

CANCER: A COLLAGEN DISEASE, SECONDARY TO
A NUTRITIONAL DEFICIENCY?

W. J. McCORMICK, M.D.

Toronto, Canada

In a previous paper¹ we advanced the hypothesis that the invasive metastasis of cancer was etiologically secondary to a degenerative change in the connective tissues, notably the condensed connective tissue of the "basement membrane" underlining the epithelium of the dermal and mucosal tissues, which in turn could be secondary to a deficiency of vitamin C. This same deficiency could involve the collagenous intercellular cement substance which normally holds the epithelial cells together in orderly arrangement, thus further contributing to faulty healing and metastasis of precancerous lesions.

Since our first paper on this subject was published, additional evidence contributory to the validity of our hypothesis has come to our attention, which we wish to present.

Gillman et al.², in a histopathological study of dermal injuries, report that 1) The dermal changes in chronically injured areas seem to represent either alterations in pre-existing collagen or elastin, resulting in the formation of "pseudo-elastic tissue", definable by both morphologic and tinctorial criteria". 2) This pseudo-elastic tissue is regularly encountered in sites of chronic injury to connective tissues in the skin, as well as in other structures such as the arteries and gall bladder. 3) This pseudo-elastic tissue, preceded by and associated with extensive, though non-malignant, epidermal invasion of the dermis, can consistently be produced experimentally in normal human subjects, with altered connective tissue in injured sites. In their summary these authors state: 1) "It is shown that similar elastotic degeneration of collagen is invariably present in the dermis in many degenerative skin conditions which may and frequently do become precancerous. 2) It is suggested that the elastotically degenerated dermal collagen may play an important role in the pathogenesis of skin cancer." These authors in no way implicated vitamin-C status as related to the development of the elastotic degeneration of collagen observed in their experiments, and no determination of the vitamin-C status of their subjects was reported.

The observations of Gillman et al. are not altogether new. Bonney³, in a study of precancerous tissue changes, finds constant

loss of connective tissue, usually hyaline changes in the collagen and fraying at the edges of epithelial cells. He states: "In the area of primary carcinoma there has always occurred a complete disappearance of yellow elastic tissue, and it is in this de-elasticized area that the first epithelial down-growths occur." (Bonney, in 1908, had no knowledge of vitamin C.)

Wolbach, S. B. and Howe, P. R.⁴ have observed that the ground substance (collagen), normally effective as an intercellular cement substance, capable of holding epithelial cells together in normal relationship, assumes a watery consistency in scurvy. Gersh, I. and Catchpole, H. R.⁵ found that the liquefaction of collagen in scurvy is a depolymerization of glycoprotein, the major constituent of the normal ground substance. Pirani, C. L. and Catchpole, H. R.⁶ found that the glycoprotein thus liquified is released into the blood stream, resulting in an increased serum level of same. Wolbach, S. B.⁷ found that administration of ascorbic acid (vitamin C) in scurvy rapidly restores the normal consistency of collagen. Simpkin, S. et al.⁸ report that an increase of serum glycoprotein is found in cancer, and other studies by Wingler, 1953, Greenspan, 1954, Locky et al., 1956, and Lansing, 1957, have confirmed this finding. A correlation of these findings gives definite support to our hypothesis. As further evidence a diagnostic test for cancer has been developed in Germany (The Whitting Reaction) based on the blood protein picture.⁹

Schneider, E.¹⁰ cites Eickhorn as finding a pronounced deficiency of vitamin C in cancer cases, averaging 4,550 mg. by the saturation method, while his non-cancerous controls averaged only 1,3550 mg. Bodansky et al.¹¹ studied the vitamin-C level of blood plasma and 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.¹² 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. These findings give further support to the etiologic relationship of vitamin-C deficiency in cancer.

In accordance with the above observations we maintain that the degree of malignancy is determined inversely by the degree of connective-tissue resistance, which in turn is dependent upon the adequacy of vitamin-C status. To illustrate this point, the scirrhus or hard cancer of the breast is slow to metastasize and may remain inactive, or "in situ", for many years; whereas the medullary or

soft cancer of the breast is extremely invasive. In the former there is predominant connective-tissue stroma which binds the cells together more effectively, while in the latter the structure is mainly cellular and almost completely lacking in connective-tissue support. It may be that cancer cells, which are known to assume amoeboid activity, do so because of an inherent propensity, which becomes manifest solely because they have lost their connective-tissue anchorage as a direct result of vitamin-C deficiency. Furthermore, the efficacy of the Papanicolaou and other diagnostic smear tests may be solely due to this same loosely-bound and easy-shedding property of cancer cells that have thus lost their anchorage. The teeth become loose in scurvy for the same reason, namely the liquefaction of the cementum which normally holds them in their sockets under adequate vitamin-C status.

That the cancer cell, per se, is not malignant is shown by the fact that even after metastasis to distant parts of the organism it continues to exercise in degree its normal genetic function. For instance, secondary breast tumors have been found to secrete milk, secondary gastric tumors to secrete hydrochloric acid and pepsin, secondary liver tumors to secrete bile, etc.

The systemic or metabolic nature is shown by the recorded occurrence of multiple primary cancers (3.7% of all cases according to U. S. statistics). In 420 such cases reported by Warren and Gates 111 had 3 or more primary lesions, 67 had primary cancer in symmetrical organs, and 242 had primary cancer in different organs. We have recently seen reports of 2 cases in which 5 primary cancers were found. If our hypothesis is valid it would appear that the term "malignant disease" is a misnomer. Cancer is not a disease that strikes its victims like a bolt of lightning from a clear sky, but rather an ailment that we unwittingly cultivate or contract by perverse habits of life. Ravdin, I. S.¹³ has said: "While surgery and radiology are helpful, they do not attack the underlying biological defects. . . . Some time, some place, the existing jigsaw puzzle will be properly put together, and we shall wonder why the correct answer evaded us for so long a time."

The therapeutic implications from the above observations suggest that our major effort should be directed toward prevention of the cause of the cellular disarrangement—collagenous breakdown of epithelial and sub-epithelial tissues—as manifested in open sores or fissures that fail to heal readily, and unusual or easily produced hemorrhage, since such lesions may readily become precancerous. Advance warning of such conditions may be noted in

female subjects who bruise easily, as indicated by unaccountable "black and blue" marks. We have found that fully 90% of our adult female population are so afflicted, yet little or nothing is done about it, although this condition can be readily reversed in a matter of days by a liberal intake of vitamin C from natural sources, supplemented by oral or parenteral ascorbic acid in pronounced cases.

Our observations have led us to the conclusion that the major cause of vitamin-C deficiency in our modern civilization may be the well-nigh universal tobacco addiction. The smoking habit not only militates against normal nutritional practice, but actually neutralizes or destroys to a great extent what little vitamin C is taken in food. We have found by clinical and laboratory means (in checking the vitamin-C requirements of subjects while smoking and not smoking) that the smoking of one cigarette, as ordinarily inhaled, tends to neutralize in the body about 25 mg. of vitamin C, or the content of an average-sized orange. This reciprocal effect is due to the pronounced chemical action of ascorbic acid as a reducing agent.¹⁴ Our findings in this respect have been confirmed in general by independent research in U. S. A. and in Europe. On the basis of our hypothesis these findings would explain the phenomenal increase in lung cancer in smokers in recent years.

This new theory of the etiological relationship of vitamin-C deficiency in cancerogenesis suggests the possibility that all physical and chemical cancerogens may act indirectly by bringing about or exaggerating a latent deficiency of vitamin-C. A comparable situation has prevailed regarding alcohol. For many years it was thought that alcohol was the specific cause of peripheral neuritis in the alcoholic subject, but it is now known that deficiency of vitamin B₁ is the culpable agent, the alcohol acting indirectly by increasing the body requirement of this vitamin.

Recently the Sloan-Kettering Institute¹⁶ reported a series of experimental transplants of live cancer cells in human subjects in an effort to get answers to the following questions: "Why will cancer strike one American in four, and why will the other three not get cancer? What are the differences between the cancer-prone and the cancer free? Why does a tumor smoulder in one human, grow slowly but steadily in another, flame wildly through the body of a third? Why does a cancer—very rarely, but demonstrably—stop growing, melt, disappear in some patients? Why does cancer growth, in other patients, seem at times temporarily checked, and then why does it accelerate again? . . . Is there im-

munity to cancer? If so, is it something that exists in the cancer-free but is lacking—or lost, or destroyed—in the cancer victim? Are there at least partial natural defenses against cancer? Can they be identified, studied, stimulated, increased, created artificially or borrowed to protect the potential cancer victim—or rescue those attacked?"

To begin with they transplanted cancer tissue under the skin of the forearm in 15 advanced cancer cases. In every case the cancer implant "took", grew vigorously, and spread, for periods ranging from 6 weeks to 6 months, before they were removed by surgery. Obviously these subjects were completely lacking in resistance to cancer. For comparison another group of 14 willing subjects (Inmates of Ohio State Penitentiary), normally healthy and cancer-free, were given similar injections of the same stock of cancer cells, and in every case there was an overwhelming defence reaction, and within 4 weeks almost all the cancer tissue had been destroyed.

In these studies no cognizance was given to the nutritional background or living habits of the subjects and no correlation in this respect was envisaged. It is our belief that if such an assessment had been made a better approach to solution of the problem would have been achieved. However, these experiments seem to confirm the concept of a systemic or metabolic etiology in cancer.

It is not expected that our hypothesis, as advanced herein, will lead to a cure for cancer in its advanced or metastatic stages; but the prospects for prophylaxis and the curbing or containing of the disease in its early stages seem most encouraging. As an aid in the solution of this vital problem it is suggested that biochemical studies of vitamin-C status should be made on all middle-aged subjects, and nutritional guidance given accordingly, in the hope of at least effecting prophylaxis of this terrible disease. A simple qualitative color test of the urine is now obtainable for this purpose. After all, "An ounce of prevention is worth a pound of cure".

SUMMARY

We submit herewith additional evidence in support of our previously advanced hypothesis¹ that deficiency of vitamin C, by bringing about disintegration of epithelial and connective tissue relationships, owing to liquefaction of the intercellular cement substance (collagen), results in a breakdown of orderly cellular arrangement, which could be the precursor to metastasis and malignancy.

The recent observations of Gillman et al. on collagen and connective tissue changes in the dermis of chronically injured areas are cited², indicating formation of "pseudo-elastic tissue". They suggest that similar collagenous degeneration is invariably found in the dermis in many degenerative skin conditions which frequently become pre-cancerous and frankly cancerous, and that elastotically degenerated dermal collagen may play an important role in the pathogenesis.

These authors in no way implicated vitamin C deficiency in the etiology of these degenerative changes, but we believe that such nutritional deficiency may be the primary cause of precancerous connective-tissue degeneration.

Other authors are cited to show that the increased serum-glycoprotein level in cancer cases, sometimes used as a diagnostic test, could readily be produced by the breakdown of collagen and associated connective tissue, and we believe that it could thus serve as a precursor of metastasis. Thus cancer could be a collagen disease of nutritional etiology.

REFERENCES

1. McCormick, W. J., CANCER: the Preconditioning Factor in Pathogenesis, Archives of Pediatrics (New York), 71:313-322, 1954.
2. Gillman, T., Penn, J., Bronks, Doris and Roux, Marie: Possible significance of abnormal dermal collagen and of epidermal regeneration in the pathogenesis of skin cancer, British J. of Cancer, 9:272-283, 1955.
3. Bonney, V. Connective-tissue Changes in Precancerous Lesions, Lancet, 1, 1889 1908.
4. Wollback, S. B. and Howe, P. R.: Watery Consistency of Collagen in Scurvy, Arch. of Path. & Lab. Med., 69:94, 1929.
5. Gersh, I and Catchpole, H. R., Liquefaction of Collagen in Scurvy a depolymerization of Glycoprotein, the major constituent of the intercellular cement substance, Amer. J. Anat., 85:457, 1949.
6. Pirani, C. L. and Catchpole, H. R., Serum-Glycoprotein in Experimental Study Arch. Path., 51:597, 1951.
7. Wollbach, S. B.: Administration of Ascorbic Acid in Scurvy restores the Normal Consistency of Collagen. (Am. J. Path., 9:689, 1923).
8. Simpkin, S., Bergman, H. and Prinzmetal, M.: An Increase of Serum-Glycoprotein is found in Cancer; Am. J. Med., 6:734, 1951.
9. Heinermann, E.: Is Diagnosis of carcinoma from Blood-Protein Picture possible? Med. Monatschr., 9:452, 1955.
10. Schneider, E.: Cites Eickhorn as finding pronounced Deficiency of Vitamin C in Cancer cases, Deutsche Med. Wchnschr. 79:15, 1954.
11. Bodansky, O.: Concentration of Ascorbic Acid in Plasma and White Blood Cells of Patients with Cancer and Non-Cancerous Chronic Disease. Cancer Research, 11:238, 1951.
12. Russell, W. A., Ortega, L. R. and Wynne, E. S.: Studies on Methylcholanthrene induction of Tumors in Scorbatic guinea pigs; Cancer Research, 12:216, 1952.
13. Ravdin, I. S.: Realignment in our Concept of Malignant Disease, Annals of Surgery, 142:765, 1955.
14. McCormick, W. J.: Ascorbic Acid as a Chemotherapeutic Agent. Arch. Pediat. 69:151, 1952.
15. Bonquin, A. and Masmanno, E.: Preliminary Report on the Effect of Smoking on the Ascorbic Content of Whole Blood, Am. J. Digest. Dis., 20: 75, 1953.
16. Sloan-Kettering Institute (New York City), Progress Report, June, 1958, page 10.

16 Gothic Avenue, Toronto.



Lee Foundation for Nutritional Research is a non-profit, public-service institution, chartered in the state of Wisconsin in 1941 to investigate and disseminate nutritional information. The attached publication is not literature or labeling for any product, nor shall it be employed as such by anyone. In accordance with the right of freedom of the press guaranteed to the Foundation by the First Amendment of the U. S. Constitution, the attached publication is issued and distributed for informational purposes.

LEE FOUNDATION FOR NUTRITIONAL RESEARCH

Milwaukee 3, Wisconsin