation	
Reverse smoking[a]	Hard palate

[a] Tobacco use is an established risk factor for these cancers. The reason these are included here and not in Table 1 is that tobacco smoke contains many genotoxic agents.

Table 3 *Established hormone-related factors associated with cancers of the endometrium, breast, and ovary*

Endometrial cancer
Risk factor: increased exposure to unopposed estrogen (*i.e.*, estrogen in absence of progesterone)
Sequential oral contraceptives
Obesity
Estrogen replacement therapy
Late menopause
Protective factor: decreased exposure to unopposed estrogen
Combination oral contraceptives
Pregnancy
Breast cancer
Risk factor: increased exposure to estrogen and/or progesterone
Early menarche
Late menopause
Obesity (postmenopausal women)
Hormone replacement therapy
Protective factor: decreased exposure to estrogen and/or progesterone
Obesity (premenopausal women)
Lactation
Ovarian cancer
Risk factor: increased number of ovulations
Late menopause
Protective factor: decreased number of ovulations
Pregnancy
Oral contraceptives

Hormones

Increased cell division caused by prolonged stimulation by steroid hormones increases the risk of cancers of the breast and endometrium and is probably associated with prostate cancer (10, 11). There is considerable evidence that the risk of both endometrial cancer and breast cancer is related to cumulative estrogen exposure modified in different ways by the presence of a progestogen (progesterone or a synthetic progesterone-like steroid). Ovarian cancer is also well studied and presents an interesting variant of this hypothesis; the stimulus for cell division is not hormonal *per se* but rather ovulation, which is a direct result of complex hormonal changes (11). (Note: For each of the hormone-related cancers discussed below, a recent review paper is cited which discusses the many relevant studies in some detail.)

Estrogen can be derived from both endogenous and exogenous sources. Endogenous sources in women include secretion of estrogens from the ovary, operative only during menstrual life, and peripheral conversion of adrenal-derived androgens to estrogen, primarily in fat cells. The primary exogenous source of estrogen during reproductive years is OCs,[3] with ERT the primary source in the postmenopausal years. Progesterone is secreted by the ovary during the second half of the menstrual cycle, while exposure to synthetic progestogens comes from OCs and from the addition of a progestogen to ERT. Exposure to estrogens and progestogens from exogenous sources can be measured directly in epidemiological studies, either through careful interviewing or by examination of medical and pharmacy records. Measurement of endogenous estrogen and progesterone exposure often must be done indirectly. Ovarian activity is usually measured by evaluating the onset, cessation, timing, and regularity of menstruation and the timing and frequency of pregnancy and lactation. Estrogen derived from peripheral conversion of adrenal androgens in adipose tissue is estimated primarily by evaluating various measurements of body fat. Hormone-related factors that increase or decrease the risk of developing cancers of the endometrium, breast, or ovary are summarized in Table 3 and are discussed below.

Endometrial Cancer. Endometrial cells divide in response to estrogen but only in the absence of progesterone (12). Epidemiological evidence shows that events that increase estrogen stimulation in the absence of progesterone (unopposed estrogen) increase endometrial cancer risk, while events that decrease unopposed estrogen exposure decrease risk (13).

During the premenopausal years, unopposed estrogen exposure, and hence endometrial proliferation, occurs during the first half of the normal menstrual cycle. Use of combination OCs, which involve daily doses of estrogen and progestogen combined for 21 days followed by 7 days with no treatment, reduces cancer risk because the endometrium is exposed to

[3] The abbreviations used are: OC, oral contraceptive; ERT, estrogen replacement therapy; RB, retinoblastoma; HBV, hepatitis B virus; EBV, Epstein-Barr virus.

unopposed estrogen only during the 7 days when no hormones are taken and the serum level of estrogen is very low during this time. Increasing parity decreases risk because progesterone levels are high throughout pregnancy. Obesity increases risk in premenopausal women because of the associated anovulation and progesterone deficiency and further increases risk in postmenopausal women because of the associated increase in unopposed estrogen levels. The marked increase in endometrial cancer risk with increasing duration of use of ERT is further evidence that increased proliferation of endometrial tissue, stimulated by increased unopposed estrogen levels, increases the risk of this disease.

Breast Cancer. Evidence from biopsy studies suggests that breast cells proliferate in response to estrogens and that the simultaneous presence of progesterone increases the rate of such cell division (14). The clearest demonstration that increased levels of these two hormones increase breast cancer risk is that early menarche (onset of menstruation) and late menopause are such important risk factors for this disease. Breast cancer risk is reduced by at least 20% for each year menarche is delayed. For a fixed age at menarche, rapid establishment of regular menstrual cycles, with the associated increased hormone levels, further enhances risk. Women who stop menstruating before age 45, either naturally or through surgical intervention, have half the risk of breast cancer of women who continue to menstruate to age 55 or beyond. The association of obesity with a decrease in breast cancer in premenopausal women can be explained by the increase in anovulatory cycles and thus a decrease in both estrogen and progesterone levels. After menopause, obese women have an increased breast cancer risk because of their higher serum estrogen levels. OCs do not protect against breast cancer as they do against endometrial cancer and may under certain circumstances convey a modest increase in risk. Studies show that OCs are associated with similar levels of breast cell division as occur in the normal menstrual cycle; the reduced production of ovarian steroids caused by OC use is compensated for by the synthetic estrogen and progestogen in the OC itself. Long-term use of postmenopausal ERT results in a modest increase in breast cancer risk in line with the serum estrogen level associated with such exposure. A recent study found a distinctly larger increase in breast cancer among women who had used a progestogen along with ERT than among women who used estrogen alone (15); this observation is in line with the increased breast cell mitotic activity during that phase of the menstrual cycle when progesterone levels rise. Women with breast cancer have been found to have higher estrogen levels than healthy control women, and estrogen levels are higher in populations characterized by high breast cancer rates (16–18).

Pregnancy is associated with very high levels of estrogen and progesterone. These high hormone levels induce cell differentiation as well as cell proliferation, however, and the resultant effect on breast cancer risk is a short-term increase in risk and a long-term decrease. Recent observations in populations characterized by frequent and long-term breast feeding support a substantial duration-related protective effect of lactation, possibly related to the associated anovulation (19).

Ovarian Cancer. Ovarian cancer develops from the epithelial cells on the surface of the ovary. The primary stimulus for division of these cells is ovulation. After each ovulation, these cells replicate to cover the exposed surface of the ovary. According to the increased cell division model, factors which prevent ovulation will be protective against ovarian cancer development. There is a large and highly consistent body of epidemiological literature supporting this hypothesis (10). Complete and incomplete pregnancies and OC use all reduce the risk of ovarian cancer. The degree of protection from all three factors clearly is related to the duration of their associated periods of anovulation.

Prostatic Cancer. Testosterone is essential for the maintenance of prostatic tissue, but there are no studies in men relating variation in normal testosterone levels to the rate of cell proliferation in the prostate. Epidemiological support for an association of increased testosterone levels and increased prostatic cancer risk is weak and apparently inconsistent (20). However, prostatic adenocarcinoma can be produced by high testosterone alone in rats, and such treatment increases proliferation of the glandular cells in the prostate which give rise to prostatic cancer (21). Testosterone may also increase the mitotic activity of prostatic cells in men, and such an increase in mitotic activity would increase the risk of prostatic cancer.

Osteosarcoma. Hormonal activity is the primary stimulus to skeletal growth; pituitary growth hormone, thyroid hormone, androgens, and estrogens are all involved (10). The incidence of osteosarcoma at various ages and in various populations appears to be a function of the amount of cellular activity in the bones (22). Evidence that cell division is required in the development of osteosarcoma comes from patients with hereditary retinoblastoma. Patients containing germ line mutations in their RB gene often develop other tumors, particularly osteogenic sarcomas, in later childhood or adolescence. Most osteosarcomas develop during the adolescent growth spurt when skeletal growth is maximal (22). Bone cell growth, which occurs throughout childhood with a final spurt at puberty, increases the possibility that the wild-type allele of chromosome 13q holding the RB gene will be lost; this results in the reduction to homozygosity for the chromosome containing the mutant allele (23). Any bone cell in which this occurs would therefore have a growth advantage if the RB gene acted as a growth inhibitor.

When osteosarcoma occurs in adults over age 50 it is commonly associated with Paget's disease, a skeletal disease in which bone becomes reconstructed by an active interplay between bone resorption and bone growth (24, 25). The sarcomas in such patients always arise in bones affected by Paget's disease and frequently occur at multiple sites.

Drugs

Human cancers associated with chronic drug use include transitional cell and renal cell carcinoma of the kidney with use of diuretics and analgesics (including aspirin which is nonmutagenic) (26–29) and liver cancer associated with older generation, high-dose OCs (discussed below). The increased cell division model is a likely explanation for these associations. There is evidence that high-dose OCs increase mitotic activity in the liver, but whether long-term use of diuretics or analgesics increases mitotic activity in the kidney remains to be investigated.

Benign and Malignant Liver Tumors. In the late 1960s an unusual type of benign liver tumor began occurring in young women. These benign liver adenomas were generally associated with long-term use of OCs. These tumors were often rapidly growing lesions which could achieve great size (30). Subsequently, very rare hepatocellular carcinomas were associated with OC use, and on occasion the malignant tumor appeared

to develop in association with an adenoma (31–33). These adenomas occurred in women with no prior history of hepatitis or jaundice, and OC use alone appeared sufficient to cause their development. Diffuse enlargement of the liver (*i.e.*, also in the lobe opposite the one where the tumor arose) was noted in these adenoma patients (30). The natural estrogens delivered as ERT to menopausal women appear not to induce similar effects, nor do the newer generation lower dose OCs. However, the anabolic steroids taken by body builders have been related to the development of benign and malignant tumors of the liver (34, 35). The associations of liver tumors with use of exogenous hormones have been extensively reviewed previously (36).

Infectious Agents

Infectious agents can cause cell death with subsequent cell proliferation, and a number of cancers are associated with chronic infections. The most important association is of liver cancer with HBV.

Liver Cancer and HBV. Persistent HBV infection is present in most patients who develop primary hepatocellular carcinoma (37). Chronic HBV infection, by destroying hepatocytes, produces a constant stimulus to hepatocellular regeneration (38). Because HBV is not incorporated into hepatocyte genomes, it seems likely that the sustained cell proliferation it causes is the explanation for its strong association with liver cancer.

Lung Cancer. The few studies that have adequately investigated the issue have found a marked increase in lung cancer risk in persons with histories of lung disease, in particular among those with prior clinical tuberculosis (39, 40). This increase in risk was observed for both smokers and nonsmokers. There are no experimental data to suggest that the tubercle bacillus is carcinogenic *per se*; rather, it seems likely that chronic active tuberculosis infection provides a constant stimulus for regeneration of damaged tissue. The alveolar cells that proliferate in response to chronic tuberculosis infection give rise to adenocarcinoma of the lung which is the histological type among Chinese women who are nonsmokers and have a history of tuberculosis (39). These tumors are sometimes described pathologically as "scar cancers" because they appear to arise in old tuberculosis lesions (41).

Lymphomas and EBV. EBV-associated Burkitt's lymphoma and acquired immunodeficiency syndrome-related lymphoma occur in patients who are immunosuppressed as a result of chronic malaria or human immunodeficiency virus infection (42). EBV stimulates B-cell production. In immunocompetent individuals, this production is held in check, whereas in immunosuppressed individuals, this proliferation can proceed unabated and lead to lymphoma occurrence.

Biliary Tract, Bladder, and Colon Cancer and Parasitic Infestations. Biliary tract cancers occur more commonly in persons with chronic infection with liver flukes which lodge in the biliary tract and cause proliferation of epithelial cells and thickening of vessel walls where cancers later arise (43). The flukes responsible are *Clonorchis sinensis* in China and Singapore (43) and *Opisthorchis viverrini* in Thailand (44). A similar response in the infected tissue also explains the high incidence of bladder cancer in Egypt where *Schistosoma haematobium* is endemic (45) and the excess of colorectal cancer in areas of China where *Schistosoma japonicum* is endemic (46). Eggs of these blood flukes are deposited mainly in the bladder with *S. haematobium* and in the intestines with *S. japonicum*. The effect of schistosomiasis on the tissue lining the bladder and colon is a thickening of the stroma and proliferation of the epithelium where the cancers arise (47).

Chemical Irritants

As with infectious agents, prolonged irritation by physical or chemical agents can cause cell death. The subsequent cell division which occurs during repair of the damaged tissue increases the risk of cancer at the irritated site.

Oral Cavity Cancer. An example of this phenomenon is oral cavity cancers which occur among betel quid users in India and other areas of Asia and the Middle East at the site where the quid is habitually held or where lime (calcium hydroxide) is applied to the buccal mucosa (48, 49). The increased risk occurs even among users of betel quid which does not contain tobacco. Aqueous extracts of betel quid with tobacco usually are carcinogenic whereas extracts of betel quid without tobacco are not (50). All quids probably cause mechanical trauma, and those grids which contain lime are also caustic and cause cell death and an increase in mitotic activity to replace lost cells.

Small Bowel Cancer. Cancer of the small bowel may also be caused by chronic irritation. More than 25% of all adenocarcinomas of the small bowel arise in the second portion of the duodenum, a 7-cm segment comprising less than 1% of the total length of the small intestine.[4] This segment contains the ampulla of Vater, through which bile and pancreatic juices are released into the duodenum. The carcinomas can often be mapped in close proximity to the ampulla. It seems likely that the constant influx of alkaline bile and of acidic pancreatic secretions may cause local cellular damage which stimulates localized mitotic activity in the small bowel epithelium and eventually leads to tumor development. Under this hypothesis one would expect the level of mitotic activity in this 7-cm segment to be greater than that in other areas of the small intestine; this has not been investigated directly. Cells of the small bowel have a high mitotic rate, and the fact that cancers of the small bowel are relatively rare has been offered as evidence against cell division being an important factor in carcinogenesis. Most cell division in the small bowel occurs, however, in cells due to differentiate and die, and the amount of cell division of the stem cells in the small bowel may not be very great. It is also possible that repair mechanisms are particularly efficient in small bowel cells. There are few data on either of these issues (51–55).

Colon Cancer and Saturated Fat. The etiology of colon cancer is not well understood, but there is some evidence that diets in which a high proportion of total calories are from saturated fat increase risk (56, 57). In rodents, diets high in saturated fats induce inflammation and superficial lysis of the colonic epithelium followed by compensatory regeneration to replace lost cells (58). Diets high in saturated fats may have a similar effect on the colonic epithelium in humans; this needs to be investigated.

Tobacco. Tobacco contains both genotoxic and nongenotoxic carcinogens (59); it is a potent irritant. Snuff users develop leukoplakia and are at greatly increased risk of cancer of the buccal mucosa, which usually develops at the site of snuff application (60). Tobacco smoke also acts as a local irritant to the epithelial tissue lining the bronchi, lungs, larynx, pharynx, oral cavity, and esophagus where smoking-related cancers arise. Endoscopically, the linings of the upper respiratory and upper

[4] Unpublished data.

digestive tracts of a smoker appear chronically inflamed. The bronchial epithelium of heavy smokers also shows evidence of chronic irritation including cell destruction and hyperplasia of basal cells (61). The increase in cancer risk with tobacco use may be partly explained by the associated increases in cell proliferation.

Stomach Cancer. Injury to the gastric mucosa results from excessive intake of salty foods leading to progressive loss of surface epithelial cells (62). In response, surviving cells in the basal epithelium are stimulated to proliferate to replace the lost cells (63). Habitual consumption of salty foods might be expected, therefore, to cause chronic proliferation of the gastric mucosa and an increase in stomach cancer risk. This hypothesis is not well studied, but several case-control studies that did investigate it found increased risk among those with the highest levels of salt intake. Also, the hypothesis appears to fit with secular and cross-cultural comparisons of salt consumption and stomach cancer rates. In 1900, stomach cancer was the leading cause of cancer death in the United States. The decline in stomach cancer rates since that time has been constant and marked and decline occurred parallel to a substantial decline in per capita salt consumption (64) resulting in part from the fact that salt is no longer a major food preservative. Gastric cancer mortality rates correlate well with average urinary excretion of sodium chloride in international comparisons (65).

Physical and Mechanical Trauma

There are numerous examples of associations of specific tumors with physical or mechanical trauma. For example, it has been suggested that the association of stomach cancer with eating coarse foods such as ground corn may be explained by the mechanical irritation to the lining of the stomach (66). We discuss several other examples below.

Gallbladder Cancer. Risk of gallbladder cancer is strongly associated with a prior history of gallstones, and gallstones are present in 65–95% of patients with gallbladder cancer (67). It seems likely that this association exists because stones abrade and irritate the wall of the gallbladder causing damage to the epithelial tissue and an increase in mitotic activity to replace damaged cells.

Asbestos. Asbestos is one of the most potent occupational carcinogens; it appears to be almost the sole cause of malignant mesothelioma (68). Although asbestos has been shown to morphologically transform cells in culture (69), it is generally considered genotoxically very weak (70); its mode of action is for fibers to lodge in the mesothelium and cause repeated episodes of cellular injury and regeneration and a proliferative reaction which is then likely to lead to the development of mesothelioma (71). Lung cancer is also greatly increased by asbestos exposure and this would appear to also be the result of chronic irritation and associated increased cell proliferation in lung epithelial cells. Asbestos exposure also increases the risk of developing large cell lymphomas of the gastrointestinal tract (72). Asbestos fibers may lodge in the gastrointestinal tract and stimulate a chronic inflammatory response which includes proliferation of lymphocytes.

Acoustic Neuromas. Risk of developing acoustic neuroma has been found to relate to job exposure to extremely loud noise, and the strength of this association increases with an increase in the number of years working in such occupations (73). Acoustic neuromas arise in the Schwann cells along the nerve sheath. Experimental studies in rodents have shown that severe acoustic trauma causes mechanical damage to various cells within the cochlea (74, 75). Later studies in birds found that sensory hair cells in the cochlea are destroyed and subsequently regenerate following acoustic trauma (76, 77). A similar phenomenon may occur with Schwann cells in humans. These cells are likely to be damaged by noise trauma, and surviving cells will be stimulated to proliferate in order to replace those cells that were lost. What seems key here is that after acoustic trauma, proliferation occurs in cells that would ordinarily not divide.

Meningiomas. Case reports suggest that head trauma can lead to the development of intracranial meningiomas (78, 79). Case-control studies have found an excess risk of meningiomas in women with histories of head trauma which was treated medically and in men who boxed competitively or had serious head injuries (80–83). It seems likely that trauma to the meninges causes damage and subsequent repair of the meninges and that the cell proliferation that occurs during the repair process increases the likelihood of tumor development.

The peculiar sex/anatomic distribution of spinal meningiomas may also be explained by trauma. Spinal tumors of all histological types are rare. The most common such tumor is a meningioma which occurs predominantly in postmenopausal women. The majority of spinal meningiomas arise in that portion of the thoracic spine where the majority of osteoporotic collapse fractures of the vertebrae occur. These fractures occur predominantly in postmenopausal women (84), suggesting that these tumors are caused by trauma to the spinal meninges resulting from such fractures.

Other Chronic Irritation

There are numerous additional examples where chronic irritation precedes neoplasia such as the following three in which cancers develop in ulcerated tissue. In each of these, the critical factor appears to be the increase in mitotic activity which occurs during repair of the ulcerated tissue.

Reverse smoking (a habit in which the burning end of a cigarette is inserted into the mouth) causes an excess of cancers of the hard palate (85). Burns and chronic tissue ulceration precede tumor development (86). Similarly, skin cancer has been observed to occur in association with chronic tropical skin ulcers (87). The squamous cell carcinomas that develop in association with these longstanding tropical ulcers tend to develop in the regenerating margin of the ulcer. Finally, chronic ulcerative colitis is a risk factor for cancer of the colon. Colitis patients who develop tumors often have tumors develop at multiple sites within the colon (88). Colitis patients, like patients with colon tumors, have recently been shown to have an increase in rectal cell proliferation when compared to normal controls (89).

Conclusion

A series of distinct genetic alterations accumulates in a cell before it becomes malignant (90–93). These changes involve the activation of cellular oncogenes and the inactivation of tumor suppressor genes (94). Several of these various genetic changes can occur only during cell division. The observation that so many molecular genetic alterations are needed for cancer development fits with the epidemiology of these cancers which usually develop relatively late in life. Thus, the epidemiological data are coincident with the molecular genetics of human cancer

and underline the importance of cell division to malignant transformation.

The epidemiological arguments presented here do not deny the importance of other known risk factors for the cancers discussed. Exposure to ionizing radiation is known, for example, to increase breast cancer risk, particularly if the X-ray exposure occurs during a period such as puberty or a first pregnancy when breast cell proliferation is heightened (95, 96). In this example, it seems likely that the increased mitotic rate leads to fixation of the DNA damage caused by the X-rays. For other human cancers the epidemiological data are simply not sufficient to characterize the interaction of risk factors as well as in the above example, much less to quantify the relative contribution of factors discussed in this paper and other known risk factors. What is clear, however, is that for some cancers (*e.g.*, endometrium and ovary) there is a strong, well-quantified relationship between cancer risk and exposure to factors the primary action of which appears to be to increase cell division. As discussed in this paper, the model that an increase in cell division *per se* increases the risk of cancer development also fits for several other cancer sites, although the quantitative relationships are less clearly defined.

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