The Complex Etiology of Cancer*

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SUMMARY

The recognized causes of cancer are briefly reviewed, and the inadequacy of present knowledge to explain cancer incidence and distribution is pointed out. New knowledge and concepts concerning carcinogenesis are then discussed, emphasizing the combined effect of multiple factors; recent advances in the knowledge of the nature, growth, and pathogenicity of viruses; and the role of host factors. The concept of a complex etiology—the concurrent or sequential action of multiple etiologic factors (co-carcinogenesis in its broadest definition)—is suggested as a plausible explanation for the incidence patterns of clinical cancer.

The etiology of cancer can be considered at two levels: (a) the fundamental derangement of normal life processes which is disease or (b) the factors which, by acting upon the organism, lead to this derangement. In considering the first, it must be admitted that the cause of cancer is unknown, although recent advances in molecular biology and cytogenetics nourish the hope that an understanding of ultimate causes may be attainable. At the second level our ignorance is of a different sort, for we recognize a confusing multiplicity of factors which are indisputably associated with the development of neoplastic disease in man.

THE CAUSES OF CANCER IN MAN

Ionizing irradiation is perhaps the most widely recognized cause of human cancer, as tragically proved by the fate of early radiotherapists who un-
The influence of hormones on the growth of certain tumors is common knowledge, and there is also evidence that hormones are implicated in the origin of human cancer. Adrenal corticosteroids appear to enhance metastasis of cancer (58). Sex steroids influence the growth of cancer of the prostate (71), breast (103, 107), and uterus (77). Sex is related (possibly by way of hormones) to the occurrence of melanoma, leukemia, lymphoma, and cancer of the gastrointestinal tract.

A carcinogenic influence of ovarian steroids is suggested by several clinical observations. Observations by Corscaden (92) suggested that evidence of high endogenous estrogen during menopause was related to the occurrence of endometrial cancer. Gusberg (56) has reported an association between administration of estrogens and incidence of endometrial carcinoma in post-menopausal women. The sustained estrogenic stimulation which occurs in patients with polycystic ovaries is sometimes accompanied by adenomatous hyperplasia of the endometrium or carcinoma \textit{in situ}, and endometrial carcinoma has been reported at an unusually high frequency and early age in such patients (72, 125). Women whose ovarian function was curtailed by surgical castration or irradiation have a slightly lower incidence of breast cancer than the general population (65).

In mice, sustained high-level stimulation by pituitary gonadotropins appears to be the cause of adenocarcinoma in ovaries which are transplanted into the spleen (15) and in the adrenals of ovariec
tomized mice (144).

Genetic factors also influence cancer genesis. Although most epidemiologic studies fail to show any familial tendency in human cancer and most examples of “cancer families” are readily explained as pure chance (100), a genetic influence on human cancer incidence has been shown in comparative studies of cancer concordance in siblings (83) and in monozygous and dizygous twins (60) and by utilization of genetic markers such as blood groups (62). Leukemia is nearly twice as frequent in boys as in girls, even in the youngest age groups when hormonal differences are minimal (129), suggesting that the sex chromosomes might carry genes which influence leukogenesis. Recent demonstrations of chromosomal aberrations in chronic myeloid and acute leukemia (61, 99, 118) indicated abnormalities at the cyto
genetic level which are either the cause or result of cancer.

There is little evidence that mechanical factors play any causal role in human cancer, but they cannot be completely dismissed. The relation of trauma to cancer is a constantly recurring medico-

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**GAPS IN PRESENT KNOWLEDGE**

In seeking to understand the etiology of cancer, we are faced not only with this embarrassing multiplicity of undeniable cancer causes, but an equally embarrassing awareness that no one of these causes is adequate to explain or even to be consistent with the patterns of cancer occurrence in man. The epidemiology of human cancer presents many perplexing questions. Do the many different types of cancer have the same etiology, or do each have a different cause? Why don't we all get cancer? Amongst the victims of atomic irradiation, amongst sailors and farmers exposed to excessive ultraviolet irradiation, amongst workers in the aniline dye and petroleum industries large numbers of individuals must have nearly
identical exposures to recognized carcinogenic influences, and yet (although cancer incidence is increased in these populations) it is still only an occasional individual who develops cancer. Why is there such a long incubation period between exposure to a recognized carcinogenic stimulus and the development of overt disease? What happens to the affected cell or the causative agent in this long interval?

This then is the dilemma—a plethora of causes and an unpredictability of responses. Where do we go from here?

**FRESH CONCEPTS CONCERNING CARCINOGENESIS**

Three areas will be considered: (a) the concept of co-carcinogenesis, (b) new knowledge in virology, and (c) the role of factors intrinsic to the host.

The **broad concept of co-carcinogenesis**.—Co-carcinogenesis is the phenomenon of an additive or synergistic effect of two agents, such that the combination causes cancer in a manner that neither can do alone. Awareness of this phenomenon is not new, but it deserves re-emphasis because it is a broad concept, applicable to any combination of factors which act jointly in carcinogenesis. The familiar examples of co-carcinogenesis with two chemical agents should be recognized as special examples of a general phenomenon. Fundamental observations were published by Shear (122) and by Rous and Kidd in 1938 (112, 119). They were confirmed and emphasized by Berenblum (9) and Shubik (12), and subsequently by numerous investigators.

A classic example of co-carcinogenesis is primary application of methylcholanthrene (at a dose which causes few or no tumors) to mouse or rabbit skin, followed by applications of croton oil, which if given alone causes no tumors. The combined treatment leads to an early and high incidence of skin cancer. Berenblum (10, 11) conceives of an essentially instantaneous and irreversible **initiation** of a change in the affected cell by the methylcholanthrene (or other initiator) such that thenceforth this change, although morphologically undetectable, can readily be **promoted** to the fully neoplastic state by the croton oil (or other promoter). Although many investigators do not accept completely the concept of stepwise initiation and promotion or the all-or-none nature of the initiation step, the fact of a co-carcinogenic synergism of various chemical agents is irrefutable.

Chemical agents other than the traditional carcinogens may influence carcinogenesis. Horton (68) has shown that the choice of solvents for carcinogens greatly influences the results. Different solvents, although having no independent carcinogenic effects, will variously accelerate the effect of the recognized carcinogen.

Estrogenic steroids have a co-carcinogenic effect with certain carcinogenic hydrocarbons (47, 81). A possible mechanism is suggested by the observation that estrogens increase the pick-up of particulate matter by cells in tissue culture (80). In contrast, Leiter and Shear (88) and Homberger and Tregier (96) found female mice less susceptible than males to induction of sarcomas by dibenz-pyrene, but it is possible that these results were due to sex-linked genetic effects rather than hormonal effects, since the same differences were found between castrated male and female mice (66). Cortisone has been variously reported as enhancing (135) and diminishing (7, 98) tumor genesis when administered in conjunction with chemical carcinogens.

Urethan augments the leukemogenic effects of x-ray or estrogens or methylcholanthrene in mice (75, 76).

Menkin reported an augmentation of methylcholanthrene carcinogenesis by certain growth factors found in inflammatous exudates (95).

Gross (53) and Kaplan (79) have demonstrated that x-radiation can activate leukemogenic viruses in mice.

Co-carcinogenic action of chemicals plus viruses has been observed in several experimental systems. The first, and still the most convincing, experiments were those of Rous who, with several co-workers (109, 111–13), showed that the combination of Shope papilloma virus plus tar or methylcholanthrene in various sequences accelerated papilloma formation in rabbits and increased the tendency of these papillomas to transform to carcinoma. Rowson et al. (116) observed enhancement of tumor incidence in mice given both polyoma virus and chemical carcinogens. F. Duran-Reynals (33) for many years championed the concept that latent infections of presumably nononcogenic viruses such as fowl pox viruses in mice and rabbits and chickens increased the carcinogenic effect of methylcholanthrene. Although his experimental results were often consistent with this hypothesis, they were not generally accepted as conclusive.

M. L. Duran-Reynals has recently published impressive evidence (34) that, if methylcholanthrene is applied to mice during primary infection by vaccinia virus, tumor incidence is increased. Confirmatory studies were reported by Martin (90), who also reported similar results with poliovirus. Wiseley and co-workers (147) demonstrated that mice subjected to artificial smog plus intranasal administration of myxo viruses (influenza and...
Newcastle disease) had a greater frequency of bronchial adenomas and carcinomas than mice subjected to either smog or virus alone. Tanaka and Southam observed an earlier appearance and greater incidence of skin papillomas in mice infected with West Nile virus or Herpes simplex virus (139) concurrently with methylcholanthrene or benzo[a]pyrene painting than occurred in animals receiving the chemical carcinogens alone.

Mazurenko (91) reported that the administration of vaccinia virus and cortisone to mice was followed frequently by the development of leukemia and that the leukemia was thenceforth transmissible by a leukemia virus distinctly different from vaccinia virus. This suggests a joint effect of two viruses, only one of which is known to have oncogenic capacity. Wyburn-Mason (148) has suggested on the basis of clinical observations that human cancer of the lip might be related to Herpes simplex infection.

**New concepts in virology.**—Since virology is currently an area of great interest and research activity and is the most controversial, at least insofar as human carcinogenesis is concerned, it is pertinent to examine recent experimental facts and resulting theoretical considerations which may bear on the problem of carcinogenesis by viruses.

It is a common misconception that virus infection means disease. Obviously, much disease is caused by viruses, but infection without disease is much more common. The ratio of clinical disease to inapparent infection is less than 1:100—probably 1:1000—for poliovirus (98), Japanese B encephalitis virus (120, 128), and St. Louis encephalitis virus (19) in man, and many viruses which frequently infect man are not known ever to cause disease (94). This is true for many of the ECHO viruses which were dubbed “orphan viruses” because they had no disease to call their own.

There is a further erroneous assumption that, if one escapes serious illness during a virus infection, that is the end of the infection. How often this is true we do not know; but it is not necessarily true, and we may learn that persistent (although asymptomatic) infection is the rule rather than a rarity. Chart 1 is a diagrammatic representation of the possible courses of virus infection. The possibilities of inapparent infections, persistent infections with or without eventual exacerbations, and prolonged incubation time (from entry of virus to appearance of disease) should be noted. The well known vagaries of Herpes simplex and viral hepatitis in man illustrate these various courses of infection. It will be recognized that the occurrence of late exacerbations necessarily means that some alteration must occur in the relationship between host and parasite. Such alterations might result from changes intrinsic to the parasite or the host, or might be caused by extrinsic influences.

Recognition that inapparent infections are commonplace raises the possibility that the range of susceptibility of different species to viruses may be much broader than we now believe, because almost all virus studies are based on an interest in the disease as it occurs naturally or as it appears in an experimental system. Little work has been addressed to the question of nonpathogenic infections in man or experimental animals.

If we consider virus infection at the level of the cell, we also find phenomena which are influencing
our thinking about viruses and cancer. Chart 2 is a
diagrammatic representation of some virus-cell
relationships. This illustrates that cell destruction
is not an inevitable consequence of cell infection,
that cell-to-cell transmission may occur without
exposure of the virus to extracellular fluids (and
therefore without exposure to serum antibody),
that virus may exist as a relatively simple nucleic
acid lacking its antigen protein coat or as com-
plete (antigen-coated) virus. If virus propagates
in the incomplete (nucleic acid) form, it would
neither elicit nor be affected by antibody.

The range of viral infectibility is determined in
part by compatibility between receptors on cell
membranes and on the protein coat of the virus.
Alterations in either may alter what is otherwise
an absolute specificity. Thus poliovirus nucleic
acid will infect rat and chicken cells with propagation
of complete virus particles (105), although com-
plete poliovirus can infect only human and simian
cells. Bacterial cells devoid of cell walls (proto-
plasts) are susceptible to infection by phages to
which the unaltered cells are resistant (130). Less
dramatic but basically similar is the heightened
susceptibility to infection of mammalian cells
treated with hypertonic salt (3, 40). At present
these are laboratory tricks, but they suggest that
viruses have versatility which will further stretch
our concepts of host specificity.

Vertical transmission (52), the transmission of
virus from one generation to another, in contrast
to horizontal transmission from neighbor to neigh-
bor, is the usual manner of transmission of animal
oncogenic viruses such as Gross's leukemia, poly-
oma, Bittner's milk agent, and lymphomatosis of
fowl. Vertical transmission may occur through
the mother's milk (or yolk of chickens) or through
the placenta, and can probably also occur through
intracellular infection of the germinal cell—either
ovum or sperm (16).

The disappearance of virus after it has infected
cells and produced a persistent change has been
noted in many experimental situations and can be
variably explained. A classic example is the ap-
parent disappearance of Shope papilloma virus
from the papillomas which it induces in domestic
rabbits. Syverton (188) used the term "masking"
for this phenomenon to express the concept that
the virus was still present in a disguised form.
Whether the virus is masked or has truly disap-
ppeared is still unresolved. Sarcomas can be
induced in turkeys by Rous virus, but the virus can-
not be demonstrated in such tumors by the usual
methods of chick or egg inoculation. Recent
studies by Bergs and Groupé (14) have demon-
strated that this apparent absence of virus is due
to its neutralization in tissue homogenates by
antibody or other serum factors. If the cells were
grown for several days in antibody-free tissue cul-
ture, the virus became detectable. Another dis-
appearing act is the phenomenon of lysogeny in
phage. In this situation the virus is present in the
bacterial cells at all times but is in a chemically
and morphologically incomplete form and does
not cause destruction of the bacterial host cell. It
can, however, be made to reveal itself by subject-
ing the cells to various conditions that upset the
balanced growth of virus and cell (63). Recently
disappearance of infective virus or even of ex-
tractable infective nucleic acid has been reported
in hamster cells which had become neoplastic be-
cause of infection by polyoma virus (146). The
evidence to date is consistent with the suggestion that
the virus has truly induced a somatic mutation
such that no further influence of the virus is re-
quired to maintain the cell in its neoplastic state.
The possibility still remains, however, that even
this virus persists undetected within transformed
cells. A new twist on the relation of virus to tumor
is the report by Pitelka (104) that virus-like par-
ticles are readily visualized by the electron micro-
scope in certain breast tumors arising in inbred
lines of mice which are apparently free of the
Bittner milk factor. This may be yet another ex-
ample of an altered form of a virus which never-
theless has a continuing causal relationship to the
neoplastic process, although the possibility that
this is merely a contaminating virus cannot be dis-
missed.

Many different types of tumor may be caused
by a single kind of virus. Polyoma virus in mice is
the most startling example—capable of causing
more than a score of different histologic forms of
tumors in mice (132), as well as causing tumors in
rats and hamsters (38, 39). Gross has made the
fascinating observation that, whereas inoculation
of mice with his leukemia virus ordinarily causes
leukemia of the lymphoid type arising from cells of
the thymus gland, if the gland is removed from
infected animals at an early age lymphatic leu-
kemia does not develop, but at a later date
myelogenous leukemia arises from bone marrow
cells (54). This virus also infects and causes leukemia in rats (55). The Lucké virus is well known
as a cause of kidney adenocarcinoma in frogs
(35, 84) but on transfer to salamanders it reported-
ly caused rhabdomyosarcoma—a tumor of skeletal
muscle (110). Even the well known Rous sarcoma
virus has multiple manifestations. It causes a non-
neoplastic hemorrhagic disease in young chicks
and chick embryos (51), and recent reports from
Russia (136, 151), Sweden (2), and Czecho-
slovakia (137) and this laboratory (97) indicate that it can also cause sarcomas and cystic tumors in rats. A virus, SV 410, discovered in tissue cultures of monkey kidney cells has no presently recognized pathogenic effect in monkeys but causes cancers in hamsters (37). Trentin has reported that it can also cause sarcomas and cystic tumors of monkey kidney cells has no presently recognized pathogenic effect in monkeys but causes cancers in hamsters (37). Trentin has reported that it can also cause sarcomas and cystic tumors in humans, causes pulmonary and subcutaneous cancers in hamsters (143).

Viruses not only have a native potentiality for diverse pathogenic effects but also are themselves subject to mutation. The earliest reports were by Mundry and Gierer (96) demonstrating mutation of tobacco mosaic virus following exposure to nitrous acid. More recently mutations have been induced in animal viruses (17, 50). Dulbecco (29) has reported spontaneous mutation of polyoma virus during growth in hamster cell tissue cultures. The transformation phenomenon of Avery (6)—the alteration of genetic characteristics of an organism by treatment with nucleic acid from a different organism—has been reported for viruses. Mixtures of live myxoma virus and noninfectious nucleic acid extracts of fibroma virus resulted in fibromas rather than myxomas when introduced into rabbits (78). Transformation resulting in hybrid viruses has been reported to occur when mixtures of two strains of influenza virus were cultivated together (21).

Host factors in carcinogenesis.—The host rarely if ever plays a passive role in disease processes. In carcinogenesis and tumor pathogenesis there are several situations in which an influence of immunologic and other host factors is recognized or suspected.

The concept of specific immune tolerance (20, 59, 92) has implications for oncology. The current concept is that an animal during the prenatal or neonatal period has no discrimination for foreignness but accepts anything present within its body during this period as being normal or “self.” Recognition of things as foreign or “not self” is achieved shortly after birth. Thus, if a neoplastic mutation should occur in, or if a virus should gain entry into, an animal during this “tolerogenic” period, it would not be recognized as foreign. No cellular reactions would occur. No antibodies would be formed. This concept raises an intriguing question as to the outcome of infection in a specifically tolerant host. If a virus were accepted as “self,” would unimpeded viral propagation lead to great pathogenesis, or might the host somehow be so adapted to the virus that no harm would ensue? The latter is clearly the case with lymphocytic choriomeningitis virus in mice (69), where neonatal infection is persistent but nonpathogenic, whereas infection initiated a few days later excites a host reaction and ends in either elimination of the virus or (more often) death of the host. A similar phenomenon has been demonstrated by Rubin (117) for chicken lymphomatosis virus. If these two examples should be representative of a common phenomenon, it is clear that undetected latent virus infection might be well nigh universal and without importance until some new factor intervened to upset the balance and lead to disease.

The possible relationship of tolerance to cancer genesis is not restricted to virus infections. Since, according to present concepts, the development of an abnormal cell during fetal life would not be recognized and resisted, such a cell would persist and multiply. This would account for the persistence of teratomas and other embryonic rests (although additional mechanisms must be postulated for the initial deviation of embryonic development and the later progression into neoplasia). In an analogous manner, other states of diminished immunologic reactivity might allow undesirable cells which normally would be resisted to propagate without hindrance. Since carcinogens may depress reticuloendothelial system functions, it seems possible that even such classical carcinogens as methylcholanthrene might act in part by depressing host resistance to the growth of spontaneous mutants, rather than solely by direct mutagenic action on the target cell. Although dose and time factors for methylcholanthrene carcinogenesis make this seem unlikely, the concept cannot be arbitrarily dismissed and is particularly appealing as a possible mechanism in carcinogenesis by polyfunctional alkylating agents (18, 64).

Maini et al. (87, 88) observed that abnormal mitoses were common in regenerating rat liver post-hepatectomy and that concurrent treatment with the carcinogen 3'-Me-DAB favored propagation of the abnormal clones. They suggested that this was probably attributable, at least in part, to an effect on host factors rather than to a direct effect on the hepatic cells.

Extension of these immunologic considerations has led several authors (24, 51, 74, 145) to propose that immunologic reactions play a more direct role in carcinogenesis. According to this hypothesis, through mutation of unspecified cause there occurs in certain cells a genetic loss which is equated to an antigenic loss. This lost antigen is now foreign to the affected cell, which consequently recognizes the normal cells of the body as being foreign because they contain the antigen which the abnormal cells now lack. This recognition of
foreignness leads the antigen-deficient cells to react in the way that normal lymphoid tissue reacts when faced with a foreign antigen—that is, by hyperplasia and production of antibody-like factors that have deleterious effects against the normal cells, in the same manner as is postulated to occur in auto-immune diseases. These two features, toxic effect on normal tissues and excessive growth of one abnormal cell type, thus resemble the picture of cancer. This hypothesis has a certain plausibility if the affected cell is of the type which is capable of immune responses—i.e., a cell of the reticuleendothelial system—and thus it deserves consideration and investigation as an explanation for such diseases as leukemia, lymphoma, Hodgkin’s disease, and multiple myeloma. However, it seems inconceivable that this concept could be extended to neoplasms of epithelial cells or neoplasms of most connective tissue cells from which arise the great preponderance of carcinomas and sarcomas.

Cortisone and related adrenal steroids inhibit the host defense mechanism. They also affect carcinogenesis and tumor growth (58, 89), possibly because of their effects on specific and nonspecific immunologic reactions.

Other studies suggest that such nonspecific host factors as fibroblasts and wandering cells may influence carcinogenesis. Orr (101) has presented evidence that the connective tissue stroma subjacent to areas of carcinogenic application plays a part in the development of epidermal carcinomas. Subcutaneous injection of diatomaceous earth in chickens and skin incisions in mice (procedures which stimulate connective tissue growth) increase susceptibility to Rous sarcoma virus (114) and chemical carcinogenesis (26, 49, 123), respectively. Clinical observations and some laboratory studies (43, 48, 128) suggest that healing wounds offer a better site for tumour growth than normal tissues, and that some tissues or organs provide a “better soil” for the implantation of tumor metastases. Even the more neglected intercellular cement may influence carcinogenesis and pathogenesis, since variations in the physical state of this substance influence the diffusion of viruses and chemicals (32) and probably metastases of transplanted tumors (44, 89).

THE CONCEPT OF A COMPLEX ETIOLOGY

From all the foregoing one is led to the concept that in carcinogenesis we are faced not simply with multiple etiologies but rather with complex etiologies: that there are not merely a score of diverse agents, each capable of causing cancer, but a number of agents and accessory factors which if they chance to act in appropriate combination or sequence may lead to cancer. The mechanisms by which such combinations of agents enhance cancer incidence might be various and unrelated. Several possibilities seem reasonable: (a) Penetration of locally acting carcinogenic chemicals into tissue or into cells might be increased by the action of solvents, irritants, or viruses. (b) Altered metabolism or defective detoxification of systemically acting chemical carcinogens might result from genetic defects or hepatic or renal damage by chemicals or viruses. These two possibilities visualize the chemical carcinogen as the prime etiologic agent and all other influences as co-carcinogenic factors. (c) Infectivity or pathogenicity of a virus might be enhanced or altered by changes in the penetrability or metabolism of the infected cells or by changes of immunologic reactivity of the host induced by chemicals, hormones, irradiation, or irritation. (d) Local or systemic alterations in immunological or hormonal conditions might favor survival and growth of mutant cells that would die in a “normal” tissue environment. These two possibilities visualize a virus or mutagenic force such as x-ray as the primary agent of carcinogenesis while hydrocarbons, hormones, and cytotoxic agents would be accessory factors. (e) A series of alterations of intrinsic cellular characteristics might be caused successively by the various carcinogenic influences, each alteration approaching but no one step being by itself the complete neoplastic transformation. This is in essence the classical concept of co-carcinogenesis as championed by Berenblum but is not restricted to chemical carcinogens. It visualizes each contribution to the total change as necessary, and hence no one cause can be singled out as the primary agent.

Thus, depending on which of the above is most nearly true, the relative importance of individual factors in the fundamental mechanisms of carcinogenesis would differ vastly. However, in another and more practical sense, each factor, no matter what its mode of action, would be of major importance because its absence would diminish the probability that a neoplastic cell would arise and grow into clinical cancer. Any method of avoiding or counteracting any of these factors would be efficacious prophylaxis against cancer.

This concept of a complex etiology of cancer seems more compatible with the epidemiology of human cancer than any concept of singly acting etiologic agents, because if a final result requires the action of multiple factors which are acting with various frequencies in a population, then the frequency with which the total etiologic require-
ments will be met is the product of their individual frequencies. To make a purely imaginary example, let us suppose that one-tenth of a given population is cigarette smokers, and that one-tenth have a genetic susceptibility to cancer. If we then assume that each of these three conditions operates as an etiologic factor in cancer of the lung, but that no two factors alone are sufficient to bring on the disease, then the incidence of lung cancer would be 1:1000. If any two of these factors were sufficient to cause lung cancer, the incidence would be 1:100, and if still a fourth factor with the same frequency of exposure were required, then the incidence would be only 1:10,000. This concept allows for the relative infrequency of specific types of cancer in a population that has a high frequency of exposure to presumed causative factors and the fact that epidemiologic studies of cancer etiology often reveal suggestive correlations but seldom provide convincing evidence of causal relationship.

CONCLUSION

In conclusion, it seems worth while to consider the hypothesis that most cancer is due not to any single causative agent but rather to a complex of multiple factors each of which contributes something to the total process. These several factors may act simultaneously or sequentially; continuously, repeatedly, or rarely. They may persist or disappear from the affected individual or cell. They may be additive or synergistic or even antagonistic. They may cause persistent or transient effects. They may act directly on the potentially neoplastic cell or indirectly by affecting other tissues of the host. They may bring about a biochemical change which is characteristic and fundamental to all neoplastic cells or may cause changes which are only superficially similar.

Such a concept adds nothing to our understanding of the fundamental intracellular change which initiates the neoplastic process. (For discussions of this area see references [67, 131].) It is annoying because it promises no easy solution. Nevertheless, it merits attention because it fits the facts of cancer incidence better than any concept of a single etiology, and it is appealing because it offers the possibility that attack upon or removal of any one of the postulated multiple factors might significantly reduce cancer incidence.

REFERENCES

Southam—The Complex Etiology of Cancer


78. KILHAM, L. The Fibroma-myxoma Virus Transforma-
113. Rous, P.; Murphy, J. B.; and Tytlery, W. H. The Role of Injury in the Production of a Chicken Sarcoma by a Filterable Agent; and A Filterable Agent the Cause of a Second Chicken Tumor, an Osteochondrosarcoma. J.A.M.A., 55:1761, 1912; 59:1798-99, 1912.
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