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CANCER COMMISSION OF HARVARD UNIVERSITY

REPRINT No. 209

THE END RESULTS OF CANCER CASES AND
THE FACTORS DETERMINING THEM

BY

ROBERT B. GREENOUGH, M.D.

BOSTON, MASSACHUSETTS

REPRINTED FROM

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

March, 1927, vol. clxxiii, No. 3, pages 412-420

**END RESULTS OF CANCER CASES AND THE FACTORS
DETERMINING THEM.***

By ROBERT B. GREENOUGH, M.D.,
BOSTON.

CANCER is a subject which is assuming more importance year by year, as one after another of the more readily controllable diseases is brought within the scope of prevention or cure by modern scientific methods.

Whether we believe, as do many good authorities, that the steadily rising death rate from cancer can be explained by increased accuracy of diagnosis, or by the attainment of a larger proportion of population to the so-called "cancer" ages; or whether, as is maintained by other and equally good authorities, we consider that the peculiar conditions of modern existence provide opportunity for an actual increase in the incidence of cancer among our population, is after all of slight significance. No one who is concerned with the practice of medicine and surgery in this country needs any argument to convince him that the cancer problem is one of the great problems of modern scientific medicine.

It has become the custom to speak of cancer as a disease like tuberculosis, manifesting itself, as does tuberculosis, in many different organs or regions of the human body, but essentially the same in all its different situations. Nothing could be more erroneous than this view. Cancer is not a single disease. It is a whole group of diseases, varying not only in its situation in the human body, but in its form, its rapidity of growth and of dissemination, its susceptibility to therapeutic measures and its typical course as well. It is perhaps for this reason that such varying observations and opinions are recorded by competent observers in regard to the characteristic symptoms, the diagnosis, the appropriate treatment and the end results of treatment in cancer of different portions of the body.

It was the surgeon who first attempted the radical cure of cancer, and it was the surgeon who first established the fact that time alone was capable of determining the success or failure of efforts to cure this disease. At first a three-year period of freedom from disease was set up as an arbitrary limit for the reporting of cases, but it soon developed that "late recurrence" of the disease, especially in cancer of certain organs, such as cancer of the breast, might develop as late as fifteen or twenty years after operation. It is generally believed that such cases of late recurrence are due to metastatic foci of disease, established prior to operation, but on

* Read before the Post-Graduate Assembly, Cleveland, October 18, 1926.

such infertile soil, or at least under such unfavorable conditions, that the cells of the metastasis are hemmed in and encapsulated, so that their growth is for a long time prevented and only under conditions arising later in the existence of the individual are these barriers or conditions altered to such an extent as to permit the further development of the latent focus of disease.

As a result of these conditions an arbitrary period of *five* years has now been generally accepted as the minimum lapse of time for reporting as "cures" or "successful" cases patients who have been operated on or otherwise treated for the radical cure of cancer; and even with a five-year period, we must make a mental reservation with regard to cases of cancer of the breast and of some other types of malignant disease that recurrence after five years, though unusual may yet take place.

The clinical diagnosis of cancer in each of its many situations demands the exclusion of a certain number of nonmalignant diseases which vary with the different organs affected; but the ultimate and final diagnosis depends always upon the pathologic picture or the tissue removed. It is for this reason that in any series of end results reported we have a right to demand the pathologic confirmation of the diagnosis in every case recorded as a "cure." These two conditions, a five-year period of observation and the pathologic proof of the diagnosis of cancer, are the criteria established by a committee of the American College of Surgeons and they are widely accepted in the surgical world, but far too many reports of the results of treatment of cancer are still published in the literature that do not fulfill these requirements and are thus of very little value.

For the purposes of this discussion we will assume that we are in agreement as to the nature of the cancer process, namely, that the disease is local in its origin, that after a longer or shorter period it extends and involves more and more of the adjoining tissues; that it spreads through the lymph channels to affect the regional lymph nodes, and that ultimately, by way of the bloodvessels and by other routes it produces more distant metastases which sooner or later cause the patient's death by interference with some vital function. While the above conditions vary enormously with different types of disease, as for instance carcinoma and sarcoma, and while the extension of disease is greatly influenced by the anatomic conditions of the point of origin, the above statement represents in general the view of the disease which is most widely accepted.

With these general considerations in mind we may then proceed to examine the factors which are operative in determining the end results of treatment, and for this study I have chosen cancer of the breast as a type of cancer which is familiar to most practising physicians. The four factors to which we may give special consideration are as follows:

1. Delay in obtaining treatment on the part of the patient and on the part of the physician.
2. Extent of disease.

3. Treatment employed.
4. The pathology of the disease.

1. *Delay in Obtaining Treatment.* The most recent figures from the Massachusetts General Hospital show that the amount of time elapsing from the patient's first discovery of a breast tumor to her first consultation with a physician averages six months; that the time elapsed from the physician's first examination to the time of operation is one and a half months, making a total of seven and a half months' delay in obtaining adequate treatment. These figures show some improvement over similar figures for an earlier period (Simmons and Daland^{1, 2}), and undoubtedly indicate that the campaign of education which has been carried on for the past ten years by organizations, such as the American Society for the Control of Cancer and by local, State and Federal health officers, is yielding important results, but they also indicate very clearly that more can be done in this direction, both as regards the education of the public and of the medical profession as well.

So far as the individual case is concerned, every day and every week of delay is of importance as we are quite unable to determine the exact moment when the disease first extends from its local point of origin by regional metastasis, but there can be little doubt that a delay of seven and a half months gives all too much opportunity for this to occur, and that the period should be shortened from seven and a half months to seven and a half weeks, or less if we are to obtain the best results from our present methods of treatment.

We must emphasize, however, that the mere duration of the disease expressed in months is of less significance than the extent to which the disease has spread during these months, because the differences in the rapidity of growth of different tumors is one of the extraordinary features of this disease. As a matter of fact there were more successful cases among those with an average duration of *over* seven and a half months in this series than there were in the cases in which the delay was less than the average. This apparent paradox, however, is readily explained when we come later to the consideration of the pathology of the disease.

2. *Extent of Disease.* The accepted measure of the extent of cancer of the breast is the condition of the axillary lymph nodes. This is not an accurate measure in every case, as it occasionally happens that tumors in the upper and inner hemispheres may extend to the supraclavicular or mediastinal nodes before they affect the axillary ones, and in other cases blood-borne metastases in the bones and elsewhere may occur early in the disease. A small focus of axillary disease may also escape the attention of the pathologist unless great care is used and a multitude of sections are examined. In general, however, axillary involvement is accepted as the most practical method of determining the degree of extent of cancer of the breast.

The percentage of five-year "cures" in cases operated upon in which the axillary nodes are proved by pathologic examination *not* to be diseased, vary from approximately 70 per cent in most of our

American clinics to as high as 91 per cent in some recent figures from the British Ministry of Health. In the more advanced cases, where the axillary nodes are involved, the percentage of "cures" at once falls off to 20 to 30 per cent, or even lower, a clear indication of the importance of early diagnosis and treatment if we are to employ our present resources in the way of treatment to the best advantage. In this connection it may be permissible to quote the profound truth enunciated by Dr. Janet Lane Claypon that "It must be remembered that every late case of cancer was at one time an early one." It is only by passing beyond this early stage, without adequate treatment, that the case becomes a late and hopeless one.

Apart from the significance of axillary involvement, other manifestations of the extent of the disease must also be considered; not perhaps of so much importance in the early case, but of great importance in the selection of appropriate treatment in later and more advanced cases. I refer especially to extension to the chest and to the bones. The lungs, pleura, mediastinum, and the bony skeleton are so frequently affected in advanced breast cancer that a careful physical and Roentgen ray examination of the chest and of the skeleton is essential to the primary examination of every case, and should be repeated periodically during the follow-up period. In this way many useless and unnecessary attempts at radical cure will be prevented and appropriate radiation treatment can be supplied at a stage of the disease when it can do some good.

3. *Treatment.* There are only two methods of treatment for cancer of the breast which hold the confidence of the medical world, surgery and radiation, and it is universally admitted that treatment by radical surgical operation is the only method which can be relied upon to cure the disease. Cures by radiation without surgery are not to be expected, although radiation treatment may be combined with surgery, and in almost every case is of the greatest value in palliative treatment.

The radical or complete operation for cancer of the breast is practically standardized in our best clinics at the present time, and consists of the removal in one piece, and with a minimum of trauma, of the whole breast, all of the skin over it, the pectoralis major and minor muscles, the axillary contents and the deep fascia from clavicle to epigastrium and from sternum to latissimus. Anything short of this is an incomplete operation and fails to give the patient the chance to which she is entitled, of being permanently cured of her disease. Statistics are available from many sources to support the assertion that the radical operation gives a vastly greater number of cures than does the incomplete. In the series of cases from the Massachusetts General Hospital, but 1 of 16 cases subjected to incomplete operation was alive and well at the end of three years.

In spite of these facts which have been well established, it is astonishing how many operations for cancer of the breast are performed by surgeons, even those in our larger hospitals, which fall far short of the so-called radical or complete operation. Of 127

cases of breast cancer which came to the Huntington Hospital in three years, 8 were operable, 34 were unoperated and inoperable, 55 were recurrent after a complete operation and 30 were recurrences after incomplete or inadequate operation in other hospitals. Thus more than a half of these cases had failed to receive proper treatment at a stage of the disease when cure could have been expected.

We must not lose sight of the fact that the earlier the patient presents herself for examination the greater the difficulty of making a positive diagnosis of cancer. The typical case with a tumor adherent to the skin, and enlarged axillary nodes is already far beyond the favorable stage for cure by operation. The specialist may make a shrewd guess in the earlier and less distinctive cases, but such a guess is not sufficiently reliable to permit a decision in which the life of an individual is concerned. It demands the confirmation of a pathologic examination, and this must be obtained by an exploratory operation. There is sufficient evidence available to justify the statement that an exploration properly conducted is safer for the patient than is the alternative of waiting for the development of more positive and distinctive signs of cancer when the possibility of operative cure will be to that extent, diminished. Such exploratory operations must be done at one sitting, with full preparation for the complete radical operation if it should prove to be required, and with a pathologist available for frozen-section diagnosis if it should be necessary. With this technique, explorations were performed at the Massachusetts General Hospital as far back as 1911, and the patients then operated upon are now alive and well.

Variations in the technical details of operative methods need not confuse the main issue. It matters little whether the operation be done with the scalpel or with one of the more recent instruments for cauterization, endothermy or electrocoagulation. My own preference is strongly for the scalpel. The value of preoperative and postoperative prophylactic radiation, however, is at present a matter of much discussion. Preoperative radiation is given with the purpose of damaging the tumor cells so that they may be less able to survive if they should be dislodged during operative procedures, or transplanted in the wound. Postoperative prophylactic radiation is given with two purposes in view—to retard or prevent the development of any tumor cells remaining after operation and to enhance the resistance of the surrounding body tissues to the subsequent development of any metastatic or recurrent nodule of tumor tissue.

The value of these two measures is at least debatable, and for lack of sufficiently reliable data still remains a matter of opinion rather than of fact. My own opinion as regards their use in cancer of the breast is as follows: A preoperative dose of Roentgen ray sufficient to do material damage to cancer cells cannot be given without serious effects upon the skin and subcutaneous tissue, as a result of which wound healing is much affected. In such cases sepsis and sloughing of the wound occurs more frequently than in nonradiated cases. Furthermore, in our experience at the Massa-

achusetts General Hospital no greater percentage of cures is obtained, local recurrence is not diminished and the progress of the disease in unsuccessful cases is not retarded by the use of preoperative radiation. This is not altogether in accord with the observation of others (Lee), and we are at present carrying on another series of cases with preoperative radiation, but we must wait another five years for the results. So far as postoperative prophylactic radiation goes, however, we have abandoned it in all cases where, at the close of operation, there is not direct evidence that cancer tissue remains in the wound beyond the limits of surgical removal.

The employment of Roentgen ray or radium for the treatment of recurrent or inoperable cases is quite another story. We have abundant evidence that under radiotherapy such cases live longer and more comfortably than those which do not have it, and the earlier such treatment can be begun the better the results. In a series of the more favorable of such recurrent or inoperable cases at the Huntington Hospital an average of nearly a year and a half in added length of life for each patient was obtained by radiation.

The use of radiation in direct combination with surgery also offers a field for further development in the treatment of advanced cases. The decortication method of Beck, to permit direct radiation of the tumor tissue, and the open operation on the maxillary antrum combined with radium implantation (Greene) are examples of what may be done in this direction and undoubtedly influence the end results in certain restricted types of disease.

4. *Pathology.* Differences in the degree of malignancy of different tumors have long been recognized by pathologists in individual cases, but this information rarely reached the surgeon, and was not controlled by study of end results. Broders,^{5, 6} of the Mayo Clinic, in 1921, published a series of cases of cancer of the lip in which he attempted to classify the cases according to their pathologic evidence of malignancy and to check these observations against the clinical results. The clinical results and the pathologic classification agreed. Since Broders' first communication others have made similar studies and confirmed his findings; not only as regards squamous-cell cancer of the lip⁷ and external skin, but also cancer of the tongue (Simmons⁸), cervix (Martzloff³), fundus (Mahle⁴), and so forth. The classification depends chiefly upon the degree to which the cancer cells have lost their characteristic differentiation (for function) and taken on more active growth. The term anaplasia was long ago suggested by von Hansemann to express this idea; but it must be noted that for each different type of epithelium a different set of criteria must be established, depending upon the differentiation for function which is normal to the cell of origin.

I have myself been interested to apply these considerations to cancer of the breast. In this case we are dealing with a gland which is intended to secrete mucoid material, and the factors which determine the malignancy therefore depend upon the loss of secretory function either in the cell itself or in the architecture of the

group of cells which normally should form a gland tubule. The size and uniformity of cells and of nuclei is also of significance, and the frequency of mitoses and especially of irregular and hyperchromatic forms is to be considered.

A series of 73 cases of breast cancer were studied from the Massachusetts General Hospital⁹ in all of which the end results had been determined. Without knowledge of these end results, however, the microscopic slides of these cases were studied and classified by Dr. C. C. Simmons, Dr. J. H. Wright and by myself. Only three classes were distinguished—high, low and medium malignancy. The data were then brought together, and with the following results (Greenough²).

	Number.	Cures.	Per cent.
Cases classed as low malignancy	19	13	68
Cases in medium class	33	11	33
Cases classed as high malignancy	21	0	0

From these figures we may draw the conclusion that a certain number of cases of cancer of the breast (say 25 to 30 per cent) are of so highly malignant a character that even in the early stages of the disease our present methods of treatment are insufficient to cope with them. When we admit this, however, we admit also that 70 to 75 per cent of all cases *are* amenable to cure by our present methods. At present we obtain five-year cures in only from 15 to 20 per cent of all cases of breast cancer which apply for treatment at our larger hospitals. There appears to be no good reason why this number should not be increased about fourfold.

In order to avoid confusion I have confined this discussion to cancer of the breast, but I fully believe that these same principles apply equally to many other forms of accessible and operable cancer, and that the possibility exists of greatly increasing the number of cures, even with our present methods, if only these general principles can be put in operation. To obtain these results, however, a very different attitude toward cancer must be adopted by the public and by the medical profession. We must learn that the disease is not so hopeless as has been too frequently maintained. We cannot sit idly by and wait for the discovery of some hypothetical parasite or for the production of an effective antitoxin. Many of us believe that such an event may never take place. Cancer exists, however, and is destroying our adult population at a frightful and increasing rate. With our present resources alone some 70 to 80 per cent of cases of accessible cancer can be cured, and we now fail to cure more than a quarter of that number. It seems to me that the time has come for us to apply to the cancer problem the same general principles of common sense we would apply to any problem of modern life and to make an effort to do the best we can, with the resources already at our command.

Summary. The end results of the treatment of cancer are determined by the following factors:

1. *Delay.* There must be no delay on the part of the patient in seeking advice immediately upon the discovery of symptoms

which are even suggestive of cancer, such as a lump, a sore, an abnormal discharge of blood or any unexplained discomfort.

There must be no delay on the part of the physician consulted in obtaining an immediate diagnosis either by examination, by consultation or if necessary by exploratory operation.

Both of these sources of delay may be done away with by education and by the provision of adequate facilities for consultation and for treatment.

2. *Extent of Disease.* With our present resources, surgery and radiation, the early local case of cancer can be cured; but the late and extended case cannot be cured, although palliative treatment of great value to the patient can be given.

3. *Treatment.* The end results in the treatment of cancer depend largely upon the effectiveness of the treatment employed. With the exception of a few situations, such as cancer of the external skin and of the cervix of the uterus, surgery is the method of choice.

The surgical treatment of cancer in most of its common manifestations has been standardized, and depends partly upon the anatomy of the region affected, and partly upon the mode of extension of the particular variety of cancer present. The complete or radical operation is the method which yields the greatest number of cures and should be performed even in the earliest and most favorable types of the disease. Incomplete operations do not give to the patient the chance of cure to which he is entitled.

Surgery may further be supplemented by preoperative and post-operative radiation, although the final decision as to the value of these measures has not yet been established.

For advanced cases, unsuited to attempts at radical cure, radiation therapy with Roentgen ray and with radium, occasionally supplemented by surgery, prolongs life and mitigates the distressing symptoms of the disease to an extent unequalled by any other treatment at present available.

4. Cancer is not a single disease but many diseases, differing not only in location but in rapidity of growth and of dissemination as well. There are a certain number of cases which are so malignant and so rapid in their development that our present methods are insufficient to cope with them. The majority of cases of accessible cancer, however, are curable by methods of treatment now available in most of our modern hospitals, if only these methods can be applied in the early and favorable stages of the disease.

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