THE PLACE OF RADIUM IN THE TREATMENT OF CANCER OF THE BREAST

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IT IS now nearly fifty years since your great countryman, William Stewart Halsted, introduced the radical operation for the treatment of cancer of the breast. The technic of the operation has undergone modifications during that period, but Halsted's principle has been accepted throughout the world of surgery, and for many years the radical operation has been more or less standardized. Moreover, the degree of standardization has been some indication of the satisfaction with which surgeons have regarded the results that have been achieved. The satisfaction has been only relative, because treatment of cancer in all parts of the body has been disappointing. The treatment of cancer in the breast has perhaps been less disappointing than in most other situations.

Standardization must not, however, be allowed to lead to an hypnotizing of surgical opinion into a fixed belief that no further improvement is possible and that any suggested change is, necessarily, to be regarded with a cold disapproval. Most surgeons who have taken the trouble to follow up their patients after performing the radical operation for cancer of the breast are, indeed, gravely dissatisfied with their results. I am sure, therefore, that the surgeons here present, representing, I believe, the most advanced body of surgical opinion in the United States of America, will give a sympathetic hearing to an account of an honest attempt to find out whether irradiation with interstitial radium needles might be used to mitigate, or possibly abolish, the necessity for so formidable a procedure as the radical operation. Encouragement is to be obtained from a survey of the present treatment of cancer in general; for irradiation has virtually supplanted surgical operation in cancer of the tongue, mouth and fauces, and in cancer of the cervix uteri. At one time there was a widespread belief that cancer of the breast was not a radiosensitive neoplasm, and it was stated, particularly in some clinics on the continent of Europe, that satisfactory irradiation of the contents of the axilla was impossible. The validity of these statements will be criticized during the course of my remarks, and the final test will be provided when the late results of irradiation are presented to you.

From the ordinary surgical standpoint it is exceedingly unorthodox to suggest that conservative methods of treatment, sometimes without any removal of tissue whatever, could possibly be better than radical operation, or even as good. Previously, I myself maintained that the earlier the disease the more radical should the operation be, since the hope of curing the disease was greater, and I was aghast when some of the older surgeons,

such as the late Sir Anthony Bowlby of my own hospital of St. Bartholomew's, stated their belief that the patients would do just as well if only a local removal of the breast were effected. I must confess that my opinion has now gone to the opposite extreme, and I am prepared to maintain that, if the axillary lymph nodes are extensively involved, dissection of the axilla may be harmful, and that, if they do not appear to be involved at all, it is unnecessary. This opinion is coupled with the assumption that radical irradiation will be carried out in every case. I have also to confess that I have had increasing difficulty in accepting the theory of centrifugal permeation by cancer cells as enunciated thirty years ago by W. Sampson Handley, since so many of his conclusions seemed to be contrary to experience and contrary to common sense. I have been greatly interested therefore in anatomic investigations on lymphatics carried out recently at St. Bartholomew's Hospital by J. H. Gray under the inspiration of Woollard.[1] By the use of thorotrast and barium, lymphatics have been made visible and their course traced more accurately than before, and it has been shown that there is no lymphatic plexus in the deep fascial layers. Thus the lymphatic system of the breast lies in the gland and on its surface, the main lymphatic trunks passing around the fold of the axilla to the axillary nodes. No evidence whatever has been discovered in support of the theory of centrifugal permeation. On the other hand normal lymphatic channels are found to connect a carcinoma with involved nodes, the only possible inference being that carcinoma cells pass to the nodes as emboli, without forming intermediate points of growth. The supposedly permeated channels have been shown to be generally infiltration in planes of tissue cleavage, or sometimes to be growth in a venule. It follows, therefore, that widespread operations based upon the permeation theory of fascial planes have no real justification. If Gray's observations are correct it will be necessary to revise our conception of the spread of cancer, and then perhaps the idea of conservative treatment of cancer of the breast may become more acceptable to us.

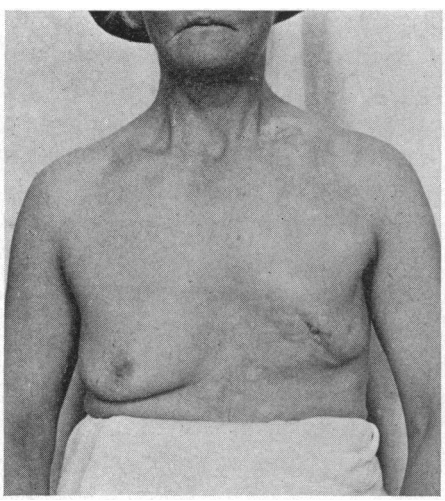

FIG. 1.—Case 1: Ten years after treatment.

It was first suggested to me by Professor George Gask, in 1922, that an attempt should be made to treat cancer of the breast with interstitial radium alone. For the first two years only patients with recurrent disease following operation were treated. In nearly every instance the growth was observed

to disappear, and the treatment was then extended to the primary disease, the first patients being treated on August 1, 1924. For the next four and one-half years only patients with very advanced or inoperable tumors were treated in this way, and the results in 50 of these were examined before it was thought justifiable to extend the treatment to the earlier stages of the disease. It was soon apparent that the belief that cancer cells in the breast were not sensitive to irradiation must be abandoned. Some remarkable results were obtained, and, although the majority of these patients are now dead from metastases, many of them remained, for periods up to eight years, without external signs of disease. Six of them are now alive nearly ten years after treatment, and five of these six—that is, 10 per cent of the whole—are without signs of disease.

ILLUSTRATIVE CASE REPORTS

Case 1.—A patient, age 40, presented herself with a large tumor in her left breast which had already produced elevation of the breast and retraction of the nipple. The

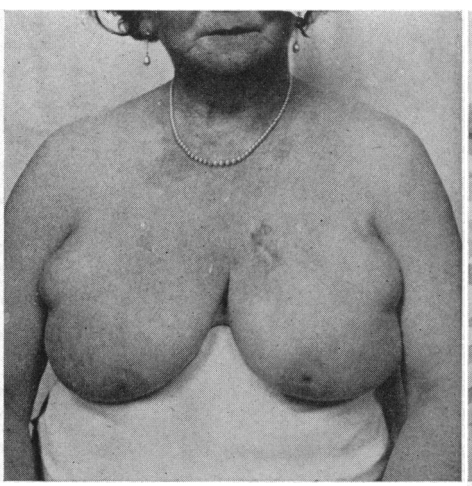

FIG. 2.—Case 2: Nine years after treatment.

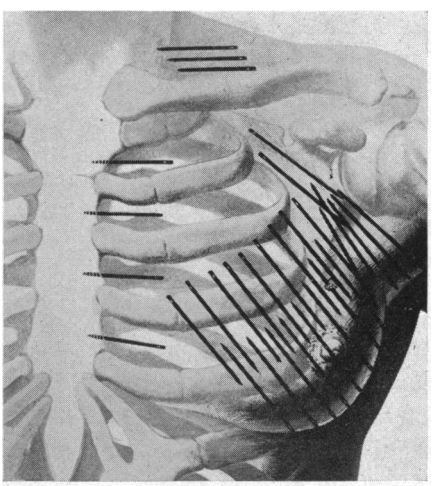

FIG. 3.—Usual distribution of radium needles.

disease was advanced, though still operable. There were palpable lymph nodes in the axilla. She was treated with radium alone, after the diagnosis had been proved by biopsy. There was some contraction of the breast, which followed the disappearance of the tumor, but the patient is without signs of disease 10¼ years after treatment (Fig. 1).

Case 2.—A stout patient, age 57, had a very large tumor in the left breast. It was infiltrating the skin and was adherent to the chest wall, so that it was judged inoperable. No secondary metastases in the axilla could be detected, but she was so stout that even large nodes might have been present. She was treated with radium only, and except for a depressed scar in the position of the tumor, she shows no trace of her disease nine years later (Fig. 2).

It was perhaps this initial investigation that gave rise to the legend that I was now and forever a convinced irradiator of cancer of the breast and

had completely abandoned surgery in this disease. Undoubtedly I was encouraged to proceed in this direction, I think with justification, but my general surgical bias has, I hope, prevented me from becoming unbalanced. The results will presently be put before you.

When this series of 50 trials of interstitial irradiation had been completed, it was felt to be justifiable to extend the method of treatment to earlier stages of the disease, and from that time to this I have systematically used radium either by itself or in combination with very conservative surgery. The radium has always been applied interstitially in the form of needles. The usual distribution of needles is shown in Fig. 3.

No radon has been used. Surgical operation, if used at all, has preceded irradiation, and has been performed with the diathermy needle. No dissection of the axilla has ever been carried out. These have been the general principles, and I am not concerned today with details of technic.[2]

The patients were carefully observed, and in due course a certain number of failures were noted. These failures were either shown by incomplete disappearance of the primary tumor or by the appearance of recurrent nodules in the breast or in the skin. In a number of patients these residual tumors were removed and examined nine months or more after the irradiation. It was then found that in 50 per cent of them there was no discoverable cancer remaining, the tumor consisting entirely of fibrous tissue. In the other 50 per cent evidence of active cancer was found. This result led to a reconsideration of the procedure, and it was realized that the failures might reasonably be attributed to the physical limitations of radium needles. The penetrating power of the rays is strictly limited, and many of the tumors were too thick and bulky for the gamma rays to penetrate them effectively from below, so that the cancer cells in the center or at the surface did not receive a lethal dose. Another more theoretic difficulty was the supposed variation in the sensitivity of the cancer cells themselves. I do not attach much importance to the second consideration, but the bulk of the tissue to be irradiated did seem to be a serious obstacle unless the dosage of radium was to be greatly increased, and to this there were other objections. I, therefore, decided to remove more frequently either the tumor or the breast before irradiation, according to circumstances. Sometimes in the earliest stages of the disease it was desirable to remove the tumor in order to establish the diagnosis. Whenever an operation was performed it was as conservative as circumstances would allow, and never included the removal of the pectoral muscles or dissection of the axilla. In the majority of patients, therefore, the amount of mutilation was negligible, and in some, radium only was still employed without any operation at all. This procedure could only be justified if it was evident that the action of radium on the axillary lymph nodes was effective. It may be stated, at once, that close observation of the patients over many years has shown that the results on the axillary nodes have been uniformly good. They have been made

to disappear almost with certainty, and they have not recurred. If the axilla did not contain palpable nodes none have developed afterwards. These facts have crystallized the procedure at the present time as follows:

(1) Local removal of the tumor if it is large, or the diagnosis is uncertain, followed by radium.
(2) Local removal of the breast if the tumor is very bulky, followed by radium.
(3) Never dissect the axilla.
(4) Radium by itself may be used. (*a*) If the tumor is of moderate size and the diagnosis certain. (*b*) If the patient refuses operation.

If the disease has extended to the supraclavicular nodes when the patient is first seen, this has usually been found to be accompanied by disease within the thorax, so that the patient will often be unsuitable for treatment by radium, which, like surgical operation, is essentially a local form of treatment. Apart from the obvious necessity of often rejecting those who showed evidence of metastases in viscera or skeleton, there has been no selection of patients.

In citing statistics I wish to emphasize again the fact that interstitial radium treatment is strictly comparable with surgical operation, in that it is a local form of treatment, although it can be extended to the area above the clavicle which is not usually included in an operation. For this reason no striking improvement in the survival rate was to be expected if radium was used as an alternative to surgery. It is the metastases, and not the primary disease, that usually cause the death of the patient, and for that reason I never shared the exaggerated hopes that were at one time placed by some people in the future of radium. On the other hand, some local advantages were to be expected if the general results seemed to justify its use. The patients have been divided into three groups:

Group I. Disease apparently confined to breast.
Group II. Disease apparently confined to breast and axilla.
Group III. Disease advanced or inoperable.

The statistical results have been prepared for me by Lady Janet Forber who has done a great deal of similar work in compiling cancer statistics for the Ministry of Health. They may be relied upon for their accuracy. Finally, please remember that I am a general surgeon on the Staff of a large teaching hospital, so that I have no special cancer or breast clinic, and the number of patients treated by me, even in the course of ten years, is not large.

The total number of patients treated up to the end of March, 1937, is 325. Of these, those treated within the last three years must be excluded from the statistics. This leaves 250 as the total available for statistical examination. These are distributed as follows among the groups: Group I, 85. Group II, 91. Group III, 74.

The percentage survival rates among these 250 patients have been ascertained by Lady Forber (Table I).

TABLE I

Group	Number	Survival Percentage	U.C.H.* Survival Percentage
PERCENTAGE OF PATIENTS ALIVE AFTER THREE YEARS			
I.....	85	83.5	79.2
II.....	91	51.2	52.3
III.....	74	31.4	—
PERCENTAGE OF PATIENTS ALIVE AFTER FIVE YEARS			
I.....	75	71.4	69.1
II.	66	29.3	30.5
III.....	60	23.6	—

* In the fourth column I have added the survival rates obtained as the result of a recent investigation carried out at University College Hospital,[3] as this seemed to be the nearest approximation that I could obtain to a comparable series of a similar number of patients treated by surgery alone.

The only category of really curable patients is that included in Group I, and this is, therefore, the most interesting to us as clinicians. You will agree that survival rates of 83.5 per cent and 71.4 per cent at three and five years are satisfactory. The University College Hospital series gave 79.2 per cent and 69.1 per cent for the same periods, and probably it is fair to assume that in round figures 80 per cent and 70 per cent may be regarded as average results with the best surgery. My figures for radium are slightly above this average. I should attach no importance to this slight difference were it not for the fact that the statistics in this group are weighted heavily against me. When Group I relates to the results obtained by the radical operation, the contents of the axilla have been removed and examined histologically, so that those patients having involved nodes which were not clinically palpable have been eliminated. My Group I, on the other hand, is necessarily a clinical group only. There can be no doubt that a proportion of them would prove to have involved nodes if the contents of the axilla were examined. My Group I is therefore composed, in reality, of a mixture of Group I and Group II patients, and is, therefore, more unfavorable than would appear at the first glance. Lady Forber informs me that there is no material for forming an accurate basis upon which to correct this error in grouping. Such material as there is indicates that the possible error is in the neighborhood of 27 per cent. She has applied this correction to my series, and she then finds that my corrected survival rate for the patients in Group I is 94.8 per cent at three years,

and 86.3 per cent at five years. I must confess that these figures frighten me, and I doubt whether it is wise to publish them in print, as they contain too large an element of conjecture. I think it is fair to assume, however, that my survival rate for true Group I patients would be substantially higher than appears in Table I.

In Group II the survival rates of approximately 51 per cent and 29 per cent at three and five years are almost exactly the same as those obtained from the series at the University College Hospital. In this group so many of the patients are necessarily doomed to die from metastases which have already started when they first come for treatment, that little improvement in the survival rate could be expected.

In Group III, where I obtained a survival rate of approximately 31 per cent and 24 per cent at three and five years, it is impossible to give any comparable figures obtained from the results of surgery, since so many of the patients are judged, wisely enough, to be inoperable. The survival rate that has been obtained among these patients is the more remarkable when it is remembered that they represent those cases which have been considered inoperable, the patients that the surgeon will not look at because he knows he cannot help them, those, in fact, that he willingly allows the radiologist to treat.

I have already mentioned that although none of the patients has been subjected to dissection of the axilla, an increasing number of them have had the tumor, or the breast, removed before the radium treatment was given. Comparatively few of these, however, come into the five or three year periods, so that the number of patients thus treated are too small to be worth computing separately as percentages. So far as they go, the figures suggest that there may be a slight further improvement following the preliminary excision, though this cannot yet be asserted with confidence. There will, however, be a considerable improvement in the incidence of secondary minor operations for local recurrences.

It is perhaps idle to seek at present for any definite cause to which the apparent rise in the survival rate of Group I patients following radium treatment may be due. I can only point out that the radical operation has a definite operative mortality. It is in the neighborhood of 3 per cent according to the University College Hospital statistics. Radium, on the other hand, has practically no operative mortality. Up to the present time only one patient has died while under treatment, and she was found to be suffering from advanced cardiac disease with decompensation, from which she might have died at any moment. This operative mortality would probably militate more against Group II patients suffering from more advanced disease than against Group I. Nevertheless, elimination of this mortality might make a difference of 1 per cent in Group I. The radical operation, undoubtedly, delivers a knock-out blow, from which many patients do not really recover for a considerable time, and it is possible that their "resistance

to the disease" (whatever that may be) is lowered by the shock which they suffer. The shock from interstitial radium, on the other hand, is practically nil, so that here again an advantage may result, though this is theoretical. Finally, there is the complete elimination of surgical interference with the lymphatic system of the axilla. I think it is not impossible that this dissection, as commonly performed, may sometimes disseminate the disease, when it has been temporarily held up in the neighborhood of the axillary lymph nodes.

Interstitial radium, on the other hand, irradiates cancer cells in that situation without disturbing them, and this may possibly be a real factor in obtaining a better survival rate. Again this is theoretical, and I am sure that more knowledge must be obtained concerning the exact mechanism of the dissemination of cancer before the matter can be settled to our satisfaction. I make the above suggestion, however, particularly in view of the results obtained with radium in Group I, and in view of the work of Gray and Woollard, which they think points to dissemination being largely the result of embolism. They even deprecate, on this basis, any more handling or squeezing of a cancerous breast than is absolutely necessary. I have often wondered in past years, as I watched patients being examined by twenty or thirty students in succession, whether this might not be seriously affecting their expectation of life, and now it seems as if the answer may be in the affirmative. Gray and Woollard are of the opinion that my suggested explanation of the improvement in Group I with radium is probably correct.

I have assured you already that I do not speak with any antisurgical bias, since pure surgery is the chief preoccupation of my life. Yet I feel that it must be the ambition of every conscientious surgeon to help in the gradual elimination of any operative procedure so extensive and severe as the radical operation for cancer of the breast. I cannot help, therefore, being interested in noting what may be achieved apart from statistics by the conservative method I have described in comparison with radical surgery. No one can deny that radical surgery entails, in addition to an appreciable operative mortality, a really hideous mutilation. There is, as a rule, remarkably little limitation of strength and movement of the arm, unless the interference with the axilla results (as it not infrequently does) in an obstruction of the lymphatics of the arm, with its attendant swelling and helplessness. This sequela, when it occurs, is very distressing indeed. Again, routine radical surgery does apparently sometimes result in actual dissemination of the disease and widespread recurrences in the skin flaps and their surroundings. It is impossible to escape the conclusion that radical surgery does sometimes do more harm than good. Finally, and, I believe, very importantly, there is the psychologic aspect. Most women know what is meant by surgical treatment of cancer of the breast, and I am sure that very often they are intimidated by the prospect. As surgeons we con-

stantly regret the fact that patients do not come to us soon enough, very often hiding their disease until two years or more have elapsed since it was first noticed. I am afraid it is the fact that we *are* surgeons that is partly responsible for this attitude on the part of the patients. They are afraid of us, and, frankly, I am not surprised that they should be. It is this feeling that deters them from seeking advice, and so prevents any considerable improvement in the end-results such as might follow earlier diagnosis and earlier treatment in the aggregate.

Let me now refer to the advantages and disadvantages of conservative treatment such as I have outlined. The mutilation is usually slight, and very often may truthfully be called negligible. A distinguished lady came to me three years ago for treatment of cancer of the breast, and to this

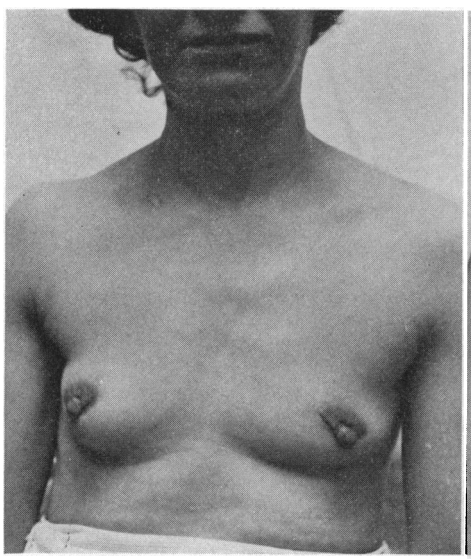

FIG. 4.—Case 1: Six years after treatment.

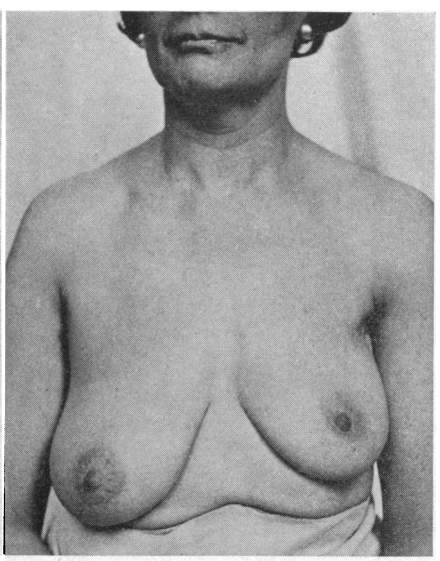

FIG. 5.—Case 2: Six years after treatment.

day her husband—who was abroad at the time—does not know that she has ever been ill.

CASES ILLUSTRATIVE OF RESULTS OF CONSERVATIVE TREATMENT

Case 1.—B., age 38, had a nodule of growth in the axillary tail of the right breast. It was excised with diathermy, and radium treatment given in August, 1931. She is without signs of disease nearly six years later (Fig. 4).

Case 2.—W., age 38, gave a similar history. The lump was excised, and she was given radium treatment only. She is also without signs of disease nearly six years later. There has been some contraction as the result of the treatment, and the breast is somewhat elevated in comparison with the other (Fig. 5).

Case 3.—C., age 34, was treated recently by excision of a nodule of cancer in the right breast, and then by radium. Eight months later the breast is practically normal (Fig. 6).

Case 4.—C., age 61, who had a small tumor in the upper part of the left breast. The treatment was the same as in Case 3, and eight months later the breast is apparently normal (Fig. 7).

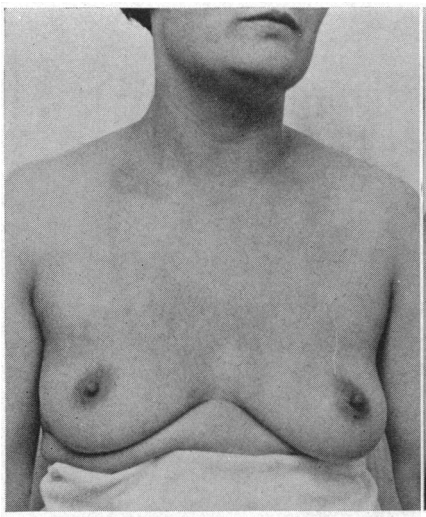

FIG. 6.—Case 3: Eight months after treatment.

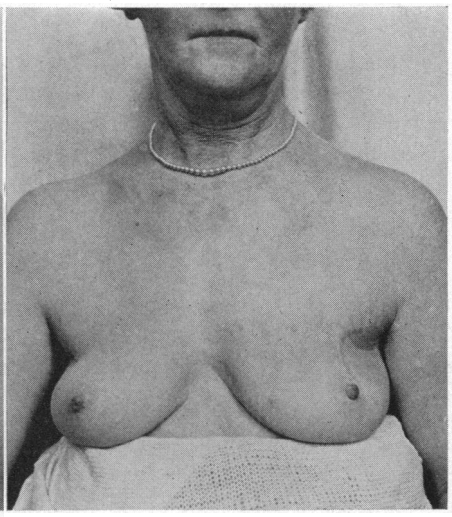

FIG. 7.—Case 6: Eight months after treatment.

There can be no doubt of the esthetic advantages of conservative treatment.

Case 5.—W., age 39, when first seen, had a very early carcinoma in the outer part of the right breast. This was treated by excision for diagnosis, followed by radium to the outer half of the breast only. Remained well for nearly five years, and then showed signs of a second carcinoma in center of same breast with deviation of nipple. Patient refused operation, and was treated with radium only. Eighteen months later a very small nodule in the left breast, which had been under observation for some time, became larger and there was a blood-stained discharge from the nipple. This nodule was excised and proved to be a third carcinoma, and radium was applied to the breast. The patient now shows some contraction of the right breast which has had two treatments, but is otherwise quite well, over eight years after being first treated (Fig. 8). She would rather have died than have submitted to removal of a breast, and is unique in my series in having had treatment for three primary growths apparently with success.

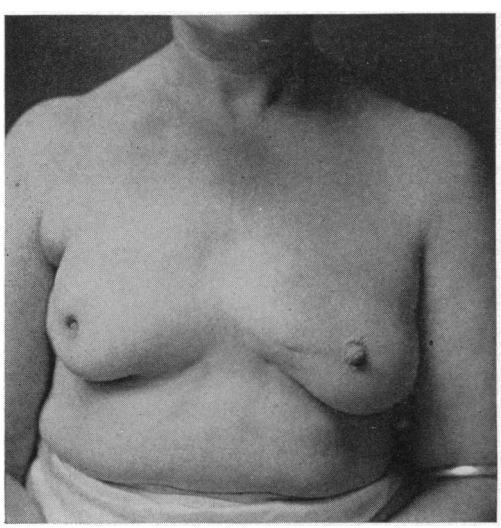

FIG. 8.—Case 5: Eight years after first treatment.

With conservative methods there is, as I have said, practically no operative mortality, and there is never any operative shock. I have never seen lymphatic edema of the arm which was due to radium. If it occurred it was always due to extension of the disease into the upper part of the thorax. Widespread, local recurrences after radium treatment are very uncommon, and they do not ever appear to be attributable to the treatment. Finally a number of patients have been encouraged to undergo treatment only because they were to be spared the mutilation entailed by surgery. Patients have sometimes said, and written to me, most moving things in this connection, and I have no doubt that if conservative treatment were to be commonly practiced, it would finally have the result of bringing more patients to the benefits of early treatment, and so improve the end-results.

Against these advantages of conservative treatment I must (if I am to be honest) set certain disadvantages. There is, for example, the difficulty of the interpretation of results. I have already mentioned the possibility of there being a residual tumor after treatment by radium alone, and the difficulty of knowing whether this contains active carcinoma or not. In addition to this there is the postirradiation fibrosis which is apt to appear, as long as two years after treatment, in the positions where the irradiation has been most intense. It is particularly liable to occur on the inner wall of the axilla, and many of my patients have fibrous lumps in that situation which would unquestionably be diagnosed as recurrent cancer by inexperienced observers. Needless excisions of these lumps, and long experience, have enabled me to distinguish, confidently, between fibrosis and recurrence, but I can see that they introduce real difficulty in the way of widespread adoption of the method. Eighteen months ago I treated a lady for a very early cancer of the breast, and subsequently she returned to South America. Events then took place which greatly alarmed the surgeons in Brazil and afterwards in Baltimore, though I feel sure, in my own mind, that the patient did not have a recurrence of carcinoma.

Another disadvantage of the conservative method is the increased liability to neuralgia or rheumatic pains in the treated areas. It is true that every woman who has had a cancer of the breast is likely to exaggerate slight pains because she always thinks that pain indicates recurrence. Nevertheless, the treated areas do certainly remain for some time more likely to give rise to pain than an operation scar, and the patients are, to that extent, more conscious of their past experiences. I have never encountered among my patients a true brachial neuritis due to placing needles too close to the brachial nerve trunks. I have seen it produced, however, in another clinic, and it must be remembered that radium needles are dangerous instruments if employed with insufficient skill (but so, also, is a scalpel or almost any of the instruments that we are accustomed to use in surgery). Postirradiation fibrosis may also affect the pectoral muscle and produce some degree of limitation of movement. This is greater when the position of the disease

in the breast or axilla necessitates placing a large dose of radium over and under the border of the pectoral muscle. In treating early disease this is not necessary, and the resulting limitation of movement is negligible.

I have tried to present to you, without too much elaboration, the results of a clinical experiment which has now extended over 14 years, and I venture to suggest that the results show that the experiment has not been a failure. Statistics seem to indicate that a definite improvement can be obtained in the most favorable group of patients by means of the treatment of cancer of the breast that I have used, and the method is therefore worthy of attention. It is conservative treatment rather than purely radiologic treatment, and I think that by combining radiology with surgery we may perhaps get the best of both methods of procedure. I do not wish, however, to make any dogmatic claim on behalf of radium. It may be that the future lies with Professor Coutard.

In conclusion may I express my gratitude to the late Dr. Joseph C. Bloodgood, to Dr. James Ewing, and to many other American surgeons, for the interest they have taken in my work, and for the encouragement they have given me. I must also express to you, my high appreciation of the honor that you have done me in inviting me to take part in this discussion.

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