Breast Cancer Management
–Early and Late

Edited by

Basil A. Stoll

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Honorary Consultant Physician to the Radiotherapy and Oncology Departments, St. Thomas' Hospital and Royal Free Hospital, London.

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Editor

Basil A. Stoll, F.R.C.R.
Honorary Consultant Physician to Radiotherapy and Oncology Departments at St. Thomas' Hospital and Royal Free Hospital, London, U.K.

Principal Authors

Thomas H. Ackland, M.D., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S.
Consultant Surgeon, Royal Melbourne Hospital, Melbourne, Victoria, Australia.

Charles B. Anderson, M.D., F.A.C.S.
Associate Professor of Surgery, Washington University School of Medicine: Chief Transplantation Surgery, Barnes Hospital, St. Louis, Missouri, U.S.A.

Michael Baum, Ch.M., F.R.C.S.
Senior Lecturer, Department of Surgery, Welsh National School of Medicine; Honorary Consultant Surgeon, University Hospital of Wales, Cardiff, U.K.

Diana Brinkley, M.B., D.M.R.T.
Consultant in Radiotherapy and Oncology, King's College Hospital, London, U.K.

Florence Chu, M.D., F.A.C.R.
Acting Chairman Radiation Therapy Department, Memorial Hospital, Clinical Professor of Radiology, Cornell University Medical College, New York, U.S.A.

Robert W. Crichlow, M.D.
Associate Professor of Surgery, Dartmouth Medical School: Staff Surgeon Mary Hitchcock Memorial Hospital, Hanover, New Hampshire, U.S.A.

George Crile, Jr., M.D., F.A.C.S.
Emeritus Consultant, Department of General Surgery, Cleveland Clinic, Cleveland, Ohio, U.S.A.

Hugh L. Davis, Jr., M.D.
Associate Professor of Human Oncology and Medicine University of Wisconsin: Special Assistant to Associate Director, Division of Cancer Treatment, N.C.I. Bethesda, U.S.A.

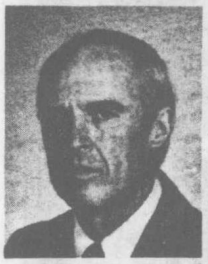
William L. Donegan, M.D.,
Professor of Surgery, Medical College of Wisconsin:
A.C.S. Professor of Clinical Oncology, Milwaukee Division,
Milwaukee, Wisconsin, U.S.A.

Arthur J. Donovan, M.D.
Professor and Chairman, Department of Surgery, University of South Alabama College of Medicine, Mobile, Alabama, U.S.A.

Bernard Fisher, M.D., F.A.C.S.
Professor of Surgery and Director of Oncology, University of Pittsburgh School of Medicine, Pittsburgh, Pa., U.S.A.

C.S.B. Galasko, Ch.M., F.R.C.S. (Eng.), F.R.C.S. (Edin.)
Professor of Orthopaedic Surgery, University of Manchester, Lancashire, U.K.

John S. Lyon, M.R.C.P., M.R.C. Psych.
Consultant Psychiatrist, Basingstoke District General Hospital, Basingstoke, Hampshire, U.K.

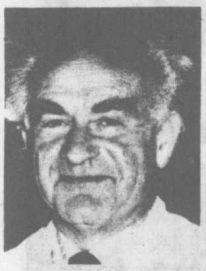


John A. McCredie, F.R.C.S. (E. & Edin.) F.R.C.S.(C.), F.A.C.S.
Associate Professor of Surgery and of Therapeutic Radiology, University of Western Ontario; Research Associate, Ontario Cancer Treatment and Research Foundation, London, Canada.

Guy F. Robbins, M.D.
Senior Attending Breast Service, Department of Surgery; Director of Cancer Control and Rehabilitation, Memorial Sloan-Kettering Cancer Center, New York, U.S.A.

P. E. Robin, M.D., F.R.C.S.
Consultant Otolaryngologist, Dudley Road Hospital, Birmingham, U.K.

G. Keith Stillwell, M.D., Ph.D.
Professor and Chairman, Department of Physical Medicine and Rehabilitation, Mayo Medical School and Mayo Clinic, Rochester, Minnesota, U.S.A.



Paul Strickland, F.R.C.P., F.R.C.R.
Consultant Radiotherapist, Mount Vernon Hospital, Northwood, Middlesex, U.K.

Douglass C. Tormey, M.D., Ph.D.
Associate Professor, Department of Human Oncology and Medicine, University of Wisconsin, Madison, Wisconsin, U.S.A.

Robert G. Twycross, M.A., B.M., M.R.C.P.
Consultant Physician, Sir Michael Sobell House, Churchill Hospital, Oxford, U.K.

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Preface

In recent years, considerable doubts have been expressed as to the effectiveness of traditional surgical techniques aiming at the cure of early breast cancer. At the same time, the value of adjuvant radiotherapy relative to its damaging effects, has come into doubt. Much of the questioning is based on increasing evidence that only a minority of women found to have "early" breast cancer will have a normal expectation of life. Increasing emphasis is therefore being placed on the possible use of systemic therapy at an earlier stage of the disease, and the avoidance of useless and possibly harmful treatment directed at the primary site of disease.

The recent literature on the topic is vast and controversial and it may be timely to assess in one volume where we stand currently in the management of both early and late breast cancer and its special aspects. Leading specialists from both sides of the Atlantic have been asked to review current thinking in their particular field of breast cancer and to provide a scientific justification for the methods they practise in its management.

A remarkable consensus of opinion is found among the authors on major principles; differences are based mainly on our inability to judge accurately the degree of spread of the tumour and the defence reactions of the host. A new concept is emerging that policies need to be adapted to each individual because breast cancer is not only heterogeneous histopathologically but also biologically and immunologically. For such an approach, it is obvious that the management of breast cancer must be multidisciplinary.

The book is planned in three sections—management of 'early" disease, palliation of advanced disease and management of special problems arising in the course of the disease. Many reviews of cancer treatment tend to highlight recent scientific or technical developments. In this book the aim has been to apply our advancing knowledge to better the quality of life of the patient with breast cancer. Length of survival is merely one measure of the efficacy of treatment. If the majority of patients cannot be cured, the quality of their survival becomes all-important.

Basil A. Stoll

London, 1977

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SECTION 1

Treatment Aiming at Cure

SECTION 1

Treatment Aiming at Cure

Chapter

1

MICHAEL BAUM

The Curability of Breast Cancer

"It is now, as it was then, as it may ever be,
Conceptions from the past blind us to facts
which almost slap us in the face."
W. S. Halsted (1908)

It has to be accepted that there is a degree of uncertainty concerning the curability of breast cancer. Rather than simply shelve this question as being irrelevant to the day-to-day treatment of the disease, it may be more fruitful to consider what lessons can be learnt from this very uncertainty as to the biological nature of the disease.

Accepting at the outset that 20-30% of patients diagnosed as early breast cancer will have a normal expectation of life after local therapy, and that only about a quarter of these are the ones with axillary node involvement detected in the mastectomy specimen, it is surely complacent to continue our current practice in an uncritical way, subjecting at least 70% of women showing primary disease to a futile mutilating procedure.

Discussion of the problem will therefore be divided under the following sub-headings:

- Does "early" diagnosis improve the cure rate?
- Survival after treatment of "curable" breast cancer.
- The natural history of untreated breast cancer.
- The metastatic potential of breast cancer.
- Alternative concept concerning the nature of breast cancer as a first step towards improving the cure rate of the disease.

DOES "EARLY" DIAGNOSIS IMPROVE THE CURE RATE?

Macdonald (1951) coined the phrase "biological predeterminism" to explain the behaviour of solid tumours in man. In a closely argued classical paper he attempted to ridicule the conventional approach to cancer therapy. He postulated that if a period of localized tumour growth is associated with either subjective or objective evidence of its presence, treatment should be able to produce a 100% cure. Therefore, providing that patients are educated to recognize these signs and symptoms, and on recognition proceed to get medical advice without delay, cure rates should continue to improve, eventually to the 100% level.

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However, in spite of a health education programme in the U.S.A. directed at the early diagnosis of cancer, and launched 20 years before Macdonald wrote his paper, the age adjusted death rates for cancer were increasing rather than decreasing. Furthermore, he presented data which suggested that "delay" on the part of the patient did not affect the stage at presentation of the tumour; the results of treatment for breast cancer were little different if the patient delayed for 1 month or 12 months.

He concluded therefore that the outcome of treatment is predetermined by the biological nature of the disease:

> This preoccupation with therapeutic seizure of time by its neoplastic forelock rests on the assumption that the cancer is treated more efficiently during the nebulous period when it is yet limited to its site of origin. . . . The wide range of biological potential exhibited by human cancer is determined early in the preclinical phase of the disease—apparently early cancer by historical and dimensional criteria may be biologically late.

Park and Lees (1951), writing in the same year as Macdonald, expressed a similar point of view. Starting with the null hypothesis that cancer is incurable until it is proved curable, they postulated that proof is impossible because the natural history of breast cancer is not known. They suggested that there was no "available time margin" between the time that the tumour reached diagnosable proportions and its dissemination.

This view was supported by evidence which failed to relate improved survival to shorter patient delay. Again their conclusion was that the outcome is predetermined by variations in the growth rate, infiltrative power and metastatic potential of the breast cancer, in addition to its chronological age. But host factors, such as age and general health, may also be important.

McKinnon (1954) took the argument one step forward. He postulated that there might be two types of breast cancer; a metastasising variety which would be incurable and a non-metastasising variety which would be curable. The former would present as Stages II, III and IV disease whilst the latter would present as Stage I disease.

The same theme was taken up again by Devitt in 1965. By this time the subject of cancer immunology was developing and the host defence factor could be inserted into the equation of biological predeterminism. Surely if the lymph node, which must be the most hostile environment for a cancer cell, becomes the focus of an established metastasis, then the biological war between tumour and host is already lost. Or as Devitt succinctly put it: "Metastases to axillary nodes are an expression of a poor prognosis rather than a determinant".

More recently Devitt (1976) has reviewed the evidence that "early" cancers are slow growing tumours and "late" cancers are aggressive tumours. He notes that the interval between treatment and recurrence, and that between recurrence and death are longer for those cancers which are diagnosed "early" than for those diagnosed "late". He concludes that the timing of initial treatment appears to have little influence on the growth behaviour of breast cancer as reflected in survival rates.

However, this conclusion cannot go unchallenged and it would be invidious to ignore the recently reported Screening Program of the New York Health Insurance Plan (Strax et al., 1967). This study included 62,000 women of 40-64 years of age, 31,000 of whom were randomly selected and offered screening by clinical examination and mammography on four occasions at annual intervals. The published results indicate that in the screened population breast cancer was detected at an earlier stage and that deaths within 7 years of enrolment were reduced by approximately one-third among the women over the age of 50 years.

This would seem powerful evidence for the traditional concept of an arithmetic spatial progression related to duration of the disease. Unfortunately, however, the treatment standards in the two populations were not controlled and the histology of the lesions detected are not reported. It is therefore vitally important that this experiment is confirmed before the clamour for a National Screening Programme pressurizes the government into diverting enormous sums of money from other areas where it might be more effectively directed towards the reduction of mortality from breast cancer.

SURVIVAL AFTER TREATMENT OF "CURABLE" BREAST CANCER

When reporting the results of therapy for breast cancer, whether from a retrospective analysis or from a prospective trial, it is conventional to use the 10 year survival as marking some kind of end-point. For example, in McKay and Sellars (1965) series of nearly 10,000 patients, there was a 10 year crude survival of 51.1% for Stage I disease (T1-2, No, Mo) and of 23.8% for Stage II disease (T1-2, NI, Mo). However, a significant proportion of women with breast cancer are already in their 6th decade or older at diagnosis and will inevitably be dying from incidental disease over this 10 year period.

As a concession to this factor, adjustments are

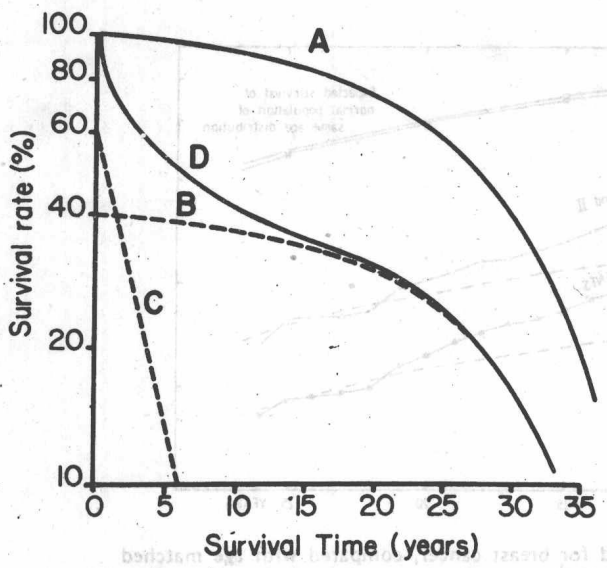

Figure 1. Definition of the cured group after treatment for cancer: Curve A, survival characteristics of age matched control population. Curve B, cancer treated group dying off at same rate as controls. Curve C, cancer treated group who are not cured. Curve D, composite survival (B and C) of all cancer treated group. (After Haybittle, 1964.)

usually made according to actuarial life tables, to give a corrected survival rate. Using such an adjustment, the overall 10 year survival rate of 30.4% in McKay and Sellars series becomes 37.5%. Again, Cutler (1968) reporting on a collected series of 1,760 cases quotes 10 year crude survival rates after a more detailed breakdown based on clinical and pathological criteria of patients subjected to "curative" treatment. These results vary from 86% for T1 primaries without cutaneous or lymph node involvement to 11% for T3 primary tumours with ulceration of the overlying skin and pathological involvement of the axillary nodes. The same two groups of patients have a corresponding annual mortality rate after treatment of 0.02 and 0.20.

Unfortunately, 10 year survival rates for breast cancer, whether crude or corrected, give no real indication of the size of the cured group within the population, because of the uncertainty as to the natural history of the disease as described later in this chapter. It is common to see recurrence of breast cancer at intervals of 15 to 20 years after apparently successful treatment of the original primary. This fact makes the problem of defining a cured group for breast cancer extremely difficult. Assuming that the population under consideration continues to die at a steady rate from breast cancer (*vide infra*), the death rate from other pathology accelerates to such an extent as to mask almost completely the cancer-associated deaths.

Bearing this in mind, the most satisfactory method of defining the cured group is probably that adopted by Haybittle (1964) as illustrated in Figure 1. Curve A describes the survival characteristics of an age matched control population. Curve D describes the survival of patients treated for cancer. The shape of Curve D can be attributed to two subpopulations, one a cured group dying off at the same rate as the control population (B), and the second an uncured group with an accelerated death rate (C). The point at which curve D parallels curve A can be taken to mean that an excess risk of death no longer exists for the treated group, and so in practical terms they can be considered cured. Extrapolation of curve D from the point of parallelism to the origin gives an index of the population of patients in the originally treated group who were in fact cured.

Applying these criteria for cure, Brinkley and Haybittle (1968) have analysed the long term results in 704 patients treated in the Cambridge area between 1947 and 1950. This group of patients probably represented the total pool of cases treated by surgery and radiotherapy in that period. In their original analysis, Brinkley and Haybittle described a 15 year crude survival of 16.6% (age corrected to 24.3%), with a third of the 10 year survivors failing to live for 15 years. Furthermore, 6% of the 15 year survivors had recurrent disease present. At the 15 year mark, parallelism had not yet occurred but they predicted that such would be the state of affairs at 18 years with a cured group representing 20% of the original total. It is worth commenting at this point, that 24% of their "cured" group had histological evidence of nodal involvement at the time of primary therapy.

More recently Brinkley and Haybittle (1975) have published a further report on this series, when all patients had been followed up for at least 22 years. The survival curves up to 25 years for the treated and the control populations are shown in Figure 2. It can be seen that parallelism between the expected and the observed curves seems to be occurring after 21 years, providing a "cured" percentage for the whole group of 18.5%, and a "cured" percentage for those presenting with "early" breast cancer of about 30%.

However, it is of particular importance to note that although the death rates between 20 and 25 years for the treated and control groups were identical, eight out of 23 deaths after 20 years in the treated series were from cancer of the breast, which is 16 times the number that would be expected in the normal population. Since the total death rates are similar, it implies that a woman who lives for 20 years with metastatic breast cancer "on her person" is less

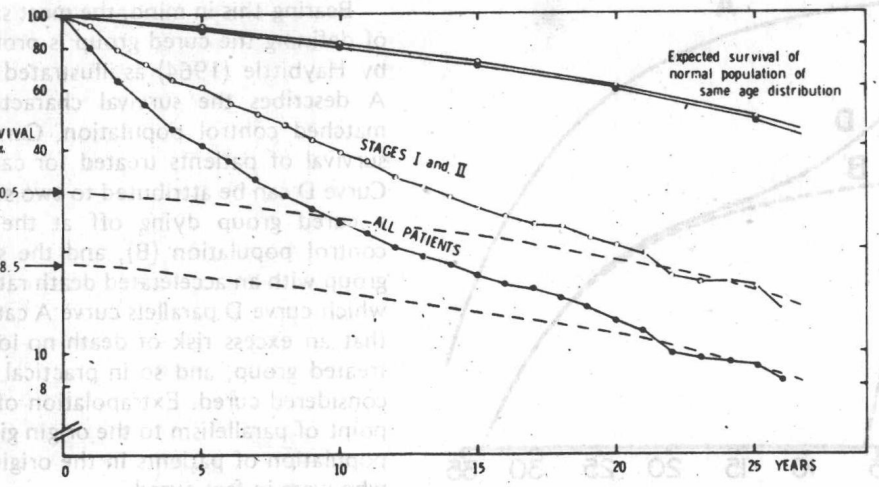

Figure 2. The 25 year survival of patients treated for breast cancer, compared with age matched control population. From Brinkley and Haybittle (1975). Reprinted by permission of Editor *Lancet*.

likely to die of *other* causes. This fact alone would support the biological concept of cancer control by host factors.

A similar state of affairs was noted by Bloom et al. (1970), who reported an abnormally high survival rate for women treated for medullary carcinoma of the breast. He suggested that this type of cancer might represent an immunogenic tumour growing within a woman who was highly immunocompetent and, as such, resistant to disease that would normally carry off less immunocompetent individuals. An alternative explanation might be that women followed up for breast cancer have an overall better standard of medical supervision, and incidental disease might be diagnosed and treated at an earlier stage. So, to use Brinkley and Haybittle's own words: "To define 'cure' in terms of the general population mortality may have its limitations".

What constitutes a cure?

There have been several other series with prolonged follow-up of cases for 15 to 30 years after primary therapy. The extremes of opinion that emerge are surprising, varying from extreme optimism to extreme pessimism bordering on nihilism.

At the most optimistic extreme we have the report of Adair and his colleagues (1974) from the Memorial Hospital, New York. They report a 30 year follow-up of a cohort of 1,458 cases treated by radical mastectomy between 1940 and 1943. Over this long period only 6.8% of patients were lost to follow-up, 826 died of carcinoma of the breast, 349 died of other causes and 184 are still alive. A third of the group alive at 30 years had histological evidence of nodal involvement in their mastectomy specimen. Only 4% of all deaths from the original cancer occurred between 20 and 30 years after mastectomy. They considered that 300 of the original series were "practical cures" after 20 years, having achieved a normal life span. The actuarial 30 year survival rate was 38%.

Campos (1972) also paints a reasonably optimistic picture from his analysis of 391 cases treated by radical mastectomy at the University of Michigan between 1940 and 1955. He concluded that 99% of the cancer mortality had occurred at the 15th anniversary, providing an actuarial survival rate of 74.2% for node-negative cases and 20.9% for node-positive cases at that point in time. However, he is careful not to define his cured population, as his analysis demonstrates that death from carcinoma of the breast proceeds as an orderly phenomenon manifested by an exponential function. As such, the chance of dying from cancer does not diminish with time and the number of patients dying during equal periods is a fixed proportion of those who were alive at the beginning of the period.

An identical conclusion was reached by Mueller and Jeffries (1975) from a study of the death rate of an unselected group of 1,500 women with carcinoma of the breast. Within the first 3 years after diagnosis there was an accelerated death rate but thereafter for the 15 years of the study, the actuarial survival curve was expressed by a single exponential function suggesting a constant rate of dying with a 50% mortality at 5.9 years. The figures indicated that any woman developing breast cancer had a greater than

80% chance of dying of that disease and the younger she was at diagnosis the greater the chance of an eventual cancer-related death. Expressed in an alternative way the percentage of women dying each year was a fixed proportion (8%) of those at risk, with the exception of the higher risk in the first 3 years.

A note of moderate pessimism is sounded by Myers (1973) on behalf of the end-results group of the National Cancer Institute. He reviews data collected from 100 hospitals throughout the U.S.A. relating to 63,000 cases of breast cancer treated between 1940 and 1969. He notes that there has been no improvement in the survival rate after treatment for the last 20 years. He also points out that the survival rate of the treated group relative to an age-matched population continues to show a downward slope up to 25 years, even for those women treated for localized disease. Myers interprets these data as suggesting a failure to cure the disease and concludes as follows: "Apparently, reduction of the excess risk of dying of breast cancer even for localized disease, awaits some new therapeutic method".

At the extreme of pessimism we have the report by Bond (1968) of the long term follow up of 6,775 cases of "early" breast cancer treated in the United Birmingham Hospitals. For each of the 25 years after treatment he calculated the ratio of cancer deaths to death from other causes. Plotting these data on semilogarithmic paper produced a straight line, and the 15% of women surviving 25 years still carried a 1 in 5 risk of dying of breast cancer when their average age was 80. He interpreted this information to mean that in all cases the cancer had disseminated before diagnosis and was therefore incurable with the methods then available.

This interpretation was, however, challenged by Haybittle (1968) following an alternative analysis of the same data. He demonstrated that the death rate from cancer in the Birmingham series was not constant (which would suggest incurability), but decreased exponentially with time. Using his extrapolated actuarial mathematical model, Haybittle calculated that well over a quarter of the patients in the Birmingham series could be considered cured, a figure close to that achieved in the Cambridge series (Brinkley and Haybittle, 1975).

From the foregoing it can be seen that there is no unanimity as to what constitutes a cure for breast cancer. For practical purposes we may consider that 20-30% of women treated for apparently localized cancer of the breast will have a normal expectation of life. The doubt still remains as to whether all patients having been diagnosed as suffering from the disease would ultimately die of the cancer if they lived long enough! Furthermore, the impact of treatment has to remain an open question. How many of these long term survivors would have lived out their natural life span without any treatment? As will later be shown, there does not exist an adequate control population of untreated "early" breast cancer in the literature to make such a comparison.

THE NATURAL HISTORY OF UNTREATED BREAST CANCER

In spite of the supposed improvements in the diagnosis and treatment of breast cancer, and in the face of an increased public awareness of the significance of lumps in the breast, the mortality rates for breast cancer in England and Wales demonstrate a disturbing upwards trend (see Table 1).

There are four possible explanations for this trend. Firstly, a greater proportion of the female population may be developing the disease. This would be in keeping with observations relating breast cancer incidence to an increase in the proportion of the older age groups in the population, although it would be difficult to argue that this alone accounted for the increase in the decade 1963-73 for England and Wales. Secondly, death registration for breast cancer may be more complete than in the past. This again is unlikely as regional cancer registries have been fully operational for the period covered by Table 1.

Table 1 Crude mortality rates per 100,000 population (England and Wales) for breast cancer

Years	*1952-7*	*1961-3*	*1969*	*1970*	*1971*	*1972*	*1973*
Reference	*Campbell (1968)*	*Campbell (1968)*	*Registrar General's Statistical Review*				
All ages	36.5	38.9	43	43	45	44	45
25-44	–	–	13	14	14	14	14
45-64	–	–	77	78	78	78	79
65-74	–	–	111	109	118	115	122
75+	–	–	161	158	171	169	170

A third possible explanation is that treatment may have become less effective. This is unlikely, as no reported prospective trial for the primary disease had demonstrated a meaningful superiority of one therapeutic modality against another (Fisher, 1973). Finally, and to my mind the most likely explanation, the biological nature of the disease may be changing towards a more aggressive form. For this and other reasons it is essential to take a critical look at our knowledge of the natural history of breast cancer which, after all, is the only reliable index of its biological nature.

In 1880, Gross published a treatise on breast cancer which provides a clear insight into the status of the disease in the immediate pre-Halsted era. He describes a series of 616 cases, 70% of whom had skin infiltration on presentation and in 25% of whom the skin was ulcerated; 64% had extensive involvement of axillary nodes and 27% had obvious supraclavicular nodal involvement. As a result of the attitude of that time that the risks of surgery outweighed the meagre benefits offered by such treatment, he considered it ethical to follow the natural course of 97 cases who received nothing other than "constitutional support".

From this study he described how skin infiltration appeared on average 14 months after a tumour is first detected, ulceration occurred on average six months after that, and fixation to the chest wall after a further two months. Invasion of the other breast was seen if the patient lived on average 32 months after the lump first appeared. The average time for the appearance of enlarged axillary nodes was 15 months in those few cases presenting with what today would be staged as T1-2, N0, M0 disease; 25% of these untreated cases exhibited obvious distant metastases within 1 year and 25% after 3 years while 5% of this series died 5 years or more after presentation.

Since then, a number of additonal series of untreated breast cancer have been reported. For example, Greenwood (1926) described a 6 year follow-up of 651 cases of untreated breast cancer with only 60 of the group remaining alive at the end of this period. Daland (1927) reported a series of 100 patients who were considered either inoperable or unfit for surgery, or who refused the offer of an operation. The average duration of life in this group was 40.5 months, being 42.8 months for those considered operable and 29 months for those considered inoperable. Similar reports appeared subsequently (Wade, 1946; Shimkin, 1951).

The study that has attracted the most attention in recent years is that of Bloom (1968). His data came from the records of 250 women dying of breast cancer in the Middlesex Hospital cancer ward between 1905-33. Of this group 95% died of breast cancer and 97% presented with Stage III or Stage IV disease. The survival rates from alleged onset of symptoms were 18% at 5 years, 3.6% at 10 years and 0.8% at 15 years. The mean survival for his series was 2.7 years which compares well with that of 1,728 untreated cases he was able to collate from other sources, which had a mean survival of a little over 3 years. The reasons for withholding treatment in Bloom's series are important to note and were as follows: old age or infirmity 35%, disease considered too advanced 30%, early death 15.4%, and treatment refused 19.6%.

There are several criticisms that can be levelled against the studies I have so far quoted, which invalidate their use as a baseline against which to judge the "curative" effect of conventional therapy. Firstly, as with all retrospective uncontrolled series there must be an element of selection. Why was treatment withheld? It is quite obvious that in the majority of cases, with the exception of those refusing treatment, they were a group with an exceptionally poor prognosis to begin with. Secondly, they all represent women seeking medical attention at a time in the early years of this century, when many women were content to co-exist with a breast lump until they died of old age or were knocked down by a Hansom cab!

Is the biology of breast cancer changing?

Most important of all, these studies may not be relevant to today's problem because it is likely that the biological nature of the disease has changed over the last 50 years. Bloom attempts to refute this suggestion by describing 86 cases observed between 1902-33 from whom pathological material suitable for the grading of malignancy was similar to that found today. Histological grading, although giving some index of prognosis, can in no way be considered the sole indicator of the biological propensity of an individual cancer. In the light of recent developments in our knowledge, host factors must be considered to carry equal weight.

In this respect, it is relevant to note a recent paper by Fisher and Taylor (1973). They analysed the grade of malignancy and the histological evidence of host response in a large contemporary series of breast cancers, and compared their findings with a review of the histology of a similar series collected a decade before. In general they found an increase in the less favourable grades of malignancy and a fall in the number of cases demonstrating a lymphocyte stromal response or sinus histiocytosis of the regional nodes.

It is therefore possible that the early series of untreated cancers may underestimate the lethal nature of today's disease, and this is in accordance with my interpretation of the mortality statistics quoted at the start of this section.

It would, of course, be inconceivable to suggest that we add a control group of untreated women when a new prospective trial for the treatment of early breast cancer is launched. However, the closest approximation to such a group comes from the report of Mackay and Sellars (1965). They published a statistical review of all cases of breast cancer seen at the Ontario Cancer clinics between 1938 and 1956. The 9,742 cases analysed accounted for about 40% of all new cases of breast cancer arising in the province of Ontario during this period. Among this group were 145 well documented cases who received no treatment of any kind. Although 100 of these cases were untreated because of late stage of disease or poor general condition, the rest were unwilling or unable to attend for treatment. As in previous series, they tended to be older, to have delayed longer before presentation and to have presented with more advanced disease.

A careful note was made in this series of the date the patient first became aware of the lump, and as a result, it was possible, with a fair degree of accuracy, to calculate survival rates from the date of clinical presentation of the disease. Unfortunately, the follow-up data are available for only a 5-year period but at least this group represents a relatively contemporary population, a proportion of whom would be considered eligible for inclusion in today's clinical trials for early breast cancer. The 5-year survival from first recorded symptoms for the whole untreated group was 35.2%, with a median interval between first symptom and death of 47 months. A most surprising figure. however, is the 68.8% 5-year survival after the first symptom in those untreated patients presenting with localized disease. Such a figure does not compare unfavourably with many treated series, although this could well be an artifact resulting from selection and the small number in the sample.

This brings us to the question raised earlier. Is carcinoma of the breast inevitably a fatal condition or could there be a group of women living in blissful ignorance of their cancer and eventually dying of other causes? This question is virtually impossible to answer with any degree of confidence, but the suggestion that such a state of affairs might exist comes from postmortem studies and anecdotal evidence based on case reports.

Sandison (1962) reported a large autopsy study of the human breast in an unselected consecutive series of 800 female postmortems, carried out at the Western Infirmary, Glasgow, over a 5-year period. He reported a 0.77% incidence of occult breast cancer in women dying of disease other than mammary carcinoma. The majority of these cases occurred in the 8th decade and he points to the analogy of occult carcinoma of the prostate in postmortem series. In addition there were three cases with overt but untreated breast cancer in the total series. But, as Sandison (1975) points out, most routine postmortems pay scant attention to the breast and to collect the type of information required would demand an enormous planned effort.

Anecdotal evidence that breast cancer is not inevitably fatal if untreated, is by its very nature suspect. The author has personal experience of four well documented cases of women who refused treatment for their breast cancer for 7, 10, 13 and 16 years respectively. Three of these are still alive and well with the cancer in situ, and one recently died of carcinoma of the stomach with the still localized breast primary weighing 2 Kg. However, the best documented case in the literature is reported by Steckler and Martin (1973). They described a 38-year-old woman with histologically proved cancer who refused mastectomy and was then followed for 20 years before she consented to surgery! We will never know how many of the cases we see in our everyday practice carry such a favourable natural history.

THE METASTATIC POTENTIAL OF BREAST CANCER

Arguments concerning the curability of breast cancer may become obscure in that a lump removed from a patient who thereafter lives a normal span of years can be claimed not to have been a cancer in the first place. However, in spite of this danger, it is still reasonable to question the absoluteness of a diagnosis of cancer based on the histological examination of a biopsy specimen. All pathologists readily admit that there are grey areas in the field of the histopathology of tumours.

Difficult sections are often circulated for a consensus opinion. The dividing lines between epithelial hyperplasia, intraduct carcinoma and early invasive ductal carcinoma are not clear-cut. Furthermore, sclerosing adenosis is notoriously difficult to diagnose, and Urban and Adair (1949) reported that 90% of such cases were being classified as carcinoma up until 1949.

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