of effectiveness, and the substance is still fit for use in medicine and surgery.

To date this method of low-temperature sterilization of vascular grafts has been employed in two humans with coarctation of the aorta, in whom the gap remaining in the aorta, after resection of the narrowed portion, could not be overcome by primary anastomosis. Frozen, irradiated aortic grafts (from human autopsy material) have been used in each case to bridge the aortic gap. These two patients have been followed 4 and 6 months postoperatively, and there has been complete relief of hypertension in each. It is believed that this represents the first time that any human organic substance sterilized by high-voltage cathode-ray irradiation at low temperatures has been sucessfully transferred from one human to another.

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Comments and Communications

Krebiozen[1]

KREBIOZEN is a term applied to an agent of unknown nature alleged to be useful in the treatment of malignant tumors. It is stated to have been discovered by Stevan Durovic, and to have been investigated for clinical activity by A. C. Ivy, head of the Department of Clinical Science, University of Illinois, in collaboration with others. A brochure concerning the agent and the experience with it was circulated as a presentation by Dr. Ivy at a meeting called by him in Chicago on March 26, 1951.[2]

Krebiozen is described as a white powder, soluble in water, mineral oil, and most organic solvents, prepared in an unspecified fashion from the serum of a horse treated in an unspecified way. It is certified as devoid of toxicity and is said to have been capable of restraining the growth of malignant neoplasms in an unstated number of dogs and cats.

The brochure describes the results of the use of Krebiozen in the treatment of 22 patients with various types of cancer. The patients can be divided into three groups on a chronological basis:

1) Seven patients treated during August, September, and October of 1941. Of these six are reported as dead.

2) Seven patients treated between January and June 1950. Two of these are reported as dead and five as living. Of the five, two are described as having early and advanced disease.

3) Eight patients treated between July and December 1950, of whom all are living. Of these, three are described as having early disease, one as having had the cancer removed surgically, and only two as having advanced lesions. In two the degree of extension is not specified.

One patient of Group 1 and three of Group 2, or four at most, of the total 14 individuals can be considered, on the basis of survival, as possibly showing evidence of control of the neoplasm, since eight of the 14 are dead, and two were not in an advanced stage. The period of observation was about a year.

Of the four patients (of the individuals included in the recently treated Group 3) who could, from the data, be regarded as having advanced cancer, the period of observation was only something over four months.

It is evident, therefore, that at the present time we cannot make any certain judgment that the claims on behalf of Krebiozen are valid.

Caution in cases like this is doubly indicated by the well-known fact that the history of the search for better means of cancer control is littered with the hidden wrecks of premature announcements based upon unwarranted conclusions. These cruel and irrevocable disappointments are due, uniformly, to three errors: (1) undue reliance on the subjective response of the patient; (2) unfamiliarity with the course of untreated cancer; (3) failure to require unequivocal objective evidence of an effect of the procedure on the cancer.

The unreliability of the subjective response of cancer patients in classic. Weil stated in 1915:

> It is a curious and interesting fact that almost every therapeutic claim made in recent years in connection with cancer has included among its virtues the relief of pain. . . . In view of this it is probably fair to assume

[1] This communication was solicited by the Editorial Board.

[2] *Krebiozen: An Agent for the Treatment of Malignant Tumors.* Discovered by S. Durovic, M.D.; presentation by A. C. Ivy, Ph.D., M.D. Chicago: Champlin-Shealy Co. Pp. 1–106 (1951).

that the result is in no small measure psychic. The improvement of function is also largely a subjective phenomenon. Improvement in the ability to chew food, to articulate words or to move a limb are familiar phenomena. The victims of this disease seem to be in a very high degree impressionable and respond nobly to every therapeutic effort (*J. Am. Med. Assoc.*, **64**, 1283 [1915]).

The protracted and variable course of untreated cancer is always surprising to those unfamiliar with it. Many medical men, demonstrably most competent in general fields, have been tragically misled by their lack of experience with the long-term care of cancer patients. Furthermore, there is frequently associated with cancer tissue any one of many types of secondary infectious processes. These, by their remissions and exacerbations, closely simulate variations in the course of the neoplasm itself; hence, conclusions based on changes in the apparent size of a neoplasm may be wholly unfounded.

The facts regarding the course of untreated cancer of different sites have been recently reviewed by Shimkin (*Cancer*, **4**, 1 [1951]). Of 100 patients with cancer of the breast, for example, approximately 85 will be alive one year, and 50, two years, from the onset of the disease.

Satisfactory objective evidence of a salutary effect of a potentially therapeutic procedure can be obtained easily for many types of cancer. A diminished level of acid phosphatase in the serum of a patient with cancer of the prostate, for example, provides essentially unequivocal proof that the growth has been restrained. No patients or observations of this type were presented in support of the claims made for Krebiozen.

In studies of cancer therapy, as in every other field of scientific endeavor, controlled and reproducible observations are required before conclusions can be drawn. The use of sham therapeutic procedures in alternate cases of similar clinical types is standard in the hands of experienced and reliable cancer investigators. In the case of Krebiozen, there were no controls reported, the clinical material was not uniform, the results were irregular, the effects were not established as due to the treatment employed, and the subjective responses were those commonly encountered and psychogenic in origin.

From the evidence presented concerning Krebiozen, it is not possible to conclude that it is capable of exerting salutary effect on the course of neoplastic disease in man.

C. P. RHOADS

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I THANK you for calling to my attention the article on Krebiozen solicited from C. P. Rhoads. I agree with everything Dr. Rhoads states in his communication.

I have not stated my position in the Krebiozen picture in order to keep the publicity regarding the substance at an irreducible minimum. This has been the aim of everyone connected with the study. We knew that every time an article, favorable or unfavorable, appeared on the subject, we would be deluged with requests. This has been demonstrated to be true as a result of the unfortunate and sensational publicity that followed a meeting in Chicago on March 26, 1951. This meeting had been planned as a private conference, to be attended only by invitation, for the purpose of presenting what we had seen and of setting up a program of clinical investigation. A leak to the city editors of the various newspapers in Chicago occurred, and the result is now a matter of history.

The booklet referred to by Dr. Rhoads presented the hypothesis of Dr. Durovic, who produced Krebiozen in Buenos Aires, in the pharmaceutical concern owned by his brother. The booklet presented observations regarding the "nontoxicity" and biological assay of the substance. It also included the changes that had been observed to occur up to January 1, 1951, in 22 cancer patients after the administration of Krebiozen. It was prepared for the purpose of indicating that Krebiozen merited a serious clinical study.

I had witnessed most of the changes recorded in the booklet and became convinced that the substance deserved a careful investigation. I felt that it was my duty as a scientist to lend assistance toward ascertaining whether the substance had merit in the management of the cancer patient. I have drawn no other conclusion and have made no other public statement. And, on the basis of what I have seen since January 1, 1951, I, on August 1, 1951, hold the same conviction, namely, that the substance merits further careful clinical investigation.

We know relatively so little about the biology of cancer that no clues should be ignored. The fact that Krebiozen has been distributed for clinical investigation free of charge constitutes unequivocal evidence of the conviction that it may prove to be of value. The implication of that conviction is the only question of any scientific and humanitarian stature.

A. C. IVY

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Chicago

The National Cancer Foundation has named **Farley W. Wheelwright** executive director. For the past two years Mr. Wheelwright has been on the staff of the Community Service Society of New York.

The American Cancer Society has named **Raymond G. Nebelung** to direct the expansion of the service facilities of the society through its 61 divisions. Dr. Nebelung for the past two years has been clinical instructor in public health and preventive medicine at Stanford University School of Medicine. For four years he directed the Public Health Fund in Honolulu.