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A REPORT ON CANCER

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A Report on Cancer

Hardin B. Jones

Since the discovery of carcinogens, hundreds of investigations have established quantitative dose-response relationships in induction of cancer by these chemical and physical agents. In every case, there is a rise in cancer risk with increasing exposure over most or all of the range examined, and each carcinogen has been investigated quantitatively to some extent. Often, increased dose of the carcinogen is also associated with decrease in the time required for cancer to become evident. Carcinogens can affect essentially all sites of cancer occurrence and the induced cancers increase systematically from a small "natural" risk of that cancer type. At very high levels of exposure to carcinogen, there is occasionally a relative decrease in effect, but the basic characteristic effect is nevertheless a relatively uniform upward trend in cancer risk associated with moderate to small dosages of carcinogens. Every known carcinogen shows this trend in dose-response relationships and most such studies support evidence for simple proportionality in cancer risk. This evidence suggests that cancers may all occur by induction and that the true "natural" rate, if any, must be smaller than the observed incidence. Such a thesis is also supported by the following:

- 1) The natural rate of cancer is usually not more than a few percent of deaths.
- 2) Cancers vary in prevalence by type, geographical location, occupation, etc., and the nonrandom distribution of "natural" cancer has often been noted.
- 3) Estimates of the true natural levels of cancer must be reduced by allowance for some carcinogens in the environment. Clearly, however, natural ionizing radiation does not account for all natural cancer; but this agency plus chemical carcinogens,

including viruses, may account for the cancer background, with the chemical-viral component by far the most significant.

- 4) The factors of genetic influence in cancer have never been clearly separated from environmental factors. Even in the case of identical twins, they -- in contrast to fraternal twins -- choose more nearly similar environments than do fraternal twins, making full separation of the genetic and environmental effects impossible.
- 5) Whatever the genetic base for explaining variation in susceptibility to cancer, a state that is definitely precancerous is not evident prior to clinical disease and each overt cancer probably has not existed for a significant length of time.
- 6) The evidence for chromosomal aberration as a cause of cancer also implies that the disease evolves as a disturbance of cell chemistry rather than as an inherent characteristic of the organism.

A reasonable tentative conclusion is that cancers occur in response to cancer-inducing agents and that there is essentially no "natural cancer" in the sense of genetic predestination to this disease.

A second important consideration about cancer is that all forms of overt cancer are associated with a random chance of survival which does not lessen with the duration of cancer. This strongly implies that there is some natural physiological restraint against progress of the disease and that the cause of the commonly observed rapid development of cancer in the terminal stages is the failure of the natural restraining influence.

Evaluation of the clinical response of cancer to treatment by surgery and radiation, separately or in combination, leads to the following findings:

- 1) The evidence for greater survival of treated groups in comparison with untreated is biased by the method of defining the groups. All reported studies pick up cases at the time of origin of the disease and follow them to death or end of the study interval. If persons in the untreated or control group die at any time in the study interval, they are reported as deaths in the control group. In the treated group, however, deaths which occur before completion of treatment are rejected from the data, since these patients do not then meet the criteria established by definition of the term, "treated." The longer it takes for completion of the treatment, as in multiple step therapy, for example, the worse the error. Even in the simpler treatments, the error amounts to about 3/4 year in average survival. With this effect stripped out, the common malignancies show a remarkably similar rate of demise, whether treated or untreated.
- 2) Beginning in 1940, through redefinition of terms, various questionable grades of malignancy were classed as cancer. After that date, the proportion of "cancer" cases having "normal" life expectancy increased rapidly, corresponding to the fraction of questionable diagnosis included.
- 3) If a treatment is effective, there is an optimal degree of treatment. This has been demonstrated with regard to cure of cancers of the skin, mouth, and large bowel by radiation or surgery. But with other cancers,

such as those of the breast or the cervix, no relationship between dose and cure has been demonstrated, even though widely varying levels of treatment have been investigated.

- 4) In regard to surgery, no relationship between intensity of surgical treatment and duration of survival has been found in verified malignancies. On the contrary, simple excision of cancers has produced essentially the same survival as radical excision and dissection of the lymphatic drainage.
- 5) In the matter of duration of malignant tumors before treatment, no studies have established the much talked about relationship between early detection and favorable survival after treatment. Curability of cancer essentially demands that the primary lesion be destroyed before metastatic spread of the disease has occurred. Serious attempts to relate prompt treatment with chance of cure have been unsuccessful. In some types of cancer, the opposite of the expected association of short duration of symptoms with a high chance of being "cured" has been observed. A long duration of symptoms before treatment in a few cancers of the breast and cervix is associated with longer than usual survival. This fact does not establish a positive benefit of no treatment, although that may be the case. It is more probable that these cases are a milder disease that has made very slow progress before detection.
- 6) In demographic considerations of cancer risks, no cures as a result of treatment were claimed prior to 1900. Most clinics began to report claims of cures by 1950, typically about 50% cure for the common malignancies such as cancer of the breast. Yet, the specific death rates for common malignancies have remained essentially the same for persons of the same age over this entire century. If the

claimed levels of "cures" are taken as valid, then it is necessary to postulate that there has been a perverse condition at work in all those countries that have kept records, whereby the gain due to clinical advances in cure has been precisely offset by an increase in incidence of each malignancy in each of the last 60 years. This is improbable.

- 7) Although there is a dearth of untreated cases, for statistical comparison with the treated, it is surprising that the death risks of the two groups remain so similar. In the comparisons, it has been assumed that the treated and untreated cases are independent of each other. In fact, that assumption is incorrect. Initially, all cases are untreated. With the passage of time, some receive treatment and the likelihood of treatment increases with the length of time since origin of the disease. Thus, those cases in which the neoplastic process progresses slowly are more likely to become "treated" cases. For the same reason, however, these individuals are likely to enjoy longer survival, whether treated or not. Life tables truly representative of untreated cancer patients must be adjusted for the fact that the inherently longer-lived cases are more likely to be transferred to the "treated" category than to remain in the untreated until death. The apparent life expectancy of untreated cases of cancer after such adjustment in the tables seems to be greater than that of the treated cases. There is a source of error in the opposite direction in that the more rapidly declining cases tend to be treated because of the desperateness of the condition. This error, however, appears to be of small magnitude because most of these cases terminate in death before completion of treatment and are thus eliminated from the data. In the cancers of shortest life expectancy, such as those of the lung, the stomach, or the rectum, treatment does not seem to accelerate the course of the disease.

Conclusions:

- 1) Evidence for benefit from cancer therapy has depended on systematic biometric errors.
- 2) Neither the timing nor the extent of treatment of the true malignancies has appreciably altered the average course of the disease. The possibility exists that treatment makes the average situation worse.
- 3) It is important to consider as a preferred mode of cancer therapy a mild degree of treatment designed to reduce the troublesome symptoms of the primary disease without adding to the health problems of the patient.
- 4) While the evidence for the falsity of claims about cancer therapy is overriding, some infrequent benefits may have been achieved but obscured by the major trend. In the absence of convincing evidence to this effect after 50 years of cancer therapy, however, these postulated benefits must be very rare indeed to have been incapable of proof.
- 5) The combined effect of ^{the} mistaken evaluation of the nature of cancer and the failure to recognize that treatment has not produced "cure" has had grave consequences. As in Arrowsmith, this example emphasizes the dangers of untested theories and uncontrolled observations.