CANCER: THE PRECONDITIONING FACTOR IN PATHOGENESIS

A New Etiologic Approach

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Cancer (Latin for crab) is a term which has been used from time immemorial to designate an "eating ulcer" of an incurable or malignant nature. Malignancy manifests itself when certain cells, which are apparently normal and have previously functioned normally, begin to grow and multiply in an abnormal way in some part of the body, relentlessly invade the surrounding tissues and extend to other parts of the body by metastasis. The unanswered question is why do these cells behave in this manner?

Various theories of the cause have been advanced: heredity, embryonic defects, chronic infections (parasitic, bacterial or viral), physical or chemical irritation, or injury, etc. The major research of recent years is based on the concept that some intrinsic biochemical or metabolic defect in the cell initially involved is responsible for the irregular growth. Accordingly, the major objective in therapy has been to destroy the erratic cell growth by surgical, medicinal or physical means, x-ray, radium, etc., while little attention has been given to possible metabolic or nutritional etiologic factors.

Cancer of epithelial tissues (carcinoma) may arise from a number of chronic lesions: fissures, moles, senile warts, lupus vulgaris, mastitis, syphilitic or varicose ulcers, ulceration of stomach or bowel, and burns (x-ray, chemical, thermal or electrical). The most generally recognized exciting cause is chronic irritation, physical or chemical, as in soot causing chimney sweep's cancer, tobacco tars causing lung cancer, etc.

Some earlier observers believed that the growth rate of cancerous tumors was determined by the degree of release of restraints of growth, but little was known of the nature of such restraints. According to Berrill[1], "cell proliferation is itself primarily a response to changing surface relationships". He also states that "in general the role of cell division and multiplication in relation to malignancy may have been over emphasized". Thus also Borst[2] concludes that "inflammatory over-growth results from exaggerated response to external irritants, while cancerous growth arises from loss of normal restraints to growth". Nineteenth-century writers expressed similar views. Ribbert[3] considered cancer cells as having a latent power of unlimited proliferation which became active on their being dislocated from the normal association. Thiersch[4] believed that cancer cells grew unceasingly because the connective tissues had lost the capacity to hold their proliferative powers in check.

The author of this treatise definitely concurs with the concepts of these earlier writers, but goes a step farther, and postulates the specific cause of this retentive incapacity of connective-tissue.

To better understand the situation a brief review of the histological structure of the skin and mucous membranes may be helpful. The corium, or true skin, being derived from the embryonic mesoderm, consists essentially of connective tissue containing blood vessels, hair follicles. sebacious and sweat glands, all of which provide the supporting tissue for the surface structure of epithelial cells. The latter are in stratified arrangement, the lower layer of columnar cells, known as the germinal layer, resting upon a "condensed formation of connective tissue" known as the basement membrane. This latter is comparable in function to the footing of a masonry foundation. anv breach of which might result in distortion and disintegration of the superstructure. The difference in this comparison is that the living cells of the epithelium, when they lose their footing, continue their inherent proliferative propensities without the normal directional limitations of the basement membrane. This membrane normally provides a complete and continuous connective-tissue barrier underlying the entire epithelium of the skin and mucous membranes of the alimentary, respiratory and genitourinary tracts and all their glandular ramifications, thus constituting an inviolate line of demarkation between the epithelial and mesenchymal tissues. Under these conditions it is apparent that the stability and continuity of this basement membrane is a most essential feature of the anatomical formation. Any breach or disarrangement of this structure could lead to a disturbance in the orderly growth pattern of the epithelial cells, resulting potentially in an inward extension of cell growth through the breach, which is the initial stage in malignancy. Once a break-through is effected, by reason of weakness or physical injury of this connective-tissue barrier, the mesenchymal defense mechanism, under normal conditions, goes into action to repair the breach by proliferation of new connective tissue to fill the gap with impervious scar tissue, thus preventing erratic inward growth of the disarranged epithelium. If, however, due to faulty metabolic and nutritional status of the subject, this repair mechanism is inadequate or ineffectual, as in chronic ulceration and slow healing of abrasions or lacerations, conditions then become favorable for unobstructed malignant invasion and consequent systemic metastasis.

The most definitely established physiological function of any food substance is that of the role of vitamin C in the maintenance of stability and elasticity of connective tissues generally and the growth of new scar tissue in wound healing, and this would include the bones, cartilages, muscles, vascular tissues, subcutaneous and submucous tissues,—in fact all tissues of mesenchymal origin. Deficiency of this vitamin results in instability and fragility of all such tissues by reason of the breakdown or liquefaction of "the intercellular cement substance (collagen), with easy rupture and ineffective healing of any and all such tissues. This would apply to the "condensed connective tissues" of the above-mentioned basement membrane, and its thus acquired instability and vulnerability is, we believe, the preconditioning factor in cancerogenesis. We now know that this frailty of connective tissues is "brought about through the loss of activation of the constructive phase of the protein-building enzymes, which is normally furnished

by vitamin C" (Editorial, J. A. M. A., 117: 937, 1941).

The application of this same principle to the pathogenesis of the connective-tissue tumors (sarcomata) may be made in modified form in assuming the possibility of the breakdown of the intercellular cement substance which normally binds together the endothelial cells of the vascular intima and the serosa of the pleural, pericardial and peritoneal cavities, thus resulting in their erratic and malignant proliferation and dissemination by metastases. The not infrequent combined incidence of carcinoma and sarcoma, as in the carcinosarcomata, is also suggestive of a common etiology.

DISCUSSION

This hypothesis would clarify the observation that metastases of carcinomata travel mostly by the lymphatics, whereas the mesenchymal neoplasms (sarcomata) spread mostly through the blood vessels. It would also account for the early encapsulation of certain benign tumors (fibromata), thus preventing metastasis. Later, in the event of C-avitaminosis, these same tumors may lose their protective barrier by spontaneous dissolution or by faulty surgery or cauterization, thus releasing their cellular contents to take on an infiltrating malignant course. Likewise, chronic or indolent ulcers which may have attained closure by cicatrization may break down in later life under accentuated deficiency of vitamin C, resulting in transition to malignancy. It would also explain the relatively benign nature of the scirrhus or hard carcinomata, with predominant connective-tissue stroma, as contrasted with the medullary or soft variety with predominant cellular composition, and extreme malignancy, the vitamin-C status and proportionate connective-tissue response determining the degree of malignancy. This hypothesis would also account for the hemorrhagic and ulcerative features of most cancers, since these are also characteristic signs of vitamin-C deficiency.

That physiological instability of the connective tissues is associated with deficiency of vitamin C is forcibly shown by the classical reports of Lind (1753), Willis (1667) and Poupart (1699) on their finding in scurvy. Lind reports that in autopsies on scurvy victims he found the muscles so lax and tender that they readily fell apart. He found the intestinal musculature in the same condition. He further comments: "Why the scurvy should so frequently, and in so singular manner, affect the cartilages of the ribs, so as sometimes to separate them altogether from their connection to the breast bone, . . . I own I am at a loss to account for". He also reported a number of scurvy cases in which old fracture calluses and old scar tissue had broken down. (These might have developed cancer if scurvy had not taken them sooner.) In fact Lind also cites Martini (1609) as stating that scurvy is nearly allied to the plague, as it occasions carbuncles, buboes and cancer. Willis, the great English anatomist, of "circle-of-Willis" fame, relates in his "Tractus de Scorbuto" a symptom which he had observed several times, viz.: "A crackling of the bones upon moving the joints. Even upon turning in bed, by rubbing of the vertebrae upon each other, a considerable noise was perceived, like to the rough handling of a skeleton". Poupart, the great French surgeon, whose name is linked with "Poupart's ligament", in reporting his findings in Paris scurvy victims, states: "In some, when moved, we heard a small grating of the bones. Upon opening their cadavers the epiphyses were found entirely separated from the bones, which by rubbing against each other had occasioned this noise. In some we perceived a small low noise when they breathed. In those (post mortem) the cartilages of the strenum were found separated from the bony part of the ribs. . . . The ligaments of the joints were found corroded and loose. . . . All the young persons under 18 had in some degree their epiphyses separated from the body of the bones."

Lind's observation of the breakdown of old fracture calluses and scar tissue is confirmed by recent research by Hunt[5], who was first to observe the breakdown of previously formed scar tissue as the result of vitamin C deficiency causing liquefaction of the intercellular cement substance. More recently, Pirani and Levenson[6] studied the effect of vitamin C deficiency on previously healed wounds. Guinea pigs bearing wounds which had been healed for six weeks were subjected to a vitamin C-free diet for 26 days, by which time severe changes were observed in the area of the scar tissue. These consisted of fibroblastic proliferation, regression of connective tissue elements and hemorrhages (very suggestive of precancerous changes—W. J. McC.). Billroth, the famous 19th-century Viennese surgeon (1829-1894), recorded a somewhat similar observation. He had expressed the belief that cancer cannot develop without long-continued precancerous changes in the tissue involved. To illustrate this point, he cited the case of an epithelioma developing after many years on the site of an extensive scar from an old burn. He, of course, did not correlate vitamin C deficiency to the connective-tissue breakdown. Bonney[7], in a study of precancerous changes, finds constant loss of connective tissue, usually hyaline changes in the collagen, and fraying of the edges of epithelial cells (Very suggestive of vitamin-C deficiency —W. J. McC.). He states: "In the area of primary carcinoma there has always occurred a complete disappearance of yellow tissue as a result of a pre-existent chronic inflammatory process, and it is in this de-elasticised area that the first epithelial down-growths occur". (Bonney had no knowledge of vitamin C.).

The recorded occurrence of multiple primary cancers (3.7 per cent of all cancerous cases according to U. S. statistics) indicates the presence of a systemic exciting factor. In 420 such cases reported by Warren and Gates (cited by Ewing) 111 had 3 or more primary lesions, 67 had primary cancer in symmetrical organs, and 242 had primary cancer in 2 different organs. These findings would indicate that in certain persons there is a predisposition to cancer, which, in the opinion of the writer (W. J. McC.), could well be deficiency of vitamin C.

There are certain observations reported in the recent flare-up of research studies on lung cancer and tobacco smoking which seem to indicate a confirming correlation with the hypothesis of the etiologic relationship of vitamin C deficiency. In a report submitted by the American Cancer Society at the 1954 convention of the American Medical Association, the death rates of 187,000 men between the ages of 50 and 70 were checked for a period of 2½ years against their tobacco-smoking habits. In general it was found that the death rate from all causes was 60 to 102 per cent higher in cigarette smokers than in non-smokers. The death rate from lung cancer was 200 to 1500 per cent higher, depending upon the degree of addiction, and that of cancer in general was 150 per cent higher in cigarette smokers as a whole than in non-smokers.

These figures definitely indicate a systemic, as well as a local cancerogenic effect from the tar and other toxic elements in the tobacco smoke; and according to the writer's hypothesis this might well be indirectly due to vitamin C deficiency. In this respect cigarette smoking has a three-fold impact on the human organism: (1) The respiratory mechanism is submitted to direct and repeated exposure to the specific cancerogenic tars of the burning tobacco. (It should be noted that these tars are not found in the tobacco plant, but are solely products of combustion and may be produced as readily in the burning of wood and paper, even

cigarette paper, as shown recently, by Lafemine[8]). These tars act locally as an irritant to the respiratory tissues and thus stimulate cancerogenic reaction. Furthermore, this irritation, per se, causes local depletion of vitamin C needed in tissue repair. (2) The systemic absorption of the tars and other toxic elements, including nicotine and carbon monoxide, interacting chemically with the systemic storage of vitamin C (the latter being a powerful reducing and oxidizing agent) still further lowers the body level of this vitamin. (3) Smoking definitely distorts the dietary pattern of its habitues, in that they incline to the use of stimulating beverages (tea, coffee, cola and alcohol) in preference to citrus, tomato and other fresh fruit and vegetable juices containing vitamin C. Thus the intake of this protective food element is reduced, while the body storage is depleted; and since the vitamin is water soluble and is constantly washing out of the system through the kidneys and perspiration, the body storage soon reaches a very low level.

During the past 15 years the writer has made close to 6,000 chemical tests of the body level of vitamin C, and in such tests on hundreds of steady smokers has yet to find a single case showing a normal level unless potent supplements of the vitamin are being taken. About ten years ago the writer determined by clinical and laboratory research that the smoking of one cigarette by the ordinary inhalation method resulted in the neutralization of 25 mg. of vitamin C in the body, or the equivalent of the vitamin C content of one average sized orange[9]. Thus the inability of the average smoker to attain a normal body level of this vitamin from dietary sources is quite apparent. The author's research in this respect has recently been confirmed by Bonquin and Masmanno[10] and by other investigators in Italy and Russia. It would thus seem possible that all cancerogenic agents, chemical and physical, act indirectly as such by reacting chemically with or increasing the body requirement of vitamin C.

A similar interaction has been found between certain chemical cancerogens and riboflavin, which also is known to have chemical reducing action. Kensler et al.[11] report marked inhibition of cancer induction by concurrent feeding of riboflavin with a well recognized chemical cancerogen. Later, Mueller and Miller[12] found this protective effect of riboflavin to be brought about by a reductive cleavage of the cancerogen, converting it into two non-cancerogenic compounds. It would thus appear that riboflavin is synergistic with vitamin C in cancer inhibition.

As a further check on this theory of indirect cancerogenesis the author made an in vitro experiment to determine the possibility of chemical interaction of vitamin C and the cancerogens. A small quantity of dibenzanthracine, a cancerogenic constituent of tobacco tar, was added to a solution of ascorbic acid of predetermined strength. A common solvent, dry alcohol, was used. A subsequent titration of the mixture showed a material drop in the ascorbic acid level. Presumably this reaction brought about a proportionate reduction in the potency of the cancerogen. Similar experimentation, in vitro and in vivo, with other cancerogenic agents is anticipated. A comparable situation has prevailed regarding alcohol. For many years it was thought that alcohol was a specific cause of peripheral neuritis, a common affection in chronic alcoholism, but it is now known that deficiency of vitamin B_1 is the real culpable agent, the alcohol acting indirectly by increasing the body requirement of this vitamin.

Regarding cancer in infants and children: Lawrence and Donlan[13] state: "It seems clear that several types of embryonic tissue have a high degree of sensitivity to cancerogenic agents. The acute leukemias are an example of disease that may have such an origin. Leukemia seems to be increasing in incidence in recent years, especially in young children under 5 years, suggestively due to carcinogenic stimulation in prenatal life". (This suggests a possible correlation with the increase in smoking by women and the indirect production of vitamin C deficiency thereby in fetal life and early infancy by the mechanism previously described. —W. J. McC.)

All forms of physical and chemical irritation predisposing to malignancy, including trauma, thermal and electric burns, ultraviolet ray, x-ray, radium, atomic fission, chronic infections and inflammatory lesions, or exposure to toxic cancerogenic agents, are known to increase the body requirements for vitamin C, the lack of which increases vulnerability of body tissues to all such agents. Accordingly, vitamin C therapy is effective in minimizing tissue damage in all such conditions, thus serving to reduce potential malignancy.

Bodansky et al.[14] studied the vitamin C level of the blood plasma and the white blood cells in healthy subjects as compared to that of cancer cases. They found the levels in the latter to be significantly lower. Russell et al.[15] report that recurrent periods of scurvy, interspersed with periods of lettuce supplementation to prevent death, resulted in a significant shortening of the time of appearance of induced cancer in guinea pigs.

Schneider[16] cites Eickhorn as finding the vitamin C deficiency of cancer cases very pronounced, averaging 4,550 mg. by the saturation method, while his non-cancerous controls averaged only 1,350 mg. On the basis of these findings, he (Schneider) applied intensive vitamin C therapy, 1,000 to 2,000 mg. daily, supplemented by vitamin A, in some hundred early and advanced cancer cases. He reports marked general improvement as shown in reduction in size of tumors, increase in body weight, lowered blood sedimentation rate, delayed cachexia, reduction in hemorrhage and ulceration. He obtained no complete cures. He considers the results as favorably comparable to sex hormone therapy in genital carcinomata, with the great advantage that it is at least harmless.

Regarding the concurrence of cancer and tuberculosis: Lebert, in 1852, stated that he had many times observed the coincidence of tubercle and cancer. This is so well recognized at the present time that the Index Medicus has a special sub-heading for "Cancer and Tuberculosis" under the index listing of "Cancer". The common factor in these two diseases would seem to be vitamin C deficiency, since both are known to be associated with pronounced C-avitaminosis.

Another suggestively significant observation reported by medical missionaries and in geographic research studies is the finding of large communities of primitive tribes in Africa, South America, Indonesia and certain islands of the Pacific ocean, to be almost completely immune to cancer. The food supply of all such people is mainly from natural sources, of which fresh fruits and vegetables, rich in vitamin C, form a prominent part.

It is not expected that the development of the writer's hypothesis, as herein advanced, will lead to a cure for cancer in its advanced or metastatic stages; but the prospects for prophylaxis and enhancement of surgical and radiation therapy by concurrent vitamin C therapy seem very encouraging. After all "an ounce of prevention is worth a pound of cure".

SUMMARY

After reviewing the history of cancer and the various theories

of its cause, the writer advances the hypothesis of vitamin C deficiency, bringing about rupture of the sub-epithelial connective-tissue basement membrane, as the critical preconditioning factor in pathogenesis. A number of 19th century writers are cited as relating the cancerous invasion by epithelial cells to weakening and consequent failure of restraint by the supporting connective tissues. The author correlates these earlier concepts with our knowledge of the function of vitamin C and observations of earlier writers on scurvy, and thus evolves this new etiologic approach. A number of research findings are cited which give direct or indirect support to the author's concept.

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