RADIATION THERAPY OF CARCINOMA OF THE BREAST*

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OWING to the size and complexity of the subject of carcinoma of the breast in relation to radiation therapy, it is difficult to present a complete picture of all its various branches. The scope of radiation therapy has been tremendously increased in the past few years as a result of a greater knowledge of the nature of diseased conditions, a progressive improvement in the technique of application of x-rays and radium, together with a better understanding of the action of these two physical agents, on the living cell. Consequently, I have endeavoured to present only the more striking features of the radiation of mammary cancer.

BIOLOGICAL EFFECT OF RADIATION

According to the law of Amat-Schulz, which has been generally accepted, small doses of radiation stimulate cells, medium doses inhibit their growth, and large doses destroy cells. From a therapeutic standpoint the important effect of radiation is the depressing action on the living cell. The cessation of growth and function or the destruction of the tissue depends on the quantity of x-rays absorbed and the radio-sensitivity of the particular type of cell.

Young, growing cells undergoing mitosis are much more sensitive than normal adult, fully differentiated cells. But there is no *selective* effect of x-rays. Every type of tissue is affected, but to a different degree, according to its particular susceptibility. Beginning with the most sensitive, normal tissues respond to radiation in the following order: lymphatic tissue, leukocytes, testicle, ovary and thymus, mucous membrane, lining of blood vessels, papilla of hair, sweat and sebaceous glands, skin of adult, liver, kidney and blood vessels, connective tissue, muscles, cartilage and bone.

The histologieal changes in the cell following intense radiation are of utmost importance, as it is upon these changes that the indications for radiation largely depend. Roentgen rays inhibit the function and growth of cells. The nucleus may show swelling or shrinkage, the latter being accompanied by destruction. Immediately following exposure mitoses are decreased in number, or absent, or may be atypical on reappearance. With sufficient radiation necrosis may result. In the absence of necrosis the injured cell may recover from these nuclear changes and become resistant to radiation.

SELECTION OF CASES FOR RADIATION THERAPY

So far there are only two forms of treatment worthy of consideration in carcinoma of the breast. The first form is surgical, by radical amputation of the breast. The second is intensive radiation, or a combination of surgery and radiation. The surgical treatment is well established and the results expected are reasonably certain. The recent advances in the more modern methods of radiation have revolutionized the treatment of certain groups of cases.

There are *three* main groups which present themselves for treatment and these may be classified by stages I, II and III.

Stage I.—The most favourable group, according to Steinthal's classification, are those growths limited to the breast, with no fixation to skin or underlying tissues, and with no axillary lymphatic involvement. Two types of cases fall in this group: (*a*) The cases with a relatively low index of malignancy clinically, and that metastasize late. (*b*) The very early lesions in which the differential diagnosis between carcinoma and a benign lesion is impossible to make clinically.

It is safe to state that 50 to 75% of the above group will be cured by radical amputation. The purpose of postoperative radiation in this group is to destroy any cancer cells which may remain after operation.

Omitting Stage II for the present, Stage III will be considered, which, quoting Steinthal again, refers to cases in which lymphatics beyond the axillary have been invaded, or ulceration or adherence of the tumour to deep tissues is present. This stage includes cases in one of three categories: (*a*) The carcinomas arising during lactation. (*b*) The most malignant group of Greenough's pathological index and of Lee's clinical index of malignancy which will be presented later. (*c*) The less malignant group in which the growth has become so extensive either directly or by metastasis as to be considered inoperable.

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Categories (*a*) and (*b*) of Stage III will undoubtedly resist any known form of treatment even if applied as soon as the lesion is discovered. In this group the best results are obtained by applying radiation primarily, provided x-ray equipment of sufficient volt capacity is available and is operable under the direction of radiologists who have had extensive experience in this form of therapy. A certain percentage of this group, after intensive radiation of both primary and secondaries, become operable. The tumour either disappears, or is reduced in size and rendered freely movable. The statistical data on the result of treatment of this group at the Toronto General Hospital, Ontario Institute of Radiotherapy are very enlightening and will be presented later in this paper.

Between these two extremes is a middle group, Stage II, that may or may not be curable. This group includes tumours which may be adherent to the skin or may cause retraction of the nipple, or which have axillary involvement. According to Lee's index these are the moderately malignant cases. The larger centres agree that 20 to 25% of this category will be cured by radical amputation or will be free from evidence of recurrence for five years or more.

The value of postoperative radiation therapy in this group has been proved in many of the larger clinics. For example, in a study of 297 cases of Stage II carcinoma of the breast made by Haagensen and Stout in the Presbyterian Hospital, approximately one-half of the cases received postoperative prophylactic radiation. The results showed that of the group which did not receive postoperative radiation 24.7% were so-called 5-year clinical cures and of the group which did receive postoperative radiation 31.5% 5-year clinical cures resulted.

The advantages of preoperative therapy in this group have been widely discussed. It is the firm belief of most radiologists that preoperative treatment should be of more value than postoperative treatment in assisting the 5-year clinical cure rate. As very few of these cases have been offered for preoperative treatment the statistical data on this subject are of very little value so far. Nevertheless, preoperative treatment brings about a partial or total regression of the tumour and of the glands involved if they are radiosensitive, as well as rendering the tumour better defined and freely movable whenever fixation to the surrounding tissue may have been present.

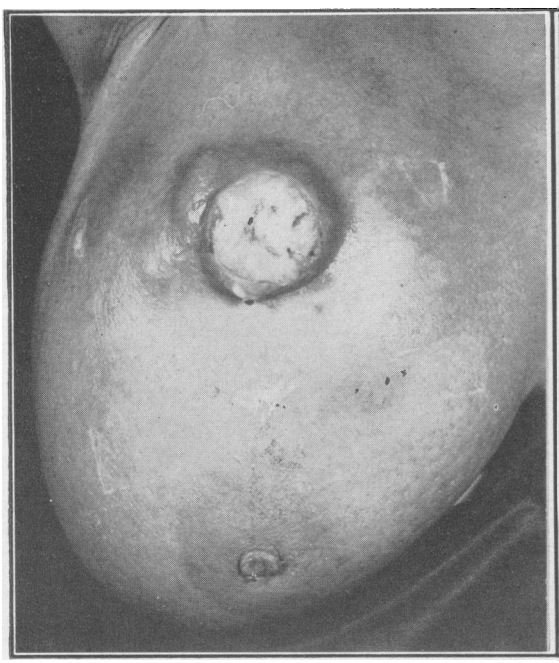


Fig. 1.—Appearance on admission, April, 1940.

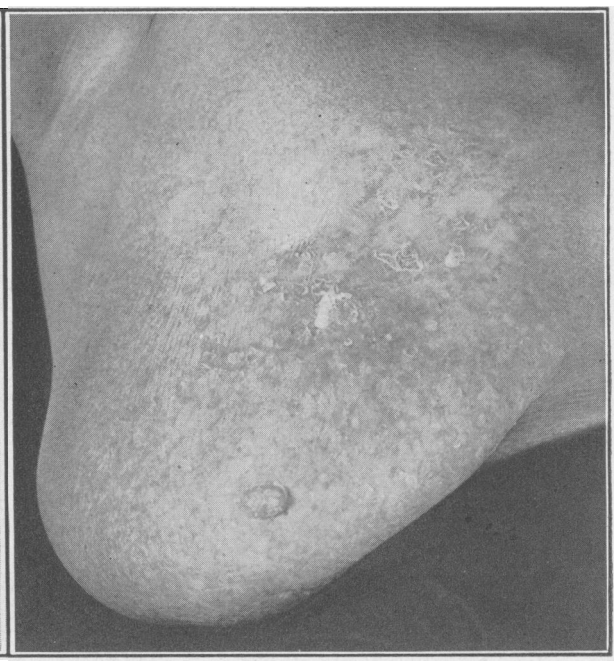


Fig. 2.—Postradiative, September, 1940.

The following pictures illustrate the effect of pre-operative radiation. This patient, aged 65, was presented for treatment in April, 1940, with a history of a rapidly growing mass in her right breast of four months' duration but which had ulcerated two weeks previous to admission. The right breast received radiation to reaction at a voltage of 400 K.V. The first photograph was

taken on admission and the second after the reaction to radiation had subsided.

In April, 1941, a simple mastectomy was performed. No postoperative radiation was advised and at the present time this patient has no evidence of local or general recurrence.

TECHNIQUE OF RADIATION THERAPY OF CARCINOMA OF THE BREAST

Stage I, previous carcinoma of the breast, P.O.—The postoperative treatment of Stage I carcinoma of the breast consists of three series of treatments, each series lasting one week. The first series is commenced as soon as the operation incision is healed. The interval between the first and second series is two months, and that between the second and third is three months. Using rays at 200 K.V. (0.5 Cu. filter and 50 cm. distance) 600 roentgen units are applied to the neck, and to the axilla from each of two directions. In addition, the chest wall receives a total of 1,800 r units. This is given in small fractionated doses from three directions tangentially, in order to avoid the lung tissue as much as possible. On the completion of these three series each Institute patient is examined at regular intervals for at least 5 years. This routine check-up applied to all other stages as well.

Stage II, previous carcinoma of the breast, P.O.—The postoperative treatment of Stage II carcinoma of the breast showing axillary glandular involvement at operation, is similar to that of Stage I with the exception of the radiation of the glandular regions. These are treated at 400 K.V. more intensively than in Stage I for two of the three series. The axillary and supraclavicular regions each receive a total of 1,800 r units and the infraclavicular region is included in one of the axillary portals. This series takes two weeks to complete. Using roentgen rays at 400 K.V. a much larger total dose may be applied than with rays generated at 200 K.V. without producing any undue skin reaction, as the filtration used is much heavier, barring the soft rays which cause more inflammation than the hard rays. Also the area treated is at a much greater distance from the target or source of the x-rays, allowing the soft rays with longer wave lengths to scatter away from the primary beam.

Thus, the patients in whom axillary involvement has been proved either before or at operation, receive at least two series of very intensive treatment lasting two weeks each, and one series as in Stage I lasting one week. The reaction on the skin is very slight, usually a mild tanning of the areas treated unless the patient has an extremely sensitive skin.

Primary carcinoma of the breast.—In this classification the preoperative group is included, as well as the inoperable and Stage III cases, since their treatment is very similar. In fact each individual presented for treatment is treated according to the size and extent of the lesion, amount and size of glandular involvement, and the presence or absence of metastases. All these factors are considered thoroughly before the method of treatment is outlined. Unless the glandular involvement is very extensive the primary lesion is treated first. The degree of skin reaction is used as a guide for the tolerance of each patient. This reaches its peak approximately two weeks after the treatments are completed. The primary is treated at 400 K.V., using a portal sufficiently large to include the whole breast but concentrating the rays of the centre of the primary beam on the lesion itself, as they are the most powerful. The rays are applied from four oblique directions, superior, inferior, mesial and lateral crossfiring the breast tissue. The amount administered varies with each individual and using fractional doses of 300 r, as much as possible is given without producing too severe a skin reaction.

The total amount of radiation to the primary lesion is gauged by the size of the lesion and the presence or absence of ulceration, or skin on the point of ulcerating. Thus, for the earlier very hopeful cases the total radiation depends on the sensitivity of the lump. The reduction in the size of the mass is carefully observed throughout the process and a minimum total of radiation is administered to ensure complete restoration of tissue substance, for the benefit of the surgeon, and still produce the optimum effect on the tumour mass.

On completing the treatment of the breast the axillary and supraclavicular areas are then radiated to reaction also, but not usually to the same extent of reaction as the primary lesion, unless the glands are very enlarged. Radiation at 400 K.V. or the teleradium bomb may be used to treat these regions. The whole course of treatment generally requires six weeks to complete. Consequently, using the above method, the skin reaction resulting from the treatment of the breast can be carefully observed and daily

dressings applied while the patient is receiving the latter treatments to the glandular areas. In this manner the more severe reaction to the breast is generally subsiding and can be treated by the patient herself after the whole series is complete.

The gradual daily radiation has a cumulative effect and the rays absorbed by the tissues continue to emit energy for approximately a month following the course of treatments. Thus, at this point, the best result of the series may be observed and the operability of the lesion determined. If a mastectomy is indicated, it may be performed as soon as the reaction has completely subsided.

Recurrent carcinoma of the breast.—This may also include the distant metastases. Consequently, the methods of treatment vary greatly according to each individual case, and cannot be discussed in detail in a short space of time. The main objective in radiating these areas is to relieve unpleasant symptoms and prolong the life of the patient. Undoubtedly, both aims are achieved to a great extent as the two most dreaded symptoms of carcinoma of the breast are ulceration and pain. Ulceration is the end-result of local recurrent skin nodules if left untreated. This may be controlled by radiation to reaction in the form of either x-rays or radium, depending on their site and extent.

A large percentage of the pain symptoms are due to skeletal secondaries which may also be controlled by x-rays. Many of the cases respond very well to the treatment of skeletal secondaries, especially if they are the first and sole form of recurrence. Recalcification of the bone takes place and life is prolonged for one to three years before additional secondaries appear.

Precautions exercised during radiation therapy.—(1) radiation sickness; (2) care of the skin; (3) blood picture; (4) psychological treatment; (5) treatment of complications.

Of prime importance on account of its prevalence is the treatment of *radiation sickness.* About 50% of those treated complain of this malady in some form, but very few patients become so ill in spite of treatment that they cannot tolerate more radiation. The most common complaints are nausea and lack of appetite. The most important factor controlling radiation sickness is the mental attitude of the patient. If they are assured that they are not likely to become nauseated and that they should live a normal life, forgetting that they are undergoing a series of treatments, the majority will not become afflicted.

Many of the patients get the impression that they should eat very lightly to avoid the nausea. But we have found from experience that the patients who eat their normal meals are less liable to become ill as a result of radiation. Therefore, we encourage the patients to force themselves to eat well. In many instances we have been able to control quite severe radiation sickness by advising the patient to eat in small amounts as often as every hour, and, especially, just before they come for their treatment.

However, in spite of diet and advice on mental control, a few patients still suffer nausea and vomiting three or four hours after their daily treatments. These may be controlled by prescribing nicotinamide or thiamine chloride in sufficient daily amounts to control the sickness. Others respond well if given a sedative, preferably nembutal, an hour before their treatment each day. The radiation sickness resulting from treatment at 400 K.V. is not generally as severe as at lower voltages on account of the filtration of the soft radiation.

With reference to the *care of the skin* each patient is advised to apply an oil or pure powder to relieve any slight irritation as a result of treatment. A sedative ointment may be necessary if the irritation becomes severe before the reaction subsides. It is important that each patient be warned against exposing the area of skin treated to direct sunlight or any form of irritant such as hot water bottles or plasters.

As a result of short series of treatments, such as postoperative routine breast series, the *blood picture* of the patient is affected very little, if at all. But if a long course of treatments is necessary the blood counts may be seriously affected, especially if treatments are administered over long bones or in the region of the spleen. The white blood count is the first to be affected and a leukopenia is carefully avoided. The administration of liver extract seems to be the quickest method of bringing the white blood count back to normal.

An interesting adjunct to the care of the patient during a course of radiation treatment is the psychology employed. Taking into account that most carcinoma patients are suffering from fear and the shock of that realization, the institution staff direct every effort towards making the patients as happy and contented as possible. As there are many out of town patients treated

in a Government institution, this consideration is very necessary. The large number of patients treated daily (approximately 120) has a good psychological effect on the individual case, especially after the first dread of the apparatus has abated. At first, the average patient pours out a long tale of woe, but very soon, on observing that there are many others with more serious, but similar, afflictions, their mental outlook is very noticeably transformed, allowing them to endure their course of treatments more successfully. There are still others whose family ties or responsibilities gives them a will to live that seems to have a definite influence on their length of life in spite of the recurrences they may develop.

The treatment of complications of radiation will not be discussed in detail as they are very rare in the treatment of carcinoma of the breast or its metastases. However, such complications as cystitis and proctitis occasionally occur and it is sufficient at this point to say that they are treated medicinally if present, but they are avoided as much as possible.

PROGNOSIS

Undoubtedly there are many factors influencing the estimation of prognosis in carcinoma of the breast. The chief of these are: degree of malignancy of the cell; age of patient; presence of lactation; rate of growth of the mass; extent or stage of the disease.

Lee and Stubenbord of Memorial Hospital, New York, in 1928 prepared the following excellent table which combined all the important clinical factors, producing a method for rapidly calculating the prognosis of an individual case. Their claim was that the clinical index proved more successful than the pathological, unless the histology of the cells revealed a very highly malignant type of tumour which rapidly extends in spite of any type of treatment.

TABLE I.

	Weighting factors		*Gradation factor*	
Age.....	A=2	A	Over 55 41 - 55 40 or less	— 1 — 2 — 5
Lactation.....	L=3	L	Absent Present	— 0 — 3
Rate of growth....	R=4	R	Slow Moderate Rapid	— 1 — 2 — 4
Extent of disease..	E=5	E	Small (3 cm. or less) Large Nodes present	— 1 — 2 — 4

Clinical index of malignancy = 2A + 3L + 4R + 5E.

The clinical index of malignancy equals twice the age-factor, plus three times the lactation factor, plus four times the rate of growth, plus five times the extent of disease. When the total adds up to less than 25, the clinical index is relatively benign. When the total adds up to 26 to 39, the index is moderately malignant. When the total adds up to 40 to 55, the index is highly malignant. The clinical index of malignancy is also important in estimating what type of treatment is most beneficial.

STATISTICAL DATA

The results of preoperative radiation of the cases treated in the Department of Radiology under Dr. Richards' direction during the years 1938 to 1940 will be analyzed, since those patients were the first to receive benefit from the 400 K.V. apparatus which was installed early in 1938. In addition, as an example of the results of postoperative radiation the statistics pertaining to the years 1937 and 1938 have been studied.

Preoperative carcinoma of the breast.—During 1938, 1939, and 1940 the great majority of cases presented for treatment were Stage III, and were largely patients having either glandular extension beyond the axilla or inoperable primaries due to size or adherence to surrounding tissues.

TABLE II.

FIVE YEAR CLINICAL CURE RATE OF PREOPERATIVE CARCINOMA OF BREAST, 1938-1940, TORONTO GENERAL HOSPITAL

Year	*Stages*	*No. cases*	*1 yr.*	*2 yr.*	*3 yr.*	*4 yr.*	*5 yr.*
1938-1940 Total	II and III	21	20	15	13	8	4
1938-1940 Percentage	II and III	21	% 95.2	% 71.8	% 61.9	% 53.3	% 44.4

The clinical factors of all the above cases were weighed and calculated according to Lee and Stubenbord's clinical index of malignancy. They all fall into either the moderate or highly malignant group of cases giving them a very unfavourable prognosis. In spite of the fact that the number of cases available for study is comparatively small, thus lessening the value of the statistical table, it is very encouraging to find such a high percentage of three- and five-year clinical cures.

These data compare very favourably with the data prepared on Stage I and II postoperative carcinoma of the breast. If it were assumed that only 4 cases survived all three-year groups, the percentage five-year clinical cures would be 19%, which is very much underrating the expected cure. In former years, the average five-year survival rate of this group has been considered 4%. However the actual five-year percentage cannot be obtained until more time has elapsed.

In studying 100 cases of primary operable carcinoma of the breast at Memorial Hospital, all of whom received preoperative and postoperative radiation as well as radical excision, Lee and Stubenbord found by the use of their C.I.M. that 69% of the relatively benign cases and 34% of the moderately malignant and 4% of the highly malignant cases were alive and well at the end of five years.

TABLE III.

RELATIONSHIP BETWEEN AGE AND (3 YR.) SURVIVAL PREOPERATIVE CARCINOMA OF BREAST

Age	*No. cases*	*3 year survival*	*3 year survival*
			%
55 plus.....	9	6	66.0
40 - 54.....	12	6	50.0
Under 39.....	2	1	50.0

The latter figure has no statistical value as there were only two cases in this age group, but the results of this Table seem to indicate a better prognosis for the older age group. There is no record of lactation being present in any of the cases.

TABLE IV.

RELATIONSHIP BETWEEN RATE OF GROWTH AND SURVIVAL, PREOPERATIVE CARCINOMA OF BREAST

	No. cases	*3 year survival*	*3 year survival*
			%
Slow (over 2 years)....	5	4	80.0
Rapid (under 2 years)..	17	8	47.0

Comparing Table IV with Table III, we find that the clinical factor of rate of growth has much more significance in prognosis than the age-factor as the percentage survival of the slow-growing type is almost double that of the rapidly advancing type. This conclusion corroborates the comparison of the weighting factors used by Lee and Stubenbord.

The relationship of extent of disease and survival cannot be estimated properly, using this group of cases, as even the Stage II group presented for treatment were comparatively late cases (taking into account the fact that Stage II refers to cases having axillary gland involvement). However, Table V has been prepared and shows a slight improvement in the percentage 3-year survival in the earlier group of cases.

TABLE V.

RELATIONSHIP BETWEEN EXTENT OF DISEASE AND 3-YEAR SURVIVAL, PREOPERATIVE CARCINOMA OF BREAST

	No. cases	*3 year survivals*	*3 year survivals*
			%
Stage II.....	8	6	75.0
Stage III.....	13	9	69.0

On the strength of the above data it is very convincing that the prognosis of a vast number of the earlier cases of carcinoma of the breast could undoubtedly be improved by preoperative radiation therapy either in preference to, or in conjunction with, postoperative radiation therapy.

Carcinoma of the breast; treated postoperatively.—This series of cases received only postoperative prophylactic irradiation therapy, unless local recurrences or metastases developed during the five year interval studies. Only cases treated during the years 1937 and the first six months of 1938 have been studied, as they include a representative group, treated recently, for which a five-year analysis can be made, while the number (165) is sufficient to render the statistics of some value. Ten of the patients died of extraneous disease during the five years following treatment, leaving only 155 for complete study. To add interest to the survey, Stage I and II carcinoma of the breast have been considered both separately and combined in the following tables, although this was not always necessary from a statistical standpoint.

In reviewing the statistics from many of the larger surgical clinics it is agreed that the average five-year survival for all operable cases is

TABLE VI.

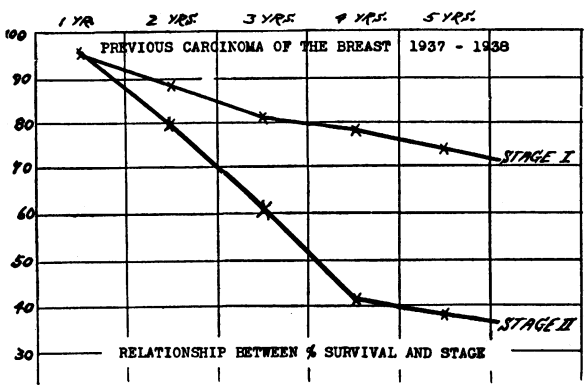
1937–38 PREVIOUS CARCINOMA OF BREAST, TORONTO GENERAL HOSPITAL

	No. cases	*1 yr.*	*2 yr.*	*3 yr.*	*4 yr.*	*5 yr.*
		%	%	%	%	%
Stage I.....	67	94.0	88.1	83.6	79.1	*74.6*
Stage II.....	88	94.3	80.7	61.4	42.0	*38.7*
Stage I and II.	155	94.2	83.9	70.9	60.0	*54.2*

25 to 35%. According to extent of disease, the survival rate for Stage I averages 65% and for Stage II, 20 to 25%.

These figures demonstrate that the prognosis, or expected 5-year cure is, on the average, approximately 19% better if postoperative radiation is included in the treatment of carcinoma of the breast. These statistics have the disadvantage, in comparison with purely surgical statistics, that the majority of cases referred for postoperative radiation had one or more unfavourable clinical factors preceding operation; also that the operations were performed by many different surgeons and were not always above criticism from the standpoint of adequate surgical procedures for mammary cancer.

It is interesting to note, from Table VI, that the per cent survival rate drops gradually from 1 to 5 years in the Stage I group, but in Stage II the greatest drop is noted around the three year mark. This is shown more clearly in the graph of the Table.



The two-year survival of Stage II is comparable to the 4-year survival of Stage I. Of important significance is the finding that the 5-year survival of Stage I is almost twice the percentage of that of Stage II. This stresses the value of the clinical factor of extent of disease in the prognosis of carcinoma of the breast.

The cases analyzed were all given much the same postoperative treatment before the installation of the 400 K.V. apparatus. Since it has been operating, the Stage II cases have received more intensive radiation to the local glandular areas. In two or more years from now, it will be possible to analyze the advantages of this method of treatment over the former schedule.

Public opinion has in the past emphasized the age-factor in relation to carcinoma of the breast. In the study of the preoperative group it was found that the older the age-group, the better the prognosis, the variation between the two-extremes of ages showing a difference of only 6%. But in this group of cases the age-factor did not seem to be of much importance in determining prognosis as is shown in Table VII.

In this group the best survival rate was obtained in those aged 41 to 55. The 27 cases, age 40 and less, (the youngest being 28 years of age), which could be expected to have a high mortality rate, compared very favourably with the other ages. The number in this group alive after 5 years was only 4% less than in the 41 to 55 age group.

Taking into consideration the stage of disease, attention is drawn to the finding that the greatest percentage of five-year cures has been obtained in Stage I, aged under 40 and over 55, while the smallest percentage is in Stage II, aged under 40 and over 55, the two age-groups having 5-year percentage survivals which are almost identical. Thus, the old adage concerning age in relation to carcinoma of the breast has been proved to be of very little import compared with other factors.

TABLE VII.

RELATIONSHIP BETWEEN AGE AND 5-YEAR SURVIVAL PERCENTAGE, 1937–38, TORONTO GENERAL HOSPITAL

		No. cases	*1 yr.*	*2 yr.*	*3 yr.*	*4 yr.*	*5 yr.*
			%	%	%	%	%
Age 56+.....	Stage I.....	28	96.4	96.4	85.7	78.5	75.0
	Stage II.....	35	91.4	80.0	68.6	42.9	34.1
	Stage I and II	63	93.6	87.3	76.2	58.7	*52.4*
Age 41–55....	Stage I.....	27	92.6	81.5	81.5	77.7	70.4
	Stage II.....	38	100.0	84.2	60.5	52.6	44.9
	Stage I and II	65	96.8	83.1	69.2	61.5	*55.4*
Age 40 or less.	Stage I.....	12	91.7	83.3	83.3	75.0	75.0
	Stage II.....	15	88.6	73.3	46.6	33.3	33.3
	Stage I and II.	27	88.8	74.0	62.9	51.9	*51.9*

The presence of lactation was not determined in this survey but the number of such cases in the 1937-38 group would be very few and consequently of little significance.

Significance of duration of disease. — With respect to duration of the disease the conclusions drawn from the following Table seem to show that this also is of minor importance in gauging prognosis when both stages of the disease are considered collectively.

From this Table it is concluded that the rate of growth ranks very high in importance as a clinical factor in determining the expected cure of carcinoma of the breast.

The group designated as "moderate" has a slightly higher percentage cure than the average of all cases which is 54.2%, but that variance is probably due to the inclusion of more cases tending to be slowly growing than those bordering on the rapidly growing variety.

TABLE VIII.

RELATIONSHIP BETWEEN DURATION OF DISEASE AND SURVIVAL RATE, 1937–38, TORONTO GENERAL HOSPITAL

Duration	*Stage*	*No. cases*	*1 yr.*	*2 yrs.*	*3 yrs.*	*4 yrs.*	*5 yrs.*
			%	%	%	%	%
Under 6 mos..	Stage I.....	36	94.4	83.3	80.5	80.5	75.0
	Stage II.....	50	92.0	78.0	62.0	50.0	42.0
	Stage I and II.	86	93.0	80.2	68.6	62.7	*55.8*
6 mos.–1 yr...	Stage I.....	22	90.9	90.9	81.8	68.1	59.0
	Stage II.....	30	96.6	86.6	63.3	40.0	33.3
	Stage I and II.	52	94.2	88.4	71.1	51.9	*50.0*
Over 1 yr.....	Stage I.....	9	88.8	88.8	77.7	77.7	77.7
	Stage II.....	7	100.0	71.4	57.1	42.8	28.6
	Stage I and II.	16	93.7	81.2	68.7	62.5	*50.6*

The five-year survival percentages are very similar in the three duration groups. Those having a duration of less than six months show a cure rate of 55.8% which is slightly better than those of more than a year's duration, the five-year survival rate of the latter being 50.6%. However, the prime object in preparing this Table was to derive a method of calculating the rate of growth of the disease, and then to draw some conclusion as to its relation to the prognosis.

From Table VIII the group of Stage I carcinoma of the breast having a duration of more than one year has been chosen as representative of the slow-growing type. Similarly, the Stage II group having a duration of less than six months was selected to represent the rapidly growing variety. The remaining groups have been combined to symbolize the moderate type in relation to rate of growth. Undoubtedly, included in the moderate group as chosen, are a few cases of both slow growing and rapidly growing types of tumours, but the average survival percentage should not be affected. The aim in the above selection was to obtain true percentage five year figures in the two extremes of rate of growth. Applying this method of computation Table IX was compiled.

TABLE IX.

RELATIONSHIP OF RATE OF GROWTH TO PERCENTAGE SURVIVAL RATE, 1937–38, TORONTO GENERAL HOSPITAL

	No. cases	*5 year survival*
		%
Slow (more than 1 year).....	9	77.7
Moderate.....	96	57.0
Rapid (less than 6 months)...	50	42.0

Combining all the clinical factors and using Lee and Stubenbord's table of prognosis estimation, as previously shown in Table I, the next table shows its application to the 155 cases studied.

TABLE X.

Clinical factor	*Weighting factor*	*Gradation factor*		*Applied % 5 year survival*
Age.....	A=2	Over 55	— 1	52.4
		41–55	— 2	55.4
		40 or less	— 5	51.9
Lactation.....	L=3	Absent	— 0	....
		Present	— 3	....
Rate of growth..	R=4	Slow	— 1	77.0
		Moderate	— 2	57.0
		Rapid	— 4	42.0
Extent of disease	E=5	Small	— 1	74.6
		Large	— 2	
		Nodes present	— 4	38.7

The only percentages in this Table which do not agree accurately with the gradation factors stipulated are those applying to the age-factor. Lee and Stubenbord have put more stress on the younger age group than the above statistics allow. Nevertheless, the chief object of this study on clinical factors has been achieved by proving the importance of rate of growth and extent of disease in determining the prognosis. Using this combined index of malignancy there should be no doubt as to the method of treatment to adopt.

Putting aside the subject of prognosis for the present, further data have been secured on the above cases which may be interesting. Of the group surviving more than 5 years there are 11 cases which developed recurrences following the postoperative series of radiation, but which were controlled by radiation and are still alive and well. Seven of these recurrences were in the chest wall, one in the axilla, and three in some part of the skeletal system. The latter 3 cases will probably eventually succumb as a result of the disease, but their span of life has been considerably prolonged.

In studying the cases who died of carcinoma of the breast during the five year period it is of interest to note the prevalence of certain locations of first recurrence. Table XI points out the dominant areas of recurrence.

TABLE XI.

1937-38 CARCINOMA OF BREAST, TORONTO GENERAL HOSPITAL

Total no. cases D. D. during 5 years	84
1st recurrence chest wall	20
" " skeletal system	10
" " lungs	9
" " supraclavicular glands	4
" " mediastinum	2
" " brain	2
" " opposite breast	1
" " liver	1
" " omentum	1
" " not determined or multiple	34

Local recurrences lead very noticeably, skeletal system and lungs being second in frequency. The statistical data concerning prognosis in the classification of recurrent carcinoma of the breast with no previous radiation therapy are of no value as the cases which survive more than three years are very rare.

CONCLUSIONS

Combining the results of this survey there are three main conclusions to be stressed. Dealing first with the hopeless cases of carcinoma of the breast, both primary and recurrent, radiation offers the only hope of relief of distressing symptoms.

Secondly, the most promising group of cases, *i.e.*, Stage I, is no doubt benefited by prophylactic radiation, although not as significantly. This survey raises the 5-year clinical cure rate from the average of 65 to 75%.

Lastly, between these two extremes, lies the large group of cases of carcinoma of the breast comprising those which are either surgically difficult or those in which, in spite of favourable circumstances for surgical excision, the clinical factors add up to a moderately high degree of malignancy. In considering these cases the question arises whether preoperative or postoperative radiation is more valuable in the treatment of such carcinomas. The statistics given in this paper have shown that postoperative x-ray therapy has raised the survival rate in this group approximately 15 to 20%. But observations from various large centres where preoperative therapy is practised, as well as the results of preoperative treatment of advanced primary carcinoma of the breast, suggest that the prognosis in mammary cancer, Stage II, would be markedly improved by the institution of preoperative radiation in preference to, and in some instances, combined with postoperative treatment.

SICKLE CELL ANÆMIA ASSOCIATED WITH CARDIAC FAILURE

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THE etiology of sickle cell anæmia is unknown. The sickling phenomenon, which is the basis of the disease, is a tendency inherited according to the Mendelian law as a dominant characteristic.[1] It is essentially a disease of young negroes (average age, 13), although Wintrobe[2] states that unchallengeable cases have occurred in 7 whites of whom 6 belonged to Mediterranean races. Sickling is the result of a defect in the red cells and is not associated with any of the known blood groups.

Sickle cell anæmia was first described by Herrick[3] in 1910. Since then an extensive literature has appeared, which forms the basis of conclusions regarding the occurrence and incidence of this condition. Sydenstricker[4] re-