purple, remove from flame immediately and plunge the vessel into a basin of cold water until cool.

The stain is ready for use as soon as it cools. Addition of 2 to 4 ml. of glacial acetic acid per 100 ml. of solution increases the intensity of the nuclear stain. Filter before use.

2. *Eosin solution* (0.5%)

Eosin (water soluble, yellow shade) 5 g.
Distilled water..... 1000 ml.
Filter before storing.

3. *Buffer*

Prepare immediately before use:
75.4 ml. of 0.1M citric acid
24.6 ml. of 0.2M sodium phosphate
pH should be 3.2 - 3.3

Technique:

Fresh clotted blood is preferred; however, heparinized blood may be used. Alcohol-cleaned slides must be used. Mix, on the slide, two drops of serum with one drop of blood and prepare a thin blood smear. Air-dry for 30 - 60 minutes.

Slides are fixed in 80% alcohol for five minutes. Wash thoroughly under running cold tap water. Place in buffer (at 30°C.) for five minutes. Wash slides again under running tap water for five minutes. Stain for five minutes with eosin. Wash eosin off with running water. Stain slides with freshly filtered hematoxylin for two to three minutes. Wash and dry in air.

The Clinical Stages of Breast Cancer—What Do They Mean?

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DURING the last 15 years, every reported prospective trial[1-5] or retrospective review[6-11] of breast cancer patients treated at one centre has failed to show any advantage of radical therapy (either surgical or radiotherapeutic) over conservative treatment. These observations clearly contradict the traditional understanding of the behaviour of breast cancer. Consequently, it seemed desirable to study some of the features of carcinoma of the breast to see if more acceptable concepts could be developed. It was realized that such concepts would be general in nature, and qualified by the need to consider as one disease what may be different diseases presenting rather similar histological appearances.

The first parameter studied was the significance of regional lymph node metastases.[12] It was concluded that the poor prognosis associated with metastatic regional lymph nodes was not due to these metastases. Rather, both prognosis and metastases were evidence of the biological potential of the tumour. The possibility was considered that the regional lymph node metastases might not be important sources for the further spread of breast cancer.

Some observations concerning the clinical stage of the tumours when the patients were first seen—the "presenting clinical stage"—are now reported, and their significance is discussed.

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MATERIAL AND METHOD

The material consists of all of the 1440 female patients reported to the Civic Hospital Division of the Ottawa Clinic of the Ontario Cancer Foundation, whose treatment for carcinoma of the breast was started between 1946 and 1961 inclusive. It seemed likely that these patients make up a typical population of the victims of breast cancer—for Canada at least.

Because some of the preoperative examination records were vague, the following retrospective method of staging was based on the pathological reports as to the measurement of the tumour size, and the presence of axillary lymph node metastases:

Stage I: The tumour was 5 cm. or less in size. There was no *peau d'orange* phenomenon, skin infiltration or ulceration (dimpling, skin "tethering" and nipple retraction were not considered as evidence of skin invasion). There was no fixation of the tumour to underlying tissues. No supraclavicular lymph nodes were palpable, and edema of the arm was absent. Histological examination of the excised axillary lymph nodes did not reveal metastases.

Stage II: The clinical signs accompanying the primary tumour were as in Stage I, but there were histologically proved axillary lymph node metastases. If these nodes were palpable clinically, they were not fixed to each other or to adjacent structures.

Stage III: The tumour was greater than 5 cm. in greatest diameter, and the patient had one or more of the clinical signs described as being absent in the first two stages.

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Stage IV: Distant metastases were detected.

Some 331 of the patients assigned to Stage I were treated by simple mastectomy, and axillary lymph nodes containing metastases may not have been removed for subsequent recognition by the pathologist. Thus some patients with Stage II disease may have been placed in the Stage I category. This artefact, however, does not alter the validity of the subsequent observations and arguments, for as McWhirter[13] has shown, its effect, if significant, should have been to lessen the observed differences in behaviour between the Stage I and Stage II groups and the Stage II and Stage III groups. It is considered improbable that the initial treatments, which consisted of almost all possible combinations of surgery and radiotherapy,[9] or that the many palliative therapies of subsequent metastases, significantly altered the differences between the observed ultimate courses of patients with the various clinical stages of the disease.

RESULTS

The detailed statistics are provided in the Appendix; statements made in the discussion of the observations can be confirmed by referring to the Appendix.

Since it is the ratios and proportions that are more easily understood, it is these that are used in the discussion.

DISCUSSION OF OBSERVATIONS

In the past the clinical staging of cancer has been used to classify the differing extent to which tumours have grown in patients presenting for treatment. The more extensive the size and local or distant spread of the tumour, the more advanced its stage. There is the implication that the advanced stages are largely due to the disease having been present and untreated for a greater rather than a lesser period of time. Expressed mathematically this might be:

STAGE = TIME x growth.

THE INFLUENCE OF THE TIME OF STARTING TREATMENT

The proportions of patients in the different clinical stages in each of the time periods during which the tumour was known to exist before treatment are recorded in Table I. Contrary to what might be expected, patients with Stage II disease had not known their tumours to have been present for longer times than the patients with Stage I disease. There is no doubt that the time recorded as to when the patient first detected the tumour is a crude measure of the actual duration of the tumour's existence, but it was the only one available to us. The distributions of the Stage I and Stage II patients are in fact identical, and, although proportionately more Stage III and IV patients had longer known pre-treatment periods, the distribution is not sufficiently different to account for the vastly different 5- and 10-year survival rates (Table II).

TABLE I.—THE TIME BEFORE TREATMENT IN EACH STAGE

	Stage I	*Stage II*	*Stage III*	*Stage IV*
1 month or less	31%	26%	18%	13%
1-3 months	29%	29%	18%	10%
4-6 months	17%	16%	17%	8%
7-12 months	7%	10%	8%	10%
1 year or more	12%	16%	35%	49%
Unknown	4%	3%	4%	10%
	100%	100%	100%	100%

TABLE II.—CRUDE 5- AND 10-YEAR SURVIVAL RATES BY STAGE

	5-Year	*10-Year*
Stage I	74%	55%
Stage II	51%	29%
Stage III	20%	10%
Stage IV	6%	0%

Thus, known pre-treatment period had a poor correlation to the presenting clinical stage. This suggests that time may not be a major factor in determining the clinical stage of a tumour in a patient presenting for treatment.

TABLE III.—FIVE-YEAR SURVIVAL RATES FOR EACH STAGE AND TIME-PERIOD BEFORE TREATMENT

	1 month or less	*1-3 months*	*4-6 months*	*7-12 months*	*1 year or more*
Stage I	75%	71%	77%	66%	80%
Stage II	56%	43%	54%	38%	54%
Stage III	20%	19%	23%	13%	21%

The five-year survival rates for the patients according to presenting clinical stage and the known pre-treatment time periods are recorded in Table III. Though survival rates bore an obvious relation to the presenting clinical stage, they were relatively independent of the time periods before therapy. (It is curious that the survival rates for the group with 7- to 12-month pre-treatment periods for each stage appeared worse, though the differences between any of these and the groups with 1-month pre-treatment periods are not statistically significant. At any rate, only 8% of patients were in the 7- to 12-month pre-treatment group.)

Fig. 1.—Time of reporting primary breast cancer, 1946 to 1961.

Thus in this study, time, as measured by the admitted existence of the tumour before treatment, had little influence on either the presenting clinical stage or the five-year survival rate. Survival rates were, however, closely related to the presenting clinical stage.

Another observation in this study suggested that the clinical stage is relatively independent of time. During the 16 years, patients in the Ottawa area appeared to be reporting for treatment earlier. Fig. 1 shows a gradual increase in the proportion of patients presenting within three months and a decreasing proportion reporting after more than one year. Yet there has been no apparent change in the proportion reporting in each of the four stages over the 16-year period (Fig. 2).

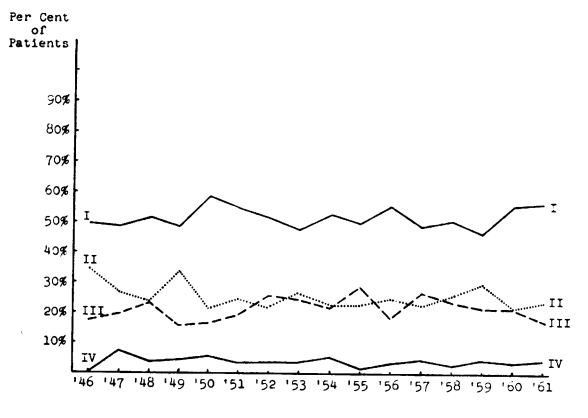

Fig. 2.—Yearly distribution of patients in each stage (1946 to 1961).

THE ROLE OF CLINICAL STAGE IN DETERMINING SURVIVAL RATES

What is it that determines the presenting clinical stage, which seems to be so important in determining the patient's outcome?

In Fig. 3 the year-by-year crude survival rates for 10 years for each stage are shown graphically. The shapes of the curves are quite different, suggesting that there may be some difference in these four groups of patients other than a difference in the physical extent of their tumours.

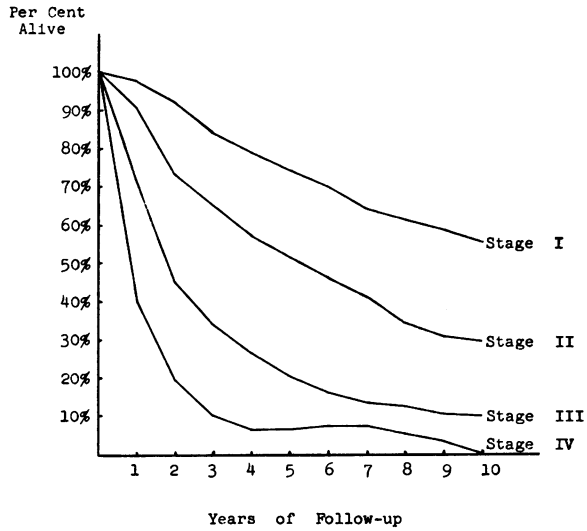

Fig. 3.—Crude 10-year survival curves of the four stages of breast cancer.

This difference is shown in Fig. 4, which records the percentage of survivors who died each year in the 10 years for three of the clinical stages. Though there are some exceptions (in the later years this is probably due to the small numbers involved), these yearly death rates were surprisingly constant even after five years. Approximately 21% of Stage III survivors, 12% of Stage II survivors and 6% of Stage I survivors died each year.

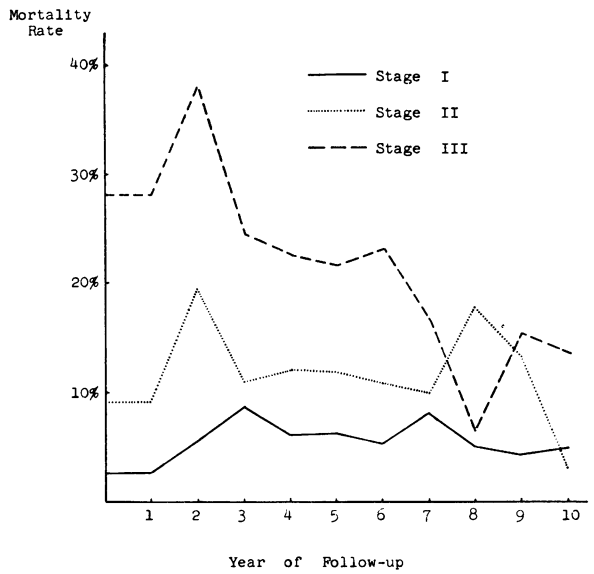

Fig. 4.—Yearly mortality rates for each stage of breast cancer.

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Though the difference in physical extent of the tumour in the different clinical stages might account for the differing death rates in the first year or two, this cannot account for the persisting difference in rates in later years. This persisting difference can only be explained on the basis of different tumour behaviour and/or different host reaction in each of the clinical stages. It would appear that Stage III lesions are Stage III, not because they have been present for a longer time, but rather because either the host resistance is weak or the tumour growth potential is great, or both. Stage I lesions are probably "early" not because they have been present for a shorter period, but because the host resistance is high and/or the tumour growth potential low. Perhaps the earlier equation should be rewritten:

$$\text{Clinical Stage} = \frac{\text{TUMOUR GROWTH POTENTIAL}}{\text{HOST RESISTANCE}} \times \text{time}$$

There is also a suggestion that whatever factors operated to produce the original clinical stage continue to operate to produce the characteristic death rates. Could these factors be similar to whatever it is that continues, apparently forever, to kill women who have suffered breast cancer at a greater rate than women who have not suffered this disease?[14]

THE RELATION BETWEEN CLINICAL STAGE AND LOCAL SKIN RECURRENCE

The local skin recurrences were also studied, as it seemed likely that these represented a measure of tumour-host biological interaction.

TABLE IV.—FIVE-YEAR SKIN RECURRENCE RATE BY STAGE

Stage	*No. of patients*	*5-year skin recurrence rate*	*5-year survival rate*
I	734	10%	74%
II	355	17%	51%
III	303	34%	20%

In Table IV it can be seen that the five-year skin recurrence rate increased with the more advanced stages. The differences in these rates are even more impressive when it is recalled that with their lower survival rates there were fewer Stage II and Stage III patients alive and therefore at risk of developing skin recurrence. Thus the incidence of skin recurrence is closely related to clinical stage.

In Fig. 5 the proportion of skin recurrences appearing in each year for the three stages is indicated. Two-thirds of the patients with Stage III lesions who developed skin recurrences did so within the first year. On the other hand, the Stage I lesions produced a much lower peak delayed to the second and third years, and skin recurrences continued to occur to a lesser extent throughout all of the 10 years of follow-up. The Stage II patients occupied an intermediate position. Thus clinical stage determined not only when a skin recurrence was likely to occur but also how likely it was to occur.

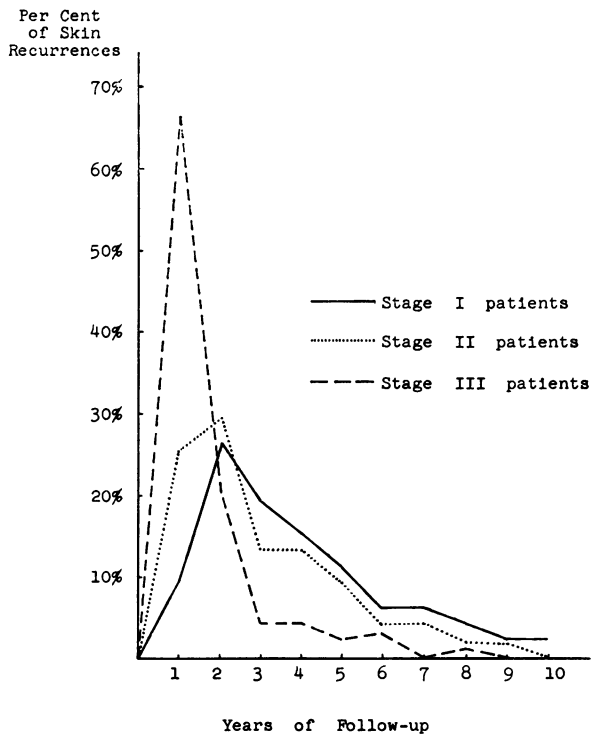

Fig. 5.—Timing of skin recurrences.

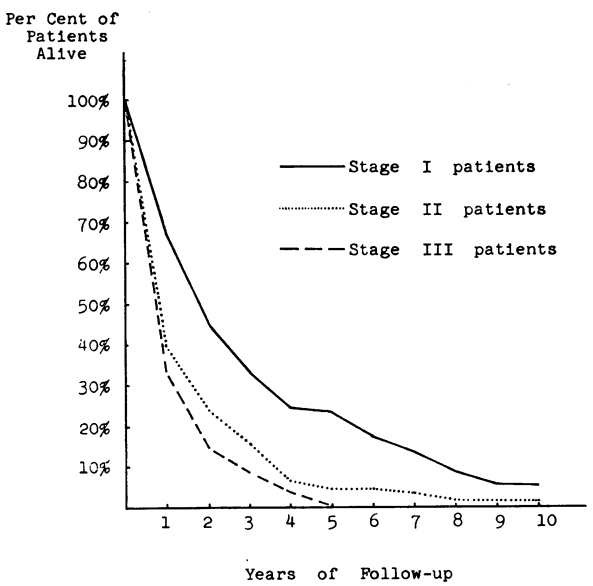

Fig. 6.—Crude survival rates after skin recurrences.

Fig. 6 shows the crude 10-year survival curves for patients with the three stages of disease, after the development of skin recurrences. The patients with Stage I lesions who developed skin recurrences had much better survival rates after these recurrences than patients with Stage III primary tumours. Again, Stage II patients occupied an intermediate position. For the first five years the annual death rates of the Stage III survivors exceed those of the Stage II survivors and both exceed those of the Stage I survivors. Once again there is evidence that clinical stage was an indication of the biological potential of the tumour and the reaction of the host, and not just an indication of physical extent.

CONCLUSION

It would seem then that the clinical stages of breast cancer may not be a measure of degree of spread or extent of growth so much as a measure of tumour biological potential and host reaction. Similarly, an earlier report suggested that regional lymph node metastases were more important as another measure of tumour-host interaction than as a way of spread. It would appear to be the tumour-host interaction that determines the clinical stage at the time of presentation for therapy (including the presence of regional lymph node metastases), the likelihood of, and the time of occurrence of local skin recurrences, and the ultimate prognosis.

Whether the tumour or the host is more important is possibly suggested by two observations. Firstly, there is the above-recorded persisting difference in death rates between patients presenting with the different clinical stages of breast cancer, as well as between breast cancer patients and the normal population. Secondly, there is the common observation that patients dying of breast cancer usually go through a stage of weeks or months where the metastatic disease is largely confined to one organ or tissue (e.g. the patient with extensive *en cuirasse* recurrence or widespread skeletal metastases, etc.).

Since little correlation has been shown between initial therapy and the subsequent timing, site and/or behaviour of metastases, and since this study suggests that "early" breast cancers are "good" ones and "late" cancers "bad", it is important that we employ therapeutic methods which produce the least suffering.

Summary A consecutive series of 1440 breast cancer patients has been retrospectively reviewed, with reference to the factors related to the presenting clinical stage of the tumours. The known time existence before presentation for treatment did not correlate with either the presenting clinical stage or the survival rates for these stages. In spite of earlier presentation for treatment over the 16 years the distribution of patients in the different clinical stages was unchanged. The crude survival rates and annual death rates suggest that the different clinical stages contain biologically different tumours. The higher incidence of skin recurrences, their earlier occurrence, and the poorer subsequent survival rates of patients with the more advanced clinical stages also indicate a biological difference between the tumours of the different stages. With the host-tumour relationship so important in determining the subsequent outcome of the patient, it is desirable that we employ methods of therapy associated with the least treatment-induced suffering.

Résumé L'auteur a étudié rétrospectivement 1440 cas de cancer mammaire, et a donné les détails des facteurs relatifs à la phase clinique de la tumeur au moment de sa présentation. Il n'a pas été possible d'établir de corrélation d'une part, entre le temps écoulé avant le moment de la présentation du cas et d'autre part, avec la phase clinique de la maladie à ce moment ni avec le taux de survie de ces phases. Même si, pendant la période de 16 ans, les malades se présentaient plus tôt pour être traitées, la distribution des malades dans les différentes phases cliniques est restée inchangée. Les taux bruts de survie et les taux annuels de décès permettent de croire que, dans les différentes phases cliniques, il s'agissait de tumeurs biologiquement différentes. La grande fréquence des métastases cutanées, leur apparition précoce, et le fait qu'on comptait moins de survivants parmi les malades dont la tumeur était plus avancée, indiquent également qu'existaient des différences biologiques entre les tumeurs aux différents stades. Quand on se souvient combien est important le potentiel hôte-tumeur pour évaluer l'issue finale, il est souhaitable d'employer les méthodes thérapeutiques qui entraînent le minimum de souffrance induite par le traitement lui-même.

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APPENDIX

NUMBERS OF PATIENTS IN EACH PERIOD OF TIME BEFORE TREATMENT IN EACH CLINICAL STAGE

	Stage I	*Stage II*	*Stage III*	*Stage IV*
1 month or less.....	228	93	55	6
1 to 3 months.....	216	101	54	5
4 to 6 months.....	124	57	52	4
7 to 12 months.....	53	37	23	5
1 year or more.....	84	56	106	23
Unknown.....	29	11	13	5
Total.....	734	355	303	48

NUMBER OF PATIENTS ALIVE AT FIVE YEARS IN EACH PERIOD OF TIME BEFORE TREATMENT IN EACH CLINICAL STAGE

	Stage I	*Stage II*	*Stage III*	*Stage IV*
1 month or less.....	170	52	11	1
1 to 3 months.....	154	43	10	0
4 to 6 months.....	96	31	12	0
7 to 12 months.....	35	14	3	0
1 year or more.....	67	30	22	1

NUMBER OF PATIENTS ALIVE EACH YEAR FOR 10 YEARS IN EACH CLINICAL STAGE

Year of follow-up	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Stage I.....	716 of 734	676 of 734	618 of 734	581 of 734	545 of 734	474 of 677	403 of 626	349 of 574	308 of 527	257 of 465
Stage II.....	323 of 355	260 of 355	232 of 355	204 of 355	180 of 355	151 of 331	129 of 311	94 of 279	77 of 256	66 of 227
Stage III.....	218 of 303	135 of 303	102 of 303	79 of 303	62 of 303	44 of 283	35 of 265	29 of 240	22 of 220	19 of 186
Stage IV.....	19 of 48	9 of 48	5 of 48	3 of 48	3 of 48	3 of 44	3 of 41	2 of 37	1 of 35	0 of 30

NUMBER OF PATIENTS REPORTING WITHIN THREE MONTHS AND MORE THAN ONE YEAR AFTER NOTICING THEIR TUMOURS AND THE NUMBER OF PATIENTS IN EACH STAGE, BY YEAR

	Less than 3 months	*More than 1 year*	*Stage I*	*Stage II*	*Stage III*	*Stage IV*
1946.....	25	15	39	27	13	0
1947.....	26	17	30	16	12	4
1948.....	41	16	44	20	20	2
1949.....	36	13	35	24	11	3
1950.....	45	23	52	19	14	4
1951.....	40	19	42	19	15	2
1952.....	48	18	43	18	21	3
1953.....	60	16	44	25	23	3
1954.....	44	21	50	21	20	5
1955.....	39	18	40	18	23	1
1956.....	59	11	46	20	15	3
1957.....	72	26	62	29	34	5
1958.....	50	17	47	23	21	2
1959.....	63	13	52	33	24	4
1960.....	54	10	52	20	20	3
1961.....	56	16	56	23	17	4

NUMBER OF PATIENTS DEVELOPING LOCAL SKIN RECURRENCES IN EACH YEAR IN EACH CLINICAL STAGE

Year of follow-up	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Stage I.....	9	25	18	14	11	6	6	4	2	2
Stage II.....	17	20	9	9	6	3	3	1	1	0
Stage III.....	70	21	4	5	2	3	0	1	0	0

NUMBER OF PATIENTS ALIVE AFTER EACH YEAR AFTER HAVING DEVELOPED A LOCAL SKIN RECURRENCE IN EACH CLINICAL STAGE

Year of follow-up after skin recurrence	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Stage I.....	65	43	32	23	22	16	12	7	5	5
Stage II.....	27	16	10	4	3	3	2	1	1	1
Stage III.....	35	15	8	3	0	0	0	0	0	0