THE ROLE OF NUTRITION IN CANCER PREVENTION[1]

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CANCER represents one of the main causes of death in the United States and is second only to heart disease in this respect. Voegtlin[2] has reported that there are about 500,000 cases of cancer in the United States, with an annual death toll of about 160,000. The incidence of cancer is increasing. During the ten years between 1930 and 1940 the population increased 7 per cent., the number of deaths increased 2 per cent., but the number of deaths from cancer increased 35 per cent. It is difficult to say whether or not this increase in the incidence of cancer is a real increase or whether it is a reflection of increased accuracy in diagnosis, decrease in deaths from other causes or increase in the average age of the population. One doubts whether the accuracy in diagnosis has increased 35 per cent. between 1930 and 1940, and the argument that more people live to be older has little weight because when one considers only the older groups, the incidence of cancer among those who do survive to old age is also increasing. As for the argument of a decrease in deaths from other causes, it should be remembered that the incidence of death due to cancer's chief competitors is also increasing: Every death due to heart disease has the effect of lowering the incidence of cancer, yet both are increasing. Brody,[3] of the University of Missouri, and others, have suggested that the increased incidence of the diseases of old age may be due to the over-nutrition and under-exercise which has accompanied our so-called civilization. The incidence of diabetes among women over 45 was reported to have doubled between 1920 and 1930, and it was shown that between 80 and 90 per cent. of diabetics had been overweight prior to the onset of the disease. There is apparently a correlation between diabetes and cancer, for it has been shown[4] that the incidence of cancer among diabetics is much higher than in the population at large. Furthermore, life insurance records have shown[5] that people who were overweight at the time insurance was taken out were more liable to cancer in later life. I do not need to remind this group that our way of life has changed greatly in the last forty years. You have seen the change with your own eyes. But as a concrete illustration which "dates" the change, let me remind you that between 1910 and 1920 this country changed from the horse-and-buggy stage to the automotive era. That decade occurred during the youth of many people who are now cancer patients. However, I wish to emphasize that we do not draw our conclusions from statistics on human cases but insist on controlled experiments with animals. It is interesting to find that when animals are placed under certain conditions analogous to those of "civilized" man, the incidence of cancer increases, as I shall show later.

One of the questions most frequently asked of cancer investigators is whether the cancer problem is amenable to research, that is, can it be solved, or is it a hopeless task? The answer of course depends upon what is meant by a solution, but I may say that we are confident of ultimate success. There have been many successes in the past, chief of which have been the development of x-ray and radium treatments and emphasis on early diagnosis. More recently, one of our colleagues, Dr. F. E. Mohs, has developed an amazingly successful technique of controlled chemosurgery for the removal of surface cancers. Surgery has also been making steady progress through the years. Nevertheless, I suspect that the public does not regard any of these methods as cures, since they are all amputative in nature, and we are all impressed by the miracles achieved in other fields with the sulfonamides, penicillin, etc. It is clear that the public conception of a cancer cure is very definite, namely, a chemotherapeutic agent for cancer, and even when one from time to time and a recent report on penicillin suggested a selective action on tumor cells *in vitro*. Nevertheless, there is at present no clinically proved chemotherapeutic agent. There are reports of success is developed it may act on only one kind of cancer. For my part I have deliberately turned my back on the search for chemotherapeutic agents, and in the present talk I wish to emphasize cancer prevention. I believe I can show that there is considerable justification for optimism regarding this approach.

CHEMOTHERAPY VS. PREVENTION

There are, then, two possible solutions to the cancer problem. One is chemotherapy, and the other is prevention. Most other diseases can be looked upon in a similiar light. As a general proposition, prevention is always preferable to cure, but the public is much more impressed with Dr. Ehrlich's "magic bullet" than they are by the hard and simple facts of syphilis prevention. Perhaps if no chemotherapy were available

[1] Address given at the annual meeting of the South Dakota Academy of Sciences, May 5, 1944, Brookings, S. D.

[2] C. Voegtlin, *Proc. Inst. Med. Chicago*, 14: 16, 1943.

[3] S. Brody, *Ann. Rev. Biochem.*, 4: 383, 1935.

[4] F. Ellinger and H. Landsman, *N. Y. State Jour. Med.*, 44: 259, 1944.

[5] A. Tannenbaum, *Arch. Path.*, 30: 509, 1940.

the demand for quarantining syphilis cases would be as forceful as the demand for quarantining cases of scarlet fever and other contagious diseases for which no chemotherapy is available. In the case of malaria, the importance of quinine and atabrine is undeniable, yet those who are in the field tell us that the most important factor in lowering the malaria toll is prevention. Naturally it must be conceded that a cure which would be as effective for cancer as penicillin is for certain types of infections would be a great blessing to mankind. But if, as I suspect, the answer to the degenerative diseases such as cancer lies in prevention through appropriate self-discipline, then it is possible that under such a program mankind would reap even greater benefits. Without impugning the motives of those who choose the chemotherapeutic approach in research, it can be said that the profit motive alone will guarantee that the search for chemotherapy will continue, and it is appropriate that the cost of this research be carried by the commercial organizations that are most likely to profit from it. On the other hand, we who carry on in State institutions at public expense are in a real sense obligated to carry through the type of research which has no profit motive. For, make no mistake, there will be no reward for a program of cancer prevention. We can not hope to sell it, and in fact I expect we will have difficulty in giving it away.

There are other reasons why we place our emphasis on cancer prevention. In the field of chemotherapy the testing of all possibilities in terms of varying dosage, varying chemicals and varying combinations of chemicals would be an infinite and uninspiring task, in which negative results are virtually worthless. Meanwhile the discovery could easily come as the result of a lucky accident. Some lone research worker could easily stumble upon a chemical or combination of chemicals that would be effective. On the other hand, no one will ever stumble upon the factors involved in cancer prevention; an organized drive, sustained over a period of years, is necessary. A cancer institute is capable of such sustained effort; the lone worker is not. A cancer institute can not afford to use stumbling as an experimental method; the lone research worker, who is earning his livelihood by teaching or practising medicine, can. In my opinion, cancer prevention is more likely to succeed in the long run than is the search for chemotherapy, but in addition I wish to point out that in gaining an understanding of the cancer problem we may be led to a rational method of searching for a chemotherapeutic agent. Furthermore, in gaining an understanding of the fundamental nature of cancer we are getting at the nature of life itself, and the solution to many diseases which are now obscure will be hastened by the results of the studies on the fundamental aspects of the cancer problem.

Experimental Cancer Production

Let us now look at the tools at our disposal. The most important fact is that we can produce cancer in experimental animals at will; we can predict the per cent. which will develop cancer, and we can produce cancer by a variety of methods and in a variety of animals. We are sure that we are dealing with cancers which are comparable in every way with human cancers. But it has taken just about forty years to reach the present position. Cancer was first successfully transmitted from one animal to another in 1898 and 1900, and the first production of a virus tumor was effected about 1908. It was not until 1915 that it was shown that successive applications of tar would produce skin cancer, and it took a further fifteen years for the isolation of a specific carcinogenic (cancer-producing) chemical from the tar. About this time the production of skin cancer by ultraviolet light was discovered accidentally. In 1935 mammary tumors were produced by means of estrin injection and at about the same time the Japanese produced liver tumors by feeding certain azo compounds in the diet. Only in the last two or three years has this technique been standardized sufficiently to be strictly reproducible with diets of known composition. Thus by 1940 we had at our disposal an excellent array of experimental cancer-producing techniques.

The Stages of Cancer Development

Various investigators have begun to realize that the development of a cancer is not confined to the grossly visible events, but that there are a series of imperceptible changes which precede the actual eruption of a malignant cancer. We prefer to divide these events into 3 stages, as follows:

I. *Induction Period:* Result of radiations, chemical carcinogens, heredity, viruses;
II. *Critical Period:* Affected by irritation, injury, caloric intake, exercise;
III. *Period of Progression:* Result of release from restraint of normal cells.

Now, of these three phases, the first is well standardized from an experimental standpoint and is easily controlled. In human cancer, the induction may be caused by excessive radiation including ultra-violet, and in certain cases by extraneous chemical carcinogens, but in most cases it is probably a result of a hereditary defect. However, the mere production of cancer cells as a result of heredity or as a result of painting with a carcinogen does not guarantee that a tumor will result, as can be easily proved. During

the second or critical period the cancer cells are susceptible to environmental changes, and they may regress or they may continue to develop until they suddenly break away from the restraint of the host cells and a malignant cancer suddenly appears.

THE CRITICAL PERIOD

The effect of the extrinsic factors could not be studied adequately until the methods for inducing cancer had been worked out, and this has been very recent. My colleague, Dr. H. P. Rusch, recently reviewed[6] the role of the extrinsic factors in cancer production, and it is interesting to note that over 50 per cent. of the 222 papers reviewed had been published between 1939 and 1942. It has been shown by various workers that a restriction of the caloric intake cuts down cancer incidence (see review by Rusch[6]). In one of Tannenbaum's experiments with mice which showed a high incidence of spontaneous (*i.e.*, hereditary) mammary tumors, restriction of the food intake to a maintenance level reduced the cancer incidence from 67 per cent. to zero per cent. There were 50 mice in each group and the experiment was continued for 86 weeks.

The production of tumors by ultra-violet light has been studied intensively by Dr. Rusch and coworkers, who have kindly allowed me to use some of their data. They used 4 groups of 48 young adult mice per group. The effect of a restricted food intake upon longevity, etc., has not always been carried out in a rigorously controlled fashion, and some nutritionists have concluded that the restriction is so severe as to make life (from the human standpoint) so undesirable as to cancel any advantages to be gained by increasing the life span. The experiments by Rusch *et al.* were admirably controlled from a number of standpoints; all four groups received exactly the same amount of protein, salts and vitamins. Two groups received high carbohydrate; the groups were furthermore arranged so that two groups received only sufficient calories to maintain their body weight. They were not emaciated or unhealthy, but they were constantly active, always searching for food; these were the low-calorie animals and received 6.4 calories of food per day. The other two groups are called the high-calorie animals; they received 9.6 calories per day, which is 50 per cent. more than is required to maintain weight. It is just slightly less than they would eat if fed *ad libitum*. The mice received a standard minimal dose of cancer-producing ultraviolet light for 30 minutes every other day. For five months, no cancers appeared. Then, in the high-calorie groups, skin cancers began to appear on the ears. Now, at nine months, none of the high-calorie: high-carbohydrate mice remain. Six of the 48 had died from unknown causes and 42, or 88 per cent., had developed cancer. Among the low-calorie: high-carbohydrate mice, only one, which is 2 per cent., has developed cancer at nine months. The high fat groups showed a similar but less striking calorie effect.

The low-calorie mice receive a great deal of exercise, since they are constantly in motion, whereas the high-calorie mice receive almost no exercise and are quite indolent. In a forced exercise experiment Dr. Rusch also showed a decreased cancer development. The exercised mice ate *less* than the controls and it is thus difficult to say how much of the calorie effect is due to exercise and how much of the exercise effect is due to calories. The calorie effects obviously are not responsible for cancer induction and therefore do not act during the first period. Tannenbaum concluded that the calorie intake did not alter the growth rate of the tumors which did develop. It is evident that the calorie effect acts during the second phase of tumor development, that is, the critical period.

THE EFFECT OF IRRITATION DURING THE CRITICAL PERIOD

The evidence for a critical period also depends on a number of experiments which involve various kinds of irritation. One of the most effective chemical irritants is croton resin, which is a constituent of croton oil. Berenblum painted mice with the carcinogenic hydrocarbon benzpyrene once a week for six months, using a subcarcinogenic concentration of 0.05 per cent. benzpyrene in acetone. Comparable groups were given similar treatment but were painted with dilute solutions of croton oil or croton resin in addition. Benzpyrene or croton oil alone was ineffective, but together they produced cancer. It was also possible to treat mice with a carcinogen for several months, completing the induction period; if the animals were then treated for several months with croton oil during the critical period, cancer resulted. If the croton oil was not applied, the critical period was passed without further development, and regression was the result. As a matter of fact the length of the critical period can be determined, because there comes a time when the application of croton oil will no longer produce cancer following treatment with a carcinogenic hydrocarbon.

Clinicians have frequently associated cancer with burns, yet many people are burned without cancer resulting. What is the relationship here? Again experiments on animals provide the answer:[6] If potential cancer cells are present, a burn can make the difference between a progressing cancer and a regressing cancer. It was shown that with a critical dose of methylcholanthrene for three months, subsequent ap-

[6] H. P. Rusch, *Physiol. Rev.*, 24: 177, 1944.

plications of a small wad of cotton which had been dipped in hot water greatly increased the cancer incidence. The burns alone never produced cancer.

There has also been the question of the relation of physical injury to cancer. Kline and Rusch have shown that a small cut applied twice a month to an area which is in the critical period following tumor induction by methylcholanthrene will cause the development of cancers, while injury alone did not produce cancer.

It is thus apparent that various types of injury, when occurring in the vicinity of potential cancer cells, are capable of completing the sequence of events which culminate in cancer. It is also easy to see how many or most cancers can be associated with injuries, while millions of injuries can occur without producing cancer. The cocarcinogenic effect of irritation and injury upon potential cancers may be expected to occur more or less independently of the plane of nutrition of the host, and the beneficial effect of cancer-preventing nutritional measures during the critical period would therefore be greatest in the absence of chronic irritations.

Restraint by Normal Tissue

It was suggested earlier in this discussion that during the critical period, the cancer cells are susceptible to the influence of the host and are restrained by the normal cells. The basis for this is the fact that the normal sequel to an injury is growth which reaches a certain level and then stops when the injury has been repaired. This growth must stop by some self-regulatory process which is possessed by normal cells but is not possessed by tumor cells. The suppression of tumor growth by normal cells during the critical period undoubtedly occurs through the operation of the mechanism by which normal cells suppress their own growth when this is desirable. The attempt to explain this phenomenon brings us to the role of enzymes and their relation to life, which is the subject of my own researches.

During the forty years between 1900 and 1940, while the tools of cancer research were being forged, a parallel development was occurring in the enzyme field. This development began in 1897 when Büchner produced a cell-free enzyme preparation from yeast and showed that it was capable of fermenting sugar to form alcohol, thereby disproving Pasteur's idea that life was necessary for the fermentation process. The role of phosphate in biological energy transformations was introduced by the Russian Iwanoff and made certain by Harden and Young in England in 1905, when they isolated hexosediphosphate from fermenting extracts. A series of brilliant discoveries, mainly by European workers, followed, and culminated in Warburg's important finding in 1939, in which it was shown that oxidative phosphorylation was the link between fermentation and respiration on the one hand, and life on the other. These many findings I have organized into one chart[7] which shows our present state of knowledge in this field. The true meaning of this slide is shown in a much simpler chart[8] in which we indicate that life is really a community of enzymes which uses part of its food for fuel and part of it for building blocks with which to construct more living matter. In these schemes the word "energy" is essentially synonymous with a particular phosphorylated compound known as adenosinetriphosphate. When a cell is stimulated, this compound is split, and energy is available for function. In addition the split products set in motion a sequence of metabolic events which are designed to restore the original energy reservoir; one of these responses is growth. The relationships were presented in a recent review[7] in which we attempted to show the various responses which may follow a stimulus. The first response is the break-down of ATP to give energy which can be used either for function or for heat. The products of the reaction are adenylic acid and inorganic phosphate, which set in motion the adaptive mechanisms which restore the ATP. The first response is glycolysis. Glycogen breaks down to lactic acid in the presence of phosphate and adenylic acid, and the glycolytic process converts the adenylic acid and inorganic phosphate back to ATP. If the stimulus is stronger and continues longer, the pharmacologic control is called in. This acts both locally, giving vasodilatation, and centrally, giving sympathetic and parasympathetic nervous discharges which result in the secretion of adrenalin, insulin and in other reactions which make increased glycolysis and respiration possible. If the stimulus is severe enough to tax the ability of the organism to resynthesize adenylic and inorganic phosphate to ATP, a compensatory growth will occur, and we believe that this growth is controlled by the fact that these products are important building blocks in the construction of protoplasm, including more enzymes for glycolysis and respiration. When, by the acceleration of metabolism, the animal is able to keep up with the stimulus, the concentration of the building blocks is so low as to prevent growth. Thus growth as well as glycolysis and the pharmacologic mechanisms appear to be organized through this one common denominator. In addition to the responses noted, it appears that in the face of an overwhelming imbalance, the organism goes into a state of shock and dies.

[7] V. R. Potter, "Advances in Enzymology," 4: 201, 1944.

[8] *Ibid.*, *Jour. Am. Diet. Asn.*, 19: 488, 1943.

If we accept for the moment these mechanisms of controlling metabolism and growth, which we shall consider normal, the further step of evolving a cancer theory is obvious. We have proposed that cancer is due to an abnormal protein which is similar to a normal aerobic enzyme protein except that it lacks the catalytic power of the normal enzyme. This abnormal protein could occur accidentally as a result of poor heredity, or it could be produced experimentally by the action of carcinogenic agents on the normal enzymes. Cocarcinogenic agents, injuries and irritations could act by breaking down ATP. Ordinarily this process would simply stimulate the control mechanisms, repair would take place, and the process would stop. However, in the presence of the cancer protein, the process would be sidetracked and there would be no way for the normal cessation of growth to occur.

The nature of the calorie effect and the exercise effect involves the metabolic response which is mediated by the pharmacologic control. It appears to be due to the increased efficiency of the trained animal in working at a lower concentration of fuel and building blocks than can be tolerated by the cancer. In other words, the trained organism can compete with the cancer during the critical period. In the absence of exercise and in a flood of nutrient there is no competition and the cancer thrives. Eventually the cancer passes the critical point and is able to damage the surrounding tissue (possibly by acid) and thereby provide itself with a border of normal cells which behave as if they were treated with a cocarcinogen. The cancer then grows until the host is killed.

In conclusion I wish to re-emphasize that the cancer problem is susceptible to experimental study and that the nature of cancer now seems fairly clear. Animal experiments provide us with a definite guide toward the prevention of cancer in humans. The answer may consist in eating no more than we need and in keeping physically fit, with the addition of proper medical care so that any chronic irritations are eliminated. These precautions demand a considerable degree of self-discipline, but I am confident that as soon as the points are thoroughly established, educational campaigns can get the message across to the people. It is here merely suggested that nutritionists, dietitians, physicians and the public remain as alert to scientific developments regarding the effect of diet restriction and the effect of exercise upon nutritional requirements as they are to developments in dietary adjuvants. The restriction of the quantity of food eaten requires that the quality of the food be carefully controlled. The metabolic studies have other implications, which involve the frequency of food ingestion. The practice of feeding workers six times per day may be sound psychology, but it does not increase the efficiency of their metabolism.[9] It is now clear[10] that the human body adapts itself to various difficult situations by improving its metabolic efficiency. Since maximal metabolic efficiency appears to be related to decreased degenerative disease, the human race is confronted with a nice problem as to how to improve our external environment without weakening our internal environment. We believe that the future of mankind rests on the physical and psychological results inherent in the solution of this problem.

OBITUARY

RECENT DEATHS

DR. ROBERT TUTTLE MORRIS, professor emeritus of surgery of the Post-Graduate Medical School of Columbia University, died on January 9 in his eighty-seventh year.

DR. OSCAR V. BRUMLEY, since 1929 dean of the College of Veterinary Medicine of the Ohio State University, died on January 13 in his sixty-eighth year.

DAVID LUMSDEN, since 1922 and until his retirement in 1941 horticulturist of the Bureau of Entomology and Plant Industry of the U. S. Department of Agriculture, died on January 22 in his seventy-fourth year.

DR. WILLIAM T. ROOT, since 1935 dean of the Graduate School of the University of Pittsburgh, previously head of the department of educational psychology, died on January 24. He was sixty-two years old.

DR. LYDIARD H. W. HORTON, consulting psychologist, Boston, and lecturer on biopsychology at the School of Medicine of Boston University, died on January 19 at the age of sixty-five years.

WILLIAM T. DAVIS, entomologist, president of the Staten Island Institute of Arts and Sciences until his retirement with the title emeritus in 1934, died on January 22 at the age of eighty-two years.

HARRY PHILLIPS TREVITHICK, chief chemist of the New York Produce Exchange, died on January 17 in his fifty-ninth year.

DR. HENRY GREENWOOD BUGBEE, urologist of New York City, died on January 18 in his sixty-fourth year.

PROFESSOR PIERRE ALLORGE, specialist in mosses

[9] See "Symposium on Physiological Fitness," *Fed. Proc.*, 2: 164, 1943.

[10] *Ibid.*, pp. 144, 158.