NATURAL HISTORY OF UNTREATED BREAST CANCER (1805–1933)

COMPARISON OF UNTREATED AND TREATED CASES ACCORDING TO HISTOLOGICAL GRADE OF MALIGNANCY

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To Samuel Whitbread and John Howard, Founders of the Middlesex Hospital Cancer Charity, 1792

There is no general agreement on the best treatment for patients with operable carcinoma of the breast. The confusion arises largely because similar methods of treatment in such cases have produced variable results, while comparable survival rates have been obtained by different lines of therapy. Thus conservative surgical procedures with ancillary radiotherapy appear to have achieved results comparable to those obtained by the classical radical mastectomy with or without post-operative irradiation. Survival rates for cases treated by simple mastectomy and post-operative radiotherapy may be identical to those for patients subjected to the so-called extended radical operation, which includes dissection of the supraclavicular and internal mammary lymph nodes (Kaae and Johansen, 1962). The value of routine post-operative irradiation in patients with small breast tumours and without axillary lymph-node metastases is uncertain, and in more advanced operable cases there is doubt about whether the irradiation is best given before or after surgical treatment.

McKinnon (1951a; 1954) and also Park and Lees (1951) go so far as to doubt whether the methods of treatment employed for breast cancer at the present time have any value at all in prolonging life—the prognosis, they claim, being determined by the type of tumour and not by the treatment. Even more difficult to assess in terms of survival is the role of palliative radiotherapy, hormone administration, and endocrine surgery in advanced cases, and the place of prophylactic castration in early as well as late cases.

The factor largely responsible for the difficulties in trying to assess the value of treatment in breast cancer is the wide variation in the natural history of the disease itself (Bloom, 1950a; Bloom and Richardson, 1957). Attention has already been drawn to the broad spectrum of malignancy which exists in all groups of cases of breast cancer which are classified according to a clinical staging system. A more homogeneous grouping of cases is possible by taking into account the histological type of the tumour (grade) in addition to its clinical extent (stage) (Bloom, 1950a, 1956, 1958). Such a classification may lead to a more accurate assessment of the different lines of treatment for this disease. However, it is only from a knowledge of the natural history of untreated cases that a background will be provided against which the merits of treatment itself can be judged.

Although many papers have been written on various aspects of breast cancer there have been few reports on the untreated disease. With the advent of radiotherapy and the discovery of the effects of various hormonal agents, adrenalectomy, and hypophysectomy upon the course of the disease, it is rare to-day for a patient with carcinoma of the breast to remain untreated. For information on the natural history of the untreated disease one must turn to case records from the past, to the publications of 20 to 30 years ago.

Greenwood (1926) published a detailed analysis of 4,238 patients with untreated cancer at seven different primary sites, seen in five centres in Great Britain. There were 651 cases of breast cancer, for which the average duration of life from onset of symptoms was 3.2 years; the median duration (when 50% of the patients were dead) was 2.3 years.

Daland (1927), in Boston, studied 100 patients with untreated cancer of the breast, of whom 11 came to necropsy. The average survival was 3.3 years and the median survival 2.5 years. Nathanson and Welch (1936) also investigated the duration of life in 100 untreated cases which included 50 of Daland's original series with results comparable to this.

Forber (1931), in a study of incurable cancer among patients seen in East London during 1928 and 1929, reported the mean duration of life from onset of symptoms in a series of 64 breast cases as 39.3 months (omitting two cases of alleged duration of 40–41 years). Forber also quoted some unpublished data of the Ministry of Health concerning 466 untreated breast-cancer patients collected from nine English cities in whom the mean natural duration of life was 50.7 months: when 45 cases with histories extending over ten years were excluded the mean duration was reduced to 31 months.

Wade (1946) collected 27 untreated patients at the National Radium Centre, General Infirmary, Leeds, between 1931 and 1941 and compared their survival with that of a group of 177 treated advanced cases from the same centre. She also reviewed the literature on untreated breast cancer up to the time of her report (777 cases in all) and found that the mean duration of life from the onset of symptoms for the whole series was 38.5 months, and for 26 of her own cases 32.6 months.

The purpose of this paper is to present a series of 250 cases of untreated breast cancer from the early clinical and post-mortem records of the Middlesex Hospital; to correlate the histological grade with survival in 86 cases in which sections of post-mortem material were available; and to compare the pattern of survival of these patients with a series of treated cases which we have previously studied at the same hospital (Bloom and Richardson, 1957).

Historical Aspects

The first hospital devoted to patients with cancer was opened at Rheims in 1740 under the will of Jean Godinet

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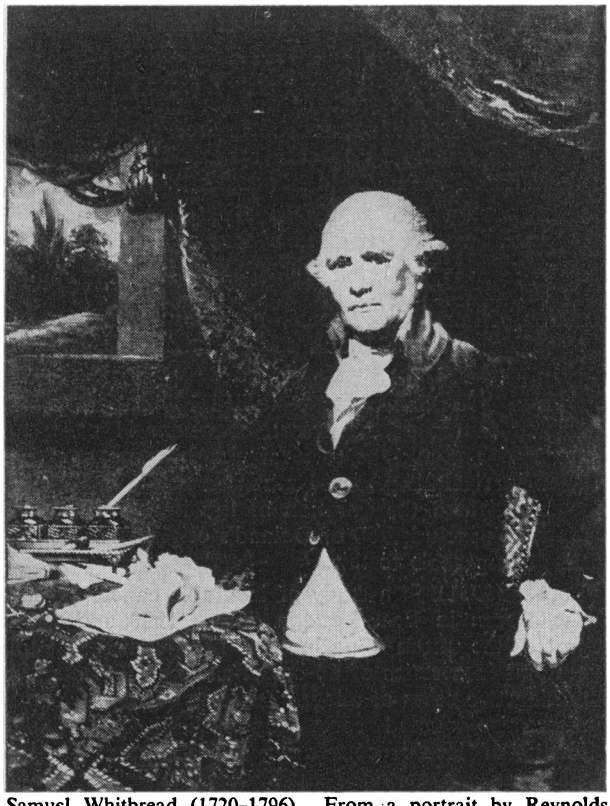
(1661–1739), a canon of the cathedral and a "charitable and pious man who had devoted his whole life to caring for poor patients and to relieving their misfortunes." The hospital contained 12 beds and was under the direction of the personnel of the Hôtel-Dieu (Ledoux-Lebard, 1906). No other special facilities were available for the care of cancer patients until some fifty years later, in 1791, when John Howard (died 1811), a London surgeon and an ex-pupil of Percivall Pott, informed the Governors of the Middlesex Hospital that a friend of his, who wished to remain anonymous, desired to contribute a sum of money for the establishment of a cancer charity for the hospital. The principal objects of the bequest were ". . . the relief of persons afflicted with cancer, and the investigation of a complaint which, though extremely common, is, both with regard to its natural history and cure, but imperfectly known."† Howard's generous friend was later known to be Samuel Whitbread (1720–1796).



Samuel Whitbread (1720–1796). From a portrait by Reynolds kindly supplied by the Board of Directors, Whitbread and Co., Ltd.

In June, 1792, a ward containing 12 beds was ready to receive cancer cases at the Middlesex Hospital. These included not only patients for whom there was a reasonable prospect of relief by operation or otherwise but also those whose disease was hopelessly advanced and who would be offered an asylum for life. The regulations stated that these patients "shall remain an unlimited time, until either relieved by art or released by death, unless it should be thought necessary to discharge them for ill-behaviour" (Wilson, 1845).

John Howard pointed out that such an institution would offer facilities for studying the natural history of cancer, and he emphasized the importance of keeping careful clinical records of all patients which should be made available for general inspection.

"This examination may be made by a medical gentleman of the hospital, with the patient before him, his notes to be corrected by himself, and kept as a record of the history and circumstances of each case, to be recurred to as an authority by any intelligent or scientific person. A copy of these notes may be kept, fairly written for general instruction, and if anything extraordinary or worthy of more particular notice arises from these sources, let them be published to the world at large."†

Howard stipulated that the nature of the disease should be investigated and trials made of new authentic methods of treatment. In 1853 the cancer wards contained 26 beds. By the beginning of the present century there was a wing with some 50 beds, and between 70 and 80 post-mortem examinations were being carried out annually in the research laboratories (Coupland, 1902). It is from these early records of the Middlesex Hospital Cancer Charity that most of our material has been gathered.

The Middlesex Hospital as it appeared soon after its opening in 1745 and at the time when the Cancer Charity was founded in 1792. From an original print in possession of the authors, approximate date 1760.

Untreated Cases

Material

The first patient with breast cancer for whom notes could be found was seen in 1805. After 1916, when radiotherapy became established as a treatment for cancer, few cases remained untreated. We have been able to find clinical records of 356 cases of untreated breast tumour seen between the years 1805 and 1933. In 250 of these, all of which came to necropsy, there was evidence, based on macroscopic pathology, that enabled the diagnosis of a malignant tumour of the breast to be made with certainty. Histological material was available for the 86 cases seen between 1902 and 1933. Two male cases have been excluded from the series (Table I).

†Extracts from a letter to the Medical Board of the Middlesex Hospital by John Howard, dated October 12, 1791 (Wilson, 1845).

TABLE I

Total No. of cases (1805–1933)	356
No necropsy or inadequate data	104
Males	2
No. available for study	250
Histological material in	86

Lazarus-Barlow and Leeming (1924), with a view to providing a series of controls for cancer treatment, presented the natural duration of cancer for a number of primary sites based on the mean survival of untreated cases seen at the Middlesex Hospital between 1883 and 1922. There were 243 cases of breast cancer in this series, and these have also been included in papers published by Greenwood (1926) and by Wade (1946). Some of these cases are undoubtedly included in the present series. Lazarus-Barlow and Leeming (1924) did not state in how many of their patients a post-mortem examination had been performed. Furthermore, in a number of the cases reported by these authors the patients died at home, and in some of these the date of death had to be estimated. All patients in the present study died in the Middlesex Hospital. The precise date of death was known and in all cases a post-mortem examination had been performed. No case was treated by any form of surgery or by irradiation. The only treatment received included the administration of opiates, dressings, and occasionally injection of metals—such as lead—sera, Coley's fluid, and thymic extract. All cases admitted to the Cancer Charity of the Middlesex Hospital were carefully examined and their details recorded by a small number of medical men who had a special interest in the study of malignant diseases (Campiche and Lazarus-Barlow, 1905).

Some idea of the total number of women with a clinical diagnosis of malignant disease of the breast seen at the Middlesex Hospital during the era in which our cases were selected for this study can be obtained from the fact that 1,950 women with this diagnosis were admitted to the wards between the years 1747 and 1903. The total number of male and female patients admitted during this period was 126,843, giving an incidence of 1.5% for breast malignancy. During the same period there were 5,526 female cases of malignant disease, of which the breast constituted the primary site in 35% (Campiche and Lazarus-Barlow, 1905).

Age Distribution

The ages of the patients when first seen at hospital are shown in Table II. The incidence of patients with cancer of the breast in the various age-groups is similar to that given by modern authors such as Haagensen (1956) for 1,544 patients with this disease seen at the Presbyterian Hospital from 1915 to 1942 and also Smithers *et al.* (1952) for 846 cases at the Royal Marsden Hospital between 1937 and 1944.

Presenting Clinical Feature

A lump in the breast was the initial symptom in 83% of cases, and by the time patients first attended hospital a large mass was usually present. Ulceration, often most extensive, was seen in 68%.

TABLE II.—*Distribution of 250 Cases According to Age*

Age-group	Cases	Age-group	Cases
26–30	2 (0·8%)	51–60	62 (24·8%
31–40	35 (14·0%)	61–70	54 (21·6%
41–50	67 (26·8%)	71–88	30 (12·0%)

Duration of Symptoms

Only 7% of the patients came to hospital within six months of the initial symptom and 29% within the first year (Table III). Nearly three-quarters (71%) of the cases delayed for over 12 months: in 24% more than three years elapsed and in 12% more than five years. The longest delay was 16 years.

Over the past 50 years the delay in seeking medical advice in patients with cancer of the breast has gradually become shorter (Lewis and Rienhoff, 1932; Eggers *et al.*, 1941; Harrington, 1952; Robbins *et al.*, 1959). In a series of treated cases also from the Middlesex Hospital seen between 1936 and 1942, 65% presented within six months and 85% within one year of the first symptom (Bloom, 1950b).

TABLE III.—*Case Distribution According to Duration of Symptoms*

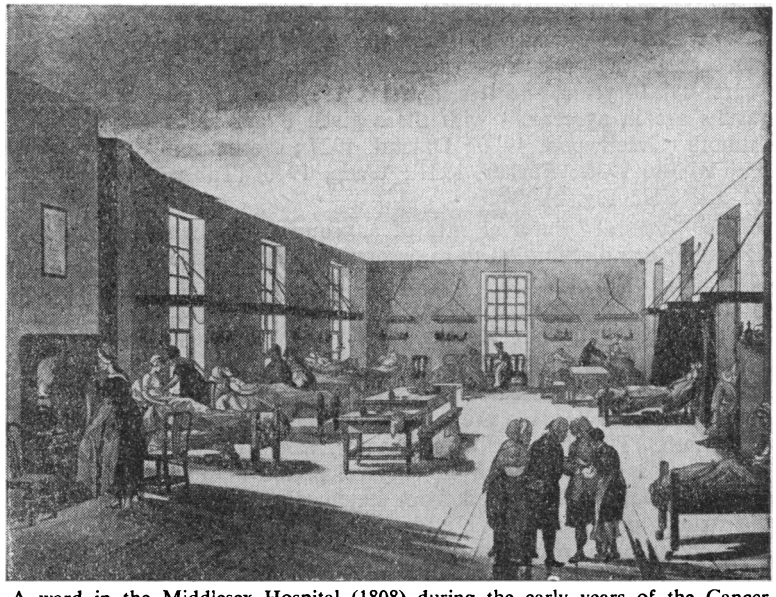
Duration of Symptoms	Cases		
3 months or less	9 (3·6%)	7·2% within 6 months	28·8% within 1 year
4–6 months	9 (3·6%)		
7–12 ,,	54 (21·6%)		
13–24 ,,	66 (26·4%)		
>2–3 years	53 (21·2%)		
>3–5 ,,	28 (11·2%)		
>5–10 ,,	27 (10·8%)	12·4% over 5 years	
>10–16 ,,	4 (1·6%)		

Clinical Staging on Admission

The extent of the disease was staged by the Manchester system (Paterson, 1948) and was carried out in retrospect from the clinical notes (Table IV). The high proportion of patients with advanced disease is to be expected in an untreated group the majority of whom presented for terminal care.

TABLE IV.—*Distribution of Cases According to Clinical Stage (Manchester System) on Admission*

Stage	1	2	3	4
No. of cases	0	6 (2·4%)	58 (23·2%)	186 (74·4%)



A ward in the Middlesex Hospital (1808) during the early years of the Cancer Charity. From an original print in possession of the authors.

Duration of Life

This has been taken as the interval between the initial symptom of the disease and death. The shortest survival was two months (three cases), and the longest 18 years and 3 months (one case). Table V and Fig. 1

TABLE V.—*Deaths Occurring Each Year, Calculated from Onset of Symptoms, for 250 Untreated Cases of Breast Cancer*

Year of Death	No. of Cases	Cumulative Total	Survivals	
1st year ..	34	34	216	86%
2nd ,, ..	52	86	164	66%
3rd ,, ..	55	141	**109**	**43·6%**
4th ,, ..	38	179	71	28%
5th ,, ..	25	204	**46**	**18·4%**
6th ,, ..	13	217	33	13%
7th ,, ..	10	227	23	9%
8th ,, ..	6	233	17	7%
9th ,, ..	5	238	12	5%
10th ,, ..	3	241	**9**	**3·6%**
11th ,, ..	4	245	5	2%
13th ,, ..	1	246	**4**	**1·6%**
15th ,, ..	2	248	**2**	**0·8%**
16th ,, ..	1	249	1	0·4%
19th ,, ..	1	250	0	0%

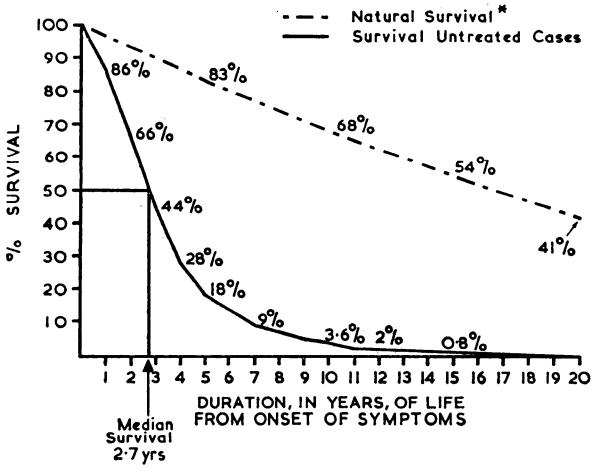


FIG. 1.—Survival of untreated breast cancer. Middlesex Hospital, 1805–1933 (250 cases). *See Appendix.

show the number of yearly deaths from the onset of symptoms. The mean duration of life from onset was three years and the median duration (when 50% of the patients were dead) 2.7 years (Fig. 1). Forty-four per cent. of the patients survived three years, 18% five years, 4% 10 years, and less than 1% 15 years. These results are in agreement with those given by previous authors (Greenwood, 1926; Daland, 1927; Nathanson and Welch, 1936; Forber, 1931; Wade, 1946) (Tables VI and VII; Fig. 2).

The "natural" survival rate of a group of women of similar age distribution to the present series has been estimated from specially computed life tables (see Appendix) and is plotted for comparison with that of the untreated patients (Fig. 1).

The duration of the disease in patients with untreated cancer of the breast is based on the length of symptoms and the interval between the first attendance at hospital and death. The duration of symptoms, which usually constitutes a major part of the survival period in such cases, has to be determined from statements made by the patient or her relatives, and can therefore at best serve only as a rough yardstick. Furthermore, the accuracy of the history will be influenced by the care with which it is taken. From the detailed nature of the clinical notes and the obvious interest in malignant

TABLE VI.—*Untreated Breast Cancer (Various Authors)*

Author	Period	Place	No. of Cases	Mean Duration of Life (Months)	Median Duration* of Life (Years)
Greenwood (1926): Lazarus-Barlow	1883–1922	Middlesex Hospital	243	39·8	
Beatson ..	—	Glasgow	61	36·5	
Wyard ..	1900–24	Cancer Hospital	273	39·6	2·3
Powell White ..	—	Manchester	59	32·1	
Carter-Braine ..	—	London	15	30·2	
Daland (1927) ..	—	Pondeville Hospital	100	40·5	2·5
Nathanson and Welch (1936) ..	1912–32	Pondeville Hospital and Huntington Memorial Hospital	100	—	2·5
Forber (1931) ..	1923–9	East London	64	39·3	—
Ministry of Health (Forber, 1931)	—	English cities	466	50·7	—
Wade (1946) ..	1931–41	Leeds	26	32·6	—
Present series (all cases necropsied)	1805–1933	Middlesex Hospital	250	35·5	2·7

* When 50% of patients are dead.
Some overlap between Lazarus-Barlow and Leeming (1924) and present series, and also between Daland (1927) and Nathanson and Welch (1936).

TABLE VII.—*Untreated Breast Cancer. Survival Rates from Onset of Symptoms (Various Authors)*

Author	No. of Cases	Survival Rate in Years			
		3	5	10	15
Greenwood (1926)	651	34%	16%	—	—
Daland (1927)	100	—	22%	5%	0%
Nathanson and Welch (1936)*	100	40%	18%	5%	0%
Forber (1931)	64	30%	17%	—	—
Present series	250	44%	18%	3·6%	0·8%

* Survival rates obtained from graph.

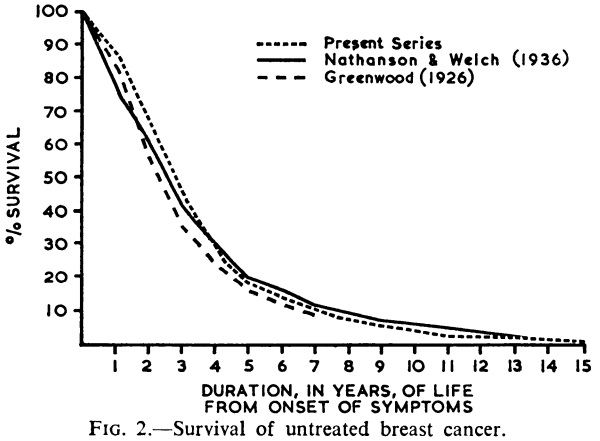


FIG. 2.—Survival of untreated breast cancer.

disease shown by the Middlesex Hospital since the foundation of the Cancer Charity, we felt that efforts were made by the small numbers of observers concerned to obtain as accurate a history as possible. Moreover, our results are in general agreement with those of the other authors in this country and also in the United States who have studied the untreated disease (Tables VI and VII; Fig. 2). The rather long mean duration of life in the Ministry of Health series for 466 patients quoted by Forber (1931) is due to the relatively high proportion of cases surviving over 10 years (9.6%). No indication is given in Forber's report of the number of cases with pathological confirmation of the disease. In the present series, which has the advantage that all 250 cases came to necropsy, only 2% of cases had a duration of more than 10 years. In Daland's series of 100 cases only 11 appear to have had pathological verification.

Long Survivors

The most striking fact that emerges from a study of untreated breast cancer is the number of patients who

survive for five or even ten or more years without any specific treatment. All published series on this subject contain instances of prolonged survival, and this must be taken into account when considering the possible benefits derived from definitive treatment.

Five per cent. of Daland's patients and approximately 4% of the present series were still alive at 10 years (Table VII). Daland (1927) cites a patient, not included in his series, who had a breast tumour for 35 years and who was still alive at the age of 80. She had been examined by Greenough in 1914 and thought to be inoperable because, even at that time, her whole breast was destroyed by growth.

Wade (1946) had one patient who lived for 22 years, and another for 13 years. Haagensen (1956) gives the history of one of his patients who was alive with breast cancer 27 years after discovering a lump in her breast and 10 years after a positive biopsy.

The longest survivor in the present series (Case C.R. 71) lived for 18 years and 3 months after the discovery of a lump of approximately half-inch (1.3 cm.) diameter in the left breast at the age of 46. She did not seek advice for 16 years, by which time the whole breast was replaced by a fungating tumour with satellite nodules in the surrounding skin. Ulceration had been present for 12 years. She finally died two years and three months after admission, and necropsy showed metastases in axillary nodes, lungs, pleura, and ribs.

One of our cases (Case C.R. 48) lived for 15 years and 7 months with a slowly growing lump in the breast which finally ulcerated. Seven months after admission to hospital she died with multiple visceral metastases: the immediate cause of death was haemorrhage from a gastric ulcer. A further patient (Case C.R. 33) survived 15 years, having been aware of a lump in the breast for 14 years, and died from pleural and hepatic metastases. The fourth long survivor (Case C.R. 741) died after 13 years and 10 months. There had been a slowly growing lump in the left breast before admission, at which time she had an ulcerated mass 5 cm. in diameter with enlarged nodes in both axillae and oedema of the arm: she died with pleural and liver secondaries and a deposit in the left kidney. Five further patients lived 10 years or more.

Spontaneous Regression

Examples of spontaneous regression of cancer have been recorded from time to time, but many of these are based on inadequate evidence. Everson and Cole (1956), who reviewed the literature, were able to find only 47 such cases with biopsy confirmation by a competent pathologist and no significant therapy. In none of the present series of untreated cases of breast cancer was spontaneous regression reported. In one case, however, the rate of growth of the primary tumour appeared to fluctuate considerably over several years.

Histological Grade of Tumour and Duration of Life

Histological sections were first prepared in the Pathology Department of the Middlesex Hospital about 1902. Sections of post-mortem material from the present series of cases were available in 91 of the 97 patients seen between 1902 and 1933. A number of these sections had to be restained and we were unable to assess the grade in five cases because of insufficient tissue or because of excessive tissue degeneration. The remaining 86 cases were graded by the method described in detail in a previous paper (Bloom and Richardson, 1957). All the histological slides were examined without knowledge of the patients' history and only when grading had been completed were the notes studied for clinical details.

Table VIII shows the mean survival in months from onset of symptoms to death for each of the three grades of malignancy. The survivals in each grade are shown graphically in Fig 3. The "natural" survival rate for a group of women with the same age composition as that of the untreated cases (see Appendix) has also been plotted in Fig. 3 for comparison. At five years 22% of grade I and also of grade II patients are still alive, while all those with grade III tumours are dead. The corresponding figures at 10 years are 9% for grade I and 3% for grade II cases. While there are examples of prolonged survival among grade I and grade II cases (up to 166 months in grade I and 122 months in grade II) no patient with a grade III tumour survived for more than 53 months (Table VIII).

TABLE VIII.—*Untreated Breast Cancer. Survival According to Histological Grade of Malignancy*

Grade	Cases	Mean Survival in Months	Range in Months
I (low)	23	47·3	6–166
II (intermediate) ..	32	39·2	5–122
III (high)	31	22·0	2–53
Total ..	86	35·2	2–166

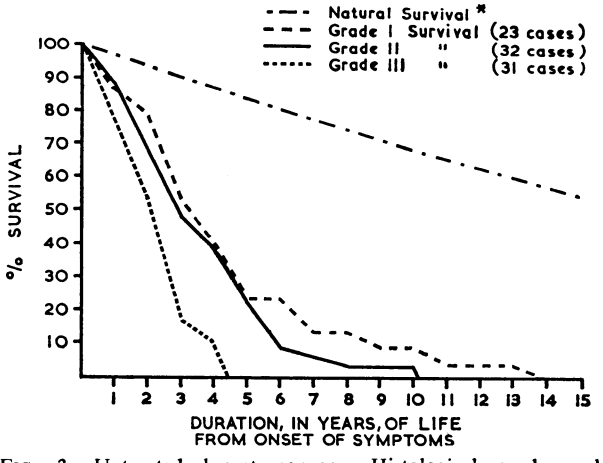


FIG. 3.—Untreated breast cancer. Histological grade and survival. Middlesex Hospital, 1902–33 (86 cases). *See Appendix.

In Daland's (1927) series only 11 cases had a post-mortem examination, and histology was available for 10 of these. Using Greenough's (1925) criteria, Daland placed six of these cases in grade II and four in grade III, but no relationship between grade and length of survival could be found in so few cases. In no other published paper on untreated breast cancer has histological grading been reported.

Age and Prognosis

In a series of 461 treated cases of breast cancer at the Middlesex Hospital, age was found to bear no relation to prognosis (Bloom, 1950b). A greater proportion of highly malignant grade III tumours was *not* found in the younger age-groups, there being a remarkably even distribution of tumours of low- and of high-grade malignancy throughout the various decades. Shimkin

(1951), using data adopted from Greenwood's series, has shown no significant or constant increase or decrease in mean life-span according to the age of onset in 623 untreated cases of breast cancer.

In the present series no significant relationship was found between age at onset of symptoms and outcome (Table IX). A slight reduction in the three-year survival rate was noted in the 50–59 age-group, and this is in keeping with the findings of Richards (1948) and also of Smithers *et al.* (1952), who report a particularly unfavourable prognosis for women in the fifties. This trend, however, was not evident in our five-year results.

TABLE IX.—*Untreated Breast Cancer. Age at Onset of Symptoms and Prognosis*

Age-group	Survivals	
	3 Years	5 Years
26–39	12/31 (39%)	5/31 (16%)
40–49	29/63 (46%)	10/63 (16%)
50–59	27/68 (40%)	13/68 (19%)
60–69	27/54 (50%)	14/54 (26%)
70–88	14/34 (41%)	4/34 (12%)

Comparison of Untreated and Treated Cases

In a previous paper (Bloom and Richardson, 1957) the survival rates in a series of treated cases of breast cancer seen at the Middlesex Hospital between 1936 and 1949 were presented according to the histological grade of the tumour. From this series we have abstracted all those patients with an adequate history (88% of the total) to permit their survival to be calculated from the first symptoms of breast cancer, in order to compare them with the present untreated series. Of the treated patients 1,246 were followed for five years from onset of symptoms, 714 for 10 years, and 303 for 15 years. The survival rates according to the grade of malignancy are shown together with those for the untreated patients of the present series in Table X and Fig. 4.

The average survival time from the onset of symptoms for the patients treated between 1936 and 1940 who died within 15 years has been calculated according to grade of malignancy. Nine post-operative deaths were excluded. These survivals were compared with those of the untreated graded cases, all of whom were dead within 14 years (Table XI). The 5-, 10-, and 15-year survival rates for all treated and untreated cases are shown in Table XII.

Discussion

There are obvious difficulties in trying to evaluate treatment in patients with breast cancer from a comparison with an untreated series containing a large number of advanced cases when first seen at hospital. We have tried to make an allowance for this by taking as our yardstick the duration of life from the onset of symptoms in both the treated and the untreated series. This, however, has the obvious weakness of any factor based upon the patient's own observations, especially when the history so often extends over many months or even years. A further consideration is that the data in our untreated cases have been obtained from records dating back to over 150 years, to the time the first case was seen in 1805. Many deaths in this series could no doubt have been postponed for a time if certain non-specific modern therapeutic agents, such as antibiotics and blood transfusion, had been available. Nevertheless, the average duration of life and the 5- and 10-year survival rates found in the present series of untreated cases agree so closely with those obtained by other authors who have studied the untreated disease

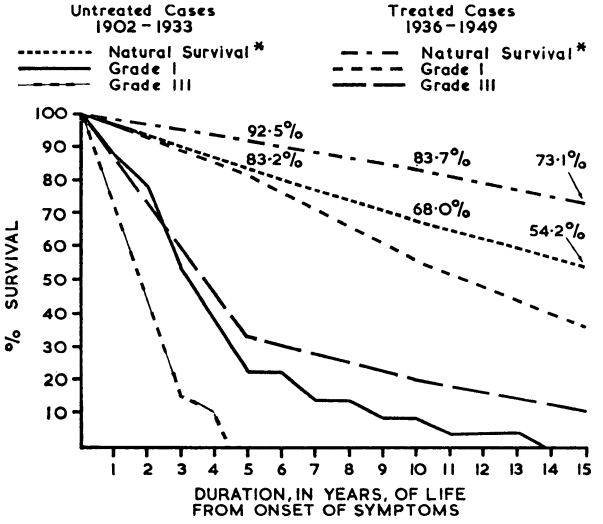


FIG. 4.—Treated and untreated breast cancer. Survival according to histological grade (low and high malignancy). *See Appendix.

TABLE XI.—*Untreated and Treated Cases. Mean Survival of Cases Dying Within 15 Years from Onset of Symptoms According to Histological Grade of Malignancy*

Series	Mean Survival in Months			
	Grade I	Grade II	Grade III	Total
Untreated cases (1902–33)	47·3 (23 cases)	39·2 (32 cases)	22·0 (31 cases)	35·2 (86 cases)
Treated cases (1936–40)	90·1 (52 cases)	61·8 (107 cases)	40·2 (76 cases)	61·2 (235 cases)

TABLE XII.—*Untreated and Treated Cases: Survival from Onset of Symptoms*

Series	Survival		
	5 Years	10 Years	15 Years
Period	1805–1933	1805–1933	1805–1933
Untreated cases	46/250 (18%)	9/250 (3·6%)	2/250 (0·8%)
Period	1936–49	1936–45	1936–40
Treated cases	683/1,246 (55%)	244/714 (34%)	68/303 (22%)

TABLE X.—*Untreated and Treated Breast Cancer. Survival According to Histological Grade from Onset of Symptoms*

Series	Survival (Years)								
	Grade I			Grade II			Grade III		
	5	10	15	5	10	15	5	10	15
Untreated cases* (1902–33)	5/23 22%	2/23 9%	0/23 0%	7/32 22%	1/32 3%	0/32 0%	0/31 0%	0/31 0%	0/31 0%
Treated cases (1936–49)	264/321 82%	107/190 56%	31/83 37%	299/563 53%	93/308 30%	29/136 21%	120/362 33%	44/216 20%	8/84 10%

* 86/250 cases with histological sections.

that we have been encouraged to proceed with the comparison of treated and untreated patients.

It must be pointed out that the treated series is composed of cases which have to some extent been selected in that only those with histological material for grading could be included. Although 84% of the patients were treated by a radical or modified radical operation (with or without ancillary irradiation) the criteria for operability during the earlier years of the period under review (1936–49) were not so strict as they are to-day and many advanced cases were subjected to surgery. Thus 27% of the cases followed for five years were classified as stage 3 or 4. The corresponding figures for those observed for 10 years and 15 years were 30% and 36% respectively.

Of the untreated series, 18% survived five years compared with 55% of those who were treated. At 10 years only 3.6% of the untreated patients were alive compared with 34% of the treated. The corresponding figure at 15 years was 0.8% compared with 22% (Table XII).

Greater accuracy in prognosis of breast cancer can be obtained by considering the histological grade of malignancy of the primary tumour (Bloom, 1950a; Bloom and Richardson, 1957). Eighty-six untreated and 1,246 treated cases have been compared in this way (Table X). A striking difference is seen between the two series. Thus no patient with an untreated highly malignant grade III tumour survived five years, in contrast to 33% of those treated with this type of tumour. More than 80% of treated patients with tumours of low malignancy (grade I) survived for this period, compared with only 22% of the untreated group. The difference between the two series becomes even greater at 10 and 15 years.

The mean survival of treated patients with grade I tumours dying within 15 years of the onset of symptoms was 90.1 months, compared with 47.3 months for those who were untreated. At the other end of the scale of malignancy, the average survival was 40.2 months for treated and 22 months for untreated grade III cases. Thus even in those patients destined to die from their disease treatment appears to prolong life appreciably.

Burdick (1961), in a series of 146 advanced cases of breast cancer, has reported on the results of palliative treatment which has included local surgery, irradiation, hormone therapy, and endocrine ablation (mainly bilateral oophorectomy). This author calculated survival from onset of symptoms to death and obtained 5- and 10-year survival rates of 38% and 12% respectively.

McKinnon (1951a; 1954), who holds the opinion that early treatment of breast cancer fails to influence the mortality, thinks there is no evidence that treatment of the primary tumour materially prolongs life in the majority of those cases in which it does not cure the disease. He believes that treatment can only prevent death in "non-progressive," "non-lethal" forms of cancer and that high survival rates reported for breast cancer are due to the inclusion of such lesions which are thought to make up the majority of stage 1 cases. McKinnon (1955) considers the microscopical diagnosis of "cancer" in such cases as incorrect and that many such lesions are in fact benign. He thinks that stage 1 cases left untreated have little tendency to progress in months or years, if at all, to more advanced stages.

It is true that approximately one-third of treated stage 1 cases have grade I tumours, but there is no doubt of the histological malignancy of these lesions and their ability in time to produce distant and progressive metastases. Thus, although the five-year survival rate for such cases following treatment is 86%, this falls to 40% at 15 years, the majority of deaths being due to breast cancer (Bloom, 1958). Twenty per cent. of stage 1 cases have grade III carcinomas with an initial high survival of 70% at five years, which by 15 years has fallen to 27%.

McKinnon (1951b) criticizes attempts to compare treated with untreated cases on the ground that the former contain a proportion of very favourable cases with lesions of low lethal potentiality that are not present in an untreated series. The distribution of cases according to grade in our treated and untreated series, however, is comparable, there being 26% grade I and 29% grade III cases in the former, compared with 27% grade I and 36% grade III cases in the latter.

Park and Lees (1951) also express the view that the survival rate of breast cancer, using the five-year survival rate as an index, is not affected by treatment, or that if it is in any way effective this effectiveness cannot influence the overall five-year survival rate by more than 5–10%. These authors furthermore think that treatment does not influence the mean survival time of those patients who die of the disease, and imply that the survival rate would have been the same even if the primary tumour had not been removed. They believe that treatment has little, if any, influence on the natural history of the disease, which is largely if not entirely determined by the intrinsic nature of the tumour itself.

We also hold the view that prognosis in breast cancer is largely determined by the type of tumour (Bloom, 1950a, 1950b; Bloom and Richardson, 1957), but, contrary to the beliefs of McKinnon and of Park and Lees, we find evidence that treatment does in fact influence outcome within each grade of carcinoma.

Treatment increases the survival rate as measured from the onset of symptoms and prolongs life of those who die within 15 years. The most striking difference is seen in the highly malignant grade III tumours. Thus we are not able to agree with McKinnon (1955) that "cures" in breast cancer can be accounted for by the presence of "non-metastasizing" forms of the disease and that undoubted malignant cases are uninfluenced by treatment. Even with grade I tumours, which are essentially of low malignancy but nevertheless are capable of metastasizing as evidenced by the steady decline in survival rate over 15 years following treatment (Fig. 4), there is a marked difference between the treated and untreated series.

In the absence of primary treatment patients often linger for many months or years with large, foul ulcerating breast tumours which penetrate deep into the chest wall and produce much pain, discharge, and intermittent haemorrhage. To this picture may be added ulceration of axillary-node masses and of skin nodules, cancer-en-cuirasse, and gross oedema of the upper limb. In 68% of our untreated patients an ulcerating mass was present on admission to hospital. On the other hand, some untreated patients may have a breast tumour of moderate size for many years attached to the pectoralis major with little or no ulceration, suffer no inconvenience from it, and die of an intercurrent

disease. Such examples, however, were rare in this series, 95% of patients dying with extensive malignant disease.

It is true that operable cases of breast cancer that have been treated by orthodox methods may subsequently have extensive local recurrence. The chief feature, however, of most failures of treatment is visceral or skeletal metastases, and these can to a greater or less extent be controlled by palliative measures such as simple analgesics, irradiation, hormones, and ablative endocrine surgery. With such treatment patients may remain comfortable and often feel reasonably well until death is much nearer.

The value of treatment of primary breast cancer cannot be measured entirely by survival statistics at 5 or 10 years. The terminal picture in most cases is less distressing for the patient and her relatives when curative treatment for suitable cases has failed than when such treatment is not given at all. It is perhaps noteworthy that those who most decry the value of treatment of breast cancer are not obliged to treat its victims.

APPENDIX: "NATURAL" SURVIVAL CURVES

The term "natural" survival is used to express the survival at different times from coming under observation of a group of people subjected to the mean national mortality, appropriately calculated to distinguish age and sex, which was prevailing at the particular time when the group was under observation.

The "natural" survival figures given here have been calculated by composite cohort analysis from a series of life tables covering the years 1851 to 1960 in quinquennial groups. These life tables have been specially calculated at the Chester Beatty Research Institute for various mortality analyses and are available on request.

The "natural" figures are as follows:

Group	% of Group Surviving at:				
	0 Years	5 Years	10 Years	15 Years	20 Years
Untreated ..	100	83·2	68·0	54·2	41·5
Treated ..	100	92·5	83·7	73·1	59·7

In the treated group not all the patients have been under observation long enough to allow their survival to the longer periods. The estimates have therefore been based on the numbers who could have survived to the stated time.

Summary

A series of 250 cases of untreated breast cancer from the records of the Middlesex Hospital between 1805 and 1933 has been reviewed. In all cases a post-mortem examination had been performed, and in 86 cases seen between 1902 and 1933 histological material was also available.

Age distribution was comparable to that seen in a large modern treated series. Only 7% of the patients presented within six months of the initial symptom and 29% within one year. Nearly three-quarters of the cases had a history longer than one year, 24% more than three years, and 12% more than five years. The vast majority of cases were advanced when first seen, 74.4% being in stage 4, 23.2% in stage 3, and only 2.4% in stage 2. There were no stage 1 cases.

A lump in the breast was the initial symptom in 83% of cases and ulceration was present when first seen at hospital in 68%.

No definite relationship was found between age and prognosis, although it is possible that the outlook for patients in the fifties may be slightly worse than for those in other age-groups.

Patients with breast cancer may survive for many years without specific treatment. Spontaneous regression was not observed in any cases in this series, although fluctuation in growth rate of the primary tumour was noted in one patient.

All patients were followed to death: 95% succumbed with distant metastases or/and extensive local cancer and in only 5% death appeared to be the result of intercurrent disease. Frequently patients suffered for many months with extensive destructive lesions of the breast and chest wall.

The mean duration of life from onset of symptoms was 3 years: 18% survived 5 years, 3.6% 10 years, and 0.8% 15 years. The longest survival was 18 years and 3 months. Three other patients survived over 13 years.

Histological grade of malignancy was correlated with prognosis in 86 untreated cases in which the microscopical sections were available for study. The average survival from onset of symptoms for tumours of low malignancy (grade I) was 47.3 months and the 5- and 10-year survival rates 22% and 9% respectively. For tumours of intermediate malignancy (grade II) the average survival was 39.2 months and the 5- and 10-year survival rates 22% and 3%. The average survival for highly malignant (grade III) tumours was 22 months; there were no survivors at five years.

It is only against the background of untreated cases in the past that the merits of treatment in breast cancer to-day can be judged more fully. The untreated cases were seen over a period of 128 years; in most the disease was very advanced at the first attendance and the greater part of its duration had to be based largely on the patient's own observations. In spite of these inherent difficulties an attempt has been made to compare the prognosis of untreated cases with a series of treated patients seen at the same hospital between 1936 and 1949. Prognosis according to the degree of histological malignancy has also been determined. Treatment increases the survival rate in all three grades of malignancy as judged by the 5-, 10-, and 15-year intervals from the onset of symptoms; the most striking difference is seen in patients with tumours of high-grade malignancy. Besides prolonging survival, treatment makes life more comfortable and in most cases it renders the terminal stages less distressing for those who die of the disease.

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TREATMENT OF RHEUMATIC FEVER WITH 12-WEEK COURSES OF CORTISONE OR SALICYLATE

BY

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The relative values of salicylate or steroid (in conjunction with bed rest and penicillin therapy) in rheumatic fever continue to be controversial. Thus Massell *et al.* (1961) found that, on the whole, patients treated with hormone subsequently did better than those given salicylate or no specific antirheumatic therapy as regards the disappearance of significant murmurs, yet Friedman *et al.* (1962) found no beneficial effect.

We have previously published our findings on the course of rheumatic fever in hospital in two series of cases—one treated by bed rest and the other by six-week courses of A.C.T.H., cortisone, or salicylate in the U.K.–U.S. Co-operative Trial (Bywaters and Thomas, 1961 ; U.K.–U.S. Trial, 1955). We concluded that most cases of rheumatic fever responded to bed rest alone and that, though salicylates bring about symptomatic relief, they do not significantly alter the course of the disease or have any effect on cardiac status. Steroids had no demonstrable beneficial effect on the heart in most cases except possibly in the disappearance of soft diastolic murmurs, and this was shown in a later paper to have little effect on the findings five years later (Thomas, 1961). They were, however, indicated in cases with cardiac enlargement and activity, for by suppressing the rheumatic activity they diminished the risk of failure. Also, they were useful in patients with established failure and activity ; for after the activity had been controlled the failure responded to drugs such as digitalis and mersalyl. The conclusion of the analysis of all cases treated in the Co-operative Trial at the end of one and five years was that cortisone and A.C.T.H. had no advantage over salicylate, and we found little difference in end-results between our cases treated by bed rest and those treated in this trial.

A criticism of the treatment in the Co-operative Trial has been that the six-week courses were too short, and that had longer ones been used steroid might have been proved more effective than salicylates. With this in mind we have treated a third series of cases, half of them with 12-week courses of cortisone and the other half with similar courses of salicylates. We now describe changes in cardiac status that occurred in hospital in these cases and compare them with those treated in the Co-operative Trial, and later consider the findings at five-year follow-up in the two groups.

Third Series, Treated with 12-week Courses of Cortisone or Salicylate

The series comprised 49 patients aged 16 years or less who fulfilled the criteria for diagnosis of rheumatic fever as defined by Duckett Jones, as did those in the U.K.–U.S. trial. All 49 had been admitted within 14 days of onset of their first attacks. Twenty-four patients (determined "blindly") received 300 mg. of cortisone by mouth daily for two days, 200 mg. for five days, 100 mg. for six weeks, and then by weekly reductions to 25 mg. in the last and twelfth week. The other 25 were given salicylates on a body-weight basis in the form of calcium aspirin. All were given penicillin prophylaxis in hospital (benzylpenicillin 200,000 units b.d. or phenoxymethylpenicillin 125 mg. b.d.), and most of them continued to take the tablets as advised after discharge.

Cardiac status on admission and any changes that occurred during the stay in hospital are shown in Table I. Also included in the table are 60 patients seen in first attacks out of a total of 86 of our own

TABLE I.—*Cardiac Status in Hospital: 49 Cases in Third Series and 60 in U.K.–U.S. Trial*

	No. of Cases	No. Developing Murmurs	Grade of Murmurs	
			1–2	3
No carditis on admission:				
Third series	19	6	5	1
U.K.–U.S. trial	13	2	2	0
Admission 0–14 days	7	2	2	0
,, 14+ days	6	0	0	0
Total	32	8	7	1
		No. Losing Murmurs		
Carditis on admission:				
Third series	30	16	16	0
U.K.–U.S. trial	47	18	17	1
Admission 0–14 days	13	7	7	0
,, 14+ ,,	34	11	10	1
Total	77	34	33	1