Papers and Originals

Host Resistance and Survival in Carcinoma of Breast: A Study of 104 Cases of Medullary Carcinoma in a Series of 1,411 Cases of Breast Cancer Followed for 20 years*

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British Medical Journal, 1970, 3, 181–188

Summary: This paper deals with a special type of mammary carcinoma, generally of high-grade malignancy, which carries a remarkably good prognosis—the so-called "medullary carcinoma of the breast with lymphoid infiltrate." Probably the increased lymphoid tissue seen in these tumours is concerned with cell-mediated and humoral immunological reactions and reflects a strong host-defence mechanism which is responsible for the remarkably high survival rates following radical treatment. Since the evidence for host resistance to malignant disease is based largely on animal data, the opportunity to study a group of patients followed for 20 years, in whom this type of defence reaction appears to exist, is of considerable clinical interest.

Among 1,411 cases of breast cancer there were 104 with medullary carcinoma (7·4%), for which the corrected 5- to 20-year survival rates have been calculated. After 20 years 74% of cases with operable medullary tumours were alive, compared with 14% of cases with similar stage non-medullary cancer. In the presence of histologically proved axillary metastases the 20-year survival rate was 61% for medullary cases, compared with only 13% for other types of breast cancer.

In 30 cases of medullary cancer in which the axilla was free, the corrected 20-year survival rate was 95% following a combination of radical operation and radiotherapy. No evidence could be found that axillary dissection or postoperative irradiation is harmful to women with operable highly malignant breast cancer in whom a well-marked host resistance is thought to be present. A combination of radical mastectomy and postoperative irradiation appears to be the most effective treatment for such cases. The present grounds for rejecting a radical approach to treatment of breast cancer, based on current immunological considerations, are regarded as being quite inadequate.

Introduction

For many years the study of human cancer was focused chiefly on the inherent characteristics and manifestations of the tumour itself. More recently there has been increasing interest in the response of the host and in the concept of a natural resistance to malignant disease.

There is mounting evidence for the presence of specific antigens in spontaneous solid tumours which are capable of producing an immune response in the host and influencing the progress of malignant disease (Hamilton Fairley, 1969; Mathé, 1969), epecially in cases of melanoma (Lewis *et al.*, 1969) and osteosarcoma (Morton and Malmgren, 1968). Much fundamental research is now being done on controlling tumours in laboratory animals by immunological methods, and a few heroic endeavours are being made to apply such observations to cancer therapy in man. Nevertheless, we should not neglect a more simple and, perhaps for the present, more rewarding approach to the study of host resistance in human cancer—namely, histological features related to lymphoid tissue within the tumour and regional nodes which several authors have found of prognostic value for cancer at certain sites, especially the breast.

Since Broders introduced grading generally in the 1920s interest has focused chiefly on using histological factors in breast cancer to gauge tumour potential (Patey and Scarff, 1928; Haagensen, 1933; Bloom, 1950a; Bloom and Richardson, 1957). MacCarty (1922) was one of the first to correlate stromal factors in malignant disease with survival, but this work attracted little attention, especially as a possible guide to host defence. More recently several workers have rekindled interest in the presence of round-cell infiltration in breast cancer which they have been able to correlate with prognosis (Black *et al.*, 1955; Black and Speer, 1958; Berg, 1962; Cutler *et al.*, 1963; Hamlin, 1968).

Since a local lymphoid infiltrate characterizes many immunological reactions, including those evoked to control tumours in animals, it is tempting to relate this feature to host resistance in human cancer. Foote and Stewart (1946) were the first to suggest that the well-marked lymphocytic infiltrate in the so-called medullary type of breast cancer probably reflects a host reaction. Though this type of cancer, with its good prognosis, is now widely recognized as an entity, clinicians and pathologists have generally shown little enthusiasm for applying histological criteria which may reflect host resistance to the study of human cancer.

On the other hand, except for Kister *et al.* (1969), most authors accept that histological tumour grade reflects the malignant potential of breast cancer, its power to spread, and the tempo at which it is likely to progress (Bloom and Richardson, 1957; Cutler *et al.*, 1963; Schiødt, 1966; Wolff, 1966; Gorski *et al.*, 1968). By combining histological grade with clinical stage breast cancer can be classified more accurately (Bloom, 1958, 1962). Grading also helps to assess more precisely the influence of various clinical factors on prognosis, such as age (Bloom, 1950b), pregnancy (Bloom, 1962), delay in treatment (Bloom, 1965), and also treatment per se (Bloom *et al.*, 1962; Bloom, 1968).

The present work is based on the belief that intrinsic tumour potential and host defence can be partly gauged from histological criteria, that these are independent variables, and that prognosis for patients with breast cancer is the result of competitive interplay between them. Though tumour grade

*Dedicated to the late Professor R. W. Scarff and based on an invited paper at the 51st Annual Meeting of the American Radium Society, Philadelphia, April 1969.

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and host reaction can each be related to prognosis, a better index of outcome is gained by considering both factors together (Black *et al.*, 1956; Hamlin, 1968). If clinical stage is also taken into account we have a more rational classification of breast cancer based on (1) inherent tumour potential, (2) host response, and (3) extent of disease when first seen.

Medullary Carcinoma of Breast

This study is concerned primarily with a special type of mammary carcinoma generally of high-grade malignancy in which there is an intense lymphoid stromal reaction consisting of varying proportions of lymphocytes and plasma cells—the so-called "medullary breast cancer with lymphoid infiltrate," first recognized as an entity by Geschickter (1945). An account of the gross and microscopical features has been given by Moore and Foote (1949) and by Richardson (1956). Though this is now widely accepted by pathologists, little has been published since the first systematic study by Moore and Foote (1949).

Analysing 1,000 cases with operable breast cancer, these workers found 52 examples of the medullary type of tumour. The five-year disease-free crude survival rate was 83%. The axilla was involved in only 42% of cases, and in the absence of axillary metastases 93% of patients were alive, compared with 68% when the nodes were involved. Similarly, Haagensen (1956), studying 56 cases out of 2,000 women with breast cancer, found a five-year recurrence-free rate of 56%. In the largest series of patients with medullary carcinoma of the breast (Richardson, 1956) there were 117 examples of this tumour among a total of 1,660 cases. The five-year and ten-year crude survival rates were 77 and 55% respectively. More recently Gorski *et al.* (1968) found 50 cases among 682 cases of mammary carcinoma with 86% alive at five years and 68% at 10 years. All these survival rates for patients with medullary tumours, even in the presence of axillary involvement, are much greater than those expected for breast cancer in general.

Present Series

Among 1,411 cases of breast cancer treated at the Middlesex Hospital between 1936 and 1949 (Bloom, 1950a, 1958, 1965; Bloom and Richardson, 1957), there were 104 examples of medullary tumour, an incidence of 7·4%. Richardson (1956) has already drawn attention to the pathological features and unusually good prognosis of this special type of mammary cancer.

The present investigation examines in greater detail the prognosis and also the influence of type of treatment on women with medullary cancer in the light of a 20-year follow-up. It compares their survival with that of non-medullary cases and determines the influence of medullary tumours on survival rates of breast cancer patients in general. Because of recent opinions that postoperative irradiation (Bond, 1967; Hamlin, 1968) or axillary node dissection (Crile, 1965, 1968) may harm patients with early breast cancer (by interfering with the host's immune mechanisms against the tumour), in the present series we have also studied the effect of treatment on women who show what appears to be a strong defence reaction against this disease. In these circumstances does axillary dissection or postoperative irradiation reduce survival?

Though the number of cases available for study is limited, the group would appear to be a particularly valuable one, since it is rare to find a natural human model in which problems relating to tumour immunity can be investigated. All 104 medullary cases are eligible for a 20-year follow-up and, in spite of many of these patients being treated during the second world war, only five remain untraced at 20 years (Table I). These few untraced patients have been counted as dead and not excluded from the study.

TABLE I.—*Proportion of Untraced Cases in the Three Series of Breast Cancer (Middlesex Hospital, 1936-49)*

Series	Cases	Untraced at		
		10 Years	15 Years	20 Years
Medullary	104	2	2	5 (4·8%)
Non-medullary (general)	1,307	15	31	49 (3·7%)
Total	1,411	17	33	54 (3·8%)

The survival of women with medullary cancer is compared by tumour stage and by tumour grade with that of the remaining 1,307 non-medullary cases, the latter also being referred to as the "general" series. The 1,411 cases, termed the "total" series (Table I), exclude 17 postoperative deaths and 15 cases untraced at five years (Bloom and Richardson, 1957). Originally, this series consisted of 1,409 cases, but two previously untraced patients have since been found and included. The total series, followed to the end of 1969, has been "at risk" for 20 years. Five-year results are available for all 1,411 cases. The untraced cases at 10, 15, and 20 years (Table I) have been counted as dead and not excluded from the present investigation.

The crude and expected 5- to 20-year survival rates are shown in Fig. 1. Because of the prolonged follow-up in this

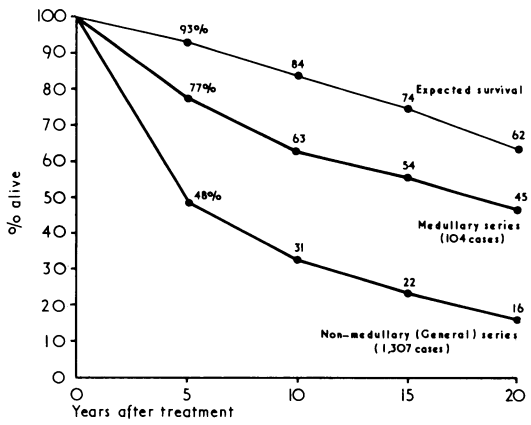

FIG. 1.—Crude survival curves for medullary and general breast cancer cases. The expected survival rates are practically identical for both series; those for the total series are shown here.

study each survival rate has been corrected for an estimated natural mortality (from all causes of death) by the method of Berkson and Gage (1950, 1958), the correction factor for each group of patients being adjusted for the age/sex/birth cohort distribution of the group. Details of the method are given in an appendix, which is available on request from the authors.

Classification.—There is a relative preponderance of early stage cases in the medullary series: the tumours in 51% of cases were stage 1 and in 11%, stage 3, compared with 32 and 22% respectively in the non-medullary or general series (Table II). The proportion of stage 2 cases in the two series is about equal. A special feature in the medullary group is the high incidence of grade III tumours—64% of stage 1 and 71% of stage 2 cases, compared with only 14 and 30% respectively of the general cases (Table II). Sixty-eight per cent. of all medullary carcinomas are of grade III malignancy, compared with 26% of non-medullary cancers (Table III). Only 3% of medullary tumours are of low malignancy (grade I) as against 27% in the general series.

Results

Total Cases.—There is a striking difference between the corrected survival curves for women with medullary tumours and women with other types of breast cancer (Fig. 2): at 20 years, for example, 71 and 25% are alive respectively.

By Grade.—At 10 years between two and three times more

TABLE II.—*Distribution of Cases by Stage (Manchester System) and Histological Tumour Grade in the Medullary and Non-medullary (General) Series. Stage Unknown in 18 Cases of the General Series*

Stage	Grade	Medullary		General	
1	I	2		161	
	II	17	51%	195	32%
	III	34 (64%)		59 (14%)	
2	I	1		119	
	II	10	37%	237	40%
	III	27 (71%)		154 (30%)	
3	I	—		63	
	II	3	11%	127	22%
	III	9		88	
4	I	—		11	
	II	—	1%	42	6%
	III	1		33	
Total	..	104	100%	1,289	100%

TABLE III.—*Distribution of Cases by Tumour grade*

Grade	Medullary	General
I	3 (3%)	360 (27%)
II	30 (29%)	610 (47%)
III	71 (68%)	337 (26%)
Total	104 (100%)	1,307 (100%)

TABLE IV.—*Corrected 10-year Survival Rates for Medullary and General Breast Cancer Cases*

Grade	Medullary		General	
	Cases	Alive	Cases	Alive
I	3	(100%)	360	62%
II	30	88%	610	34%
III	71	67%	337	16%
Total	104	74%	1307	37%

TABLE V.—*Corrected 10-year Survival Rates for Medullary and General Breast Cancer Cases by Clinical Stage (Manchester System)*

Stage	Medullary		General	
	Cases	Alive	Cases	Alive
1	53	88%	415	64%
2	38	67%	510	28%
3	12	43%	278	25%
4	1	–	86	4%
Total	104	74%	1289	37%

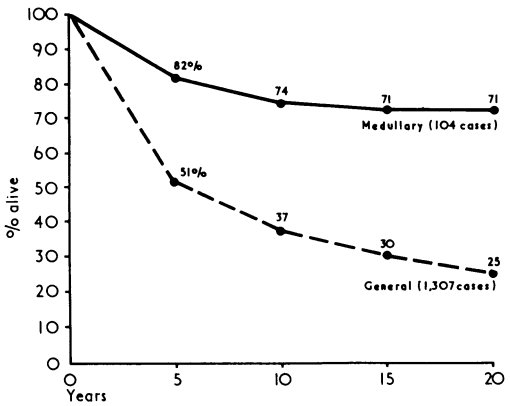

FIG. 2.—Corrected survival curves for medullary and general breast cancer cases.

grade II and four times as many grade III cases with medullary tumours are alive compared with the general cases (Table IV). The definite difference in prognosis for the two groups with highly malignant tumours (grade III) is maintained throughout the 20 years following treatment (Fig. 3); by this time 67% of women with medullary tumours are still alive, compared with a mere 12% for other types of breast cancer. A similar picture is seen for grade II cases (Fig. 4).

By Stage.—The cases classified by the Manchester system of staging which was in use when they were first reviewed are shown in Table V. In each group the 10-year survival rate is considerably higher for patients with medullary cancer : 67% of stage II cases with this tumour are alive, compared with 28% for other types of breast cancer in the same stage. The extended follow-up for all operable cases (stages 1 and 2) with grade III tumours (Fig. 5) illustrates again the superior survival rates for patients with medullary

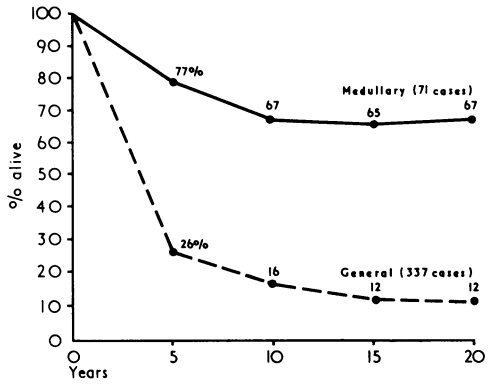

FIG. 3.—Corrected survival curves for grade III breast cancer in the medullary and general series.

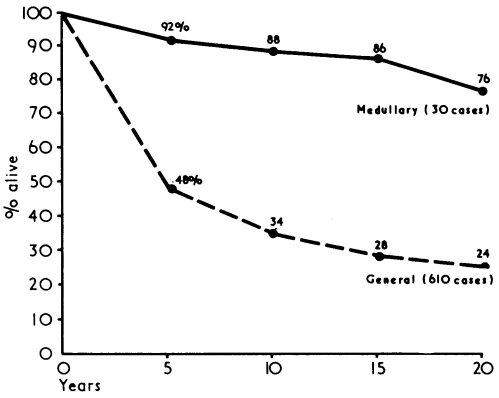

FIG. 4.—Corrected survival curves for grade II breast cancer in the medullary and general series.

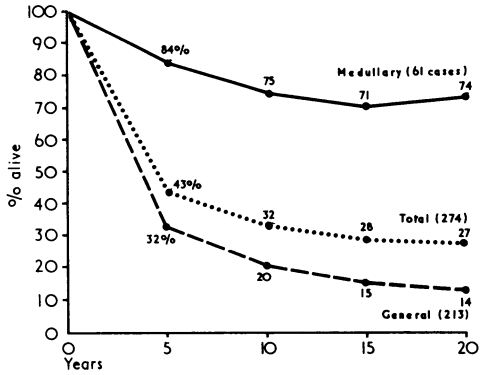

FIG. 5.—Corrected survival curves for operable grade III breast cancer (stages 1 and 2) in the medullary, total and general series.

compared with non-medullary tumours (74% compared with 14% at 20 years).

By Axillary Involvement.—The incidence of proved axillary metastases in the medullary series is only 39% (of 90 cases examined histologically), as against 64% (of 1,071 cases) in the general series. Patients with medullary tumours have a substantially better prognosis than the general cases, whether the axillary nodes are involved or not (Fig. 6): 63% of women with axillary metastases from medullary tumours are alive at 10 years, compared with only 22% of those with other types of breast cancer. Interestingly, the prognosis in medullary cancer with involvement of the axilla is comparable to that found in other tumours when the axilla is free (Fig. 6).

Influence of Medullary Tumours on Results

Medullary carcinoma is found in only some 7% of all breast cancer cases. This special tumour, however, constitutes 17% of the total grade III cases in the present series, and 37% of stage 1 cases with grade III tumours. In spite of the relatively small number of medullary tumours, their occurrence may exert an appreciable influence on the overall survival rate of women with high-grade breast cancer. Thus 21% of the total grade III cases are alive at 20 years, compared with 67% of medullary and 12% of non-medullary cases with tumours of the same grade (Fig. 7).

The survival curve for the total patients with grade III tumours limited to stage 1 (Fig. 8) consists of two components, representing the medullary and non-medullary tumours. The recognition of medullary cancer here is particularly important since it constitutes 37% of the whole group. Though all cases represented in Fig. 8 are "early" (stage 1), clearly the prognosis for medullary cancer is far superior to that for other types of tumour of the same grade and stage: at 20 years 94% of women with medullary tumours are still alive, compared with only 39% for other types of breast cancer.

The prognosis for patients with grade III tumours in stage 2 is shown in Fig. 9. The survival rates from 10 years onwards for medullary carcinoma are at least seven times greater than for other types of breast cancer of comparable stage and grade.

Potential Malignancy of Medullary Carcinoma

Can the remarkably good prognosis associated with medullary cancer be ascribed solely to an inherent low tumour malignancy? The corrected five-year survival rate of 82% for all women with this type of cancer (Fig. 2) and 94% for those with stage 1 grade III lesions (Fig. 8) might suggest that this was so. Medullary carcinoma, however, is usually of high-grade malignancy, 68% of tumours in the present series falling into this category, with only 3% being classified as low grade (Table III). Though half the cases had tumours limited to stage 1, in 37% they had advanced to stage 2, and in 11% to stage 3. Axillary metastases were present in 39% of cases. The potential danger from medullary carcinoma is further emphasized by the poor survival rate in 14 patients following conservative surgery (Fig. 10). Furthermore, compared with breast cancer in general, unsuccessfully treated patients with medullary carcinoma die early, the patients in this group studied by McDivitt *et al.* (1968) having a median survival of 2·2 years—the shortest period compared with that for other types of tumour studied. Deaths due to this tumour are rare after five years.

These facts clearly show that medullary breast cancer can spread and kill. It is postulated that these tumours are essentially of high malignancy, as indicated by their tumour grade, but that their biological potential is countered to a considerable extent by an effective host resistance. Thus poorly differentiated tumours, showing the greatest deviation

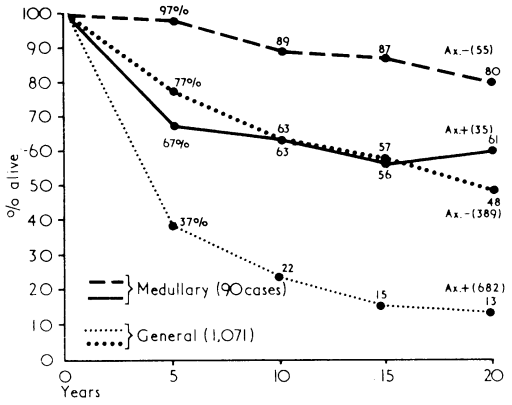

FIG. 6.—Corrected survival rates for medullary and general breast cancer cases by histological assessment of axilla.

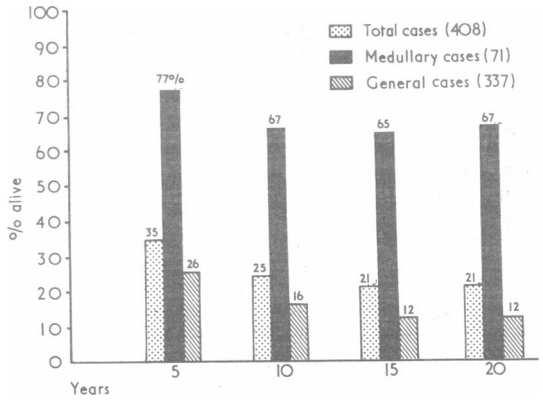

FIG. 7.—Corrected survival rates for cases with grade III breast cancer. Note the extraordinarily high survival rates for patients with medullary tumours and the influence of these tumours on the results of grade III breast cancer in general.

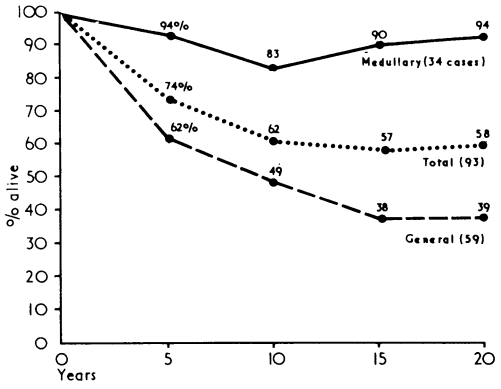

FIG. 8.—Corrected survival curves for cases with stage 1 breast cancer of grade III malignancy in the total, medullary, and general series.

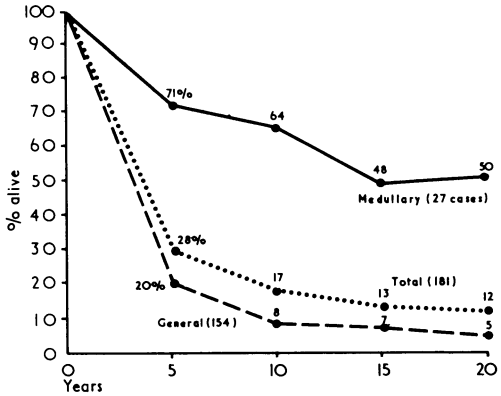

FIG. 9.—Corrected survival curves for cases with stage 2 breast cancer of grade III malignancy in the total, medullary, and general series.

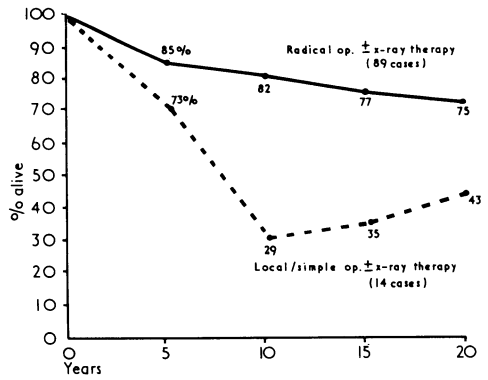

FIG. 10.—Corrected survival rates for medullary breast cancer cases. Note the poor survival following conservative surgery compared with radical operation.

from the normal breast epithelial pattern, are probably the ones most likely to evoke a defence reaction in the host.

Lymphoid Infiltrate

Though medullary tumours constitute only about 7% of all breast cancers, many of the remaining tumours may show some local lymphoid reaction (Hultborn and Törnberg, 1960; Schiodt, 1966; Hamlin, 1968). In general, however, it is only between cases showing a well-marked cellular reaction and those in whom such a reaction is virtually absent that a real difference in prognosis has been shown. Berg (1962) considered that the significant stromal cell in host defence against anaplastic breast cancer of "no special type" was the plasma cell. On the other hand, Schiodt (1966), and also Richardson (1956), found no correlation between prognosis and differing proportions of lymphocytes and plasma cells.

At least in transplanted animal tumours of syngeneic hosts the lymphocyte and its progeny are the principal cells involved in the host reaction against cancer. Probably the sensitized lymphocytes "home in" and destroy target tumour cells. Furthermore, humoral antibodies, produced by an increased number of plasma cells near tumours and within regional and distant lymphoid tissue, play an important part in the defence system.

Tumour Contour

A well-defined tumour boundary is the characteristic gross feature of medullary breast cancer. Microscopically, the growth is seen to be more or less limited by connective tissue containing a varying degree of lymphoid infiltrate. Tumours with a well-defined contour per se appear to have a substantially better prognosis than those with an irregular outline. A clearly defined border, however, is not necessarily accompanied by a well-marked lymphoid reaction; less than one-third of such cases in the series of Lane *et al.* (1961) were examples of classical medullary breast cancer. It is not known whether the well-defined boundary of medullary cancer represents an intrinsic property of the tumour itself, perhaps related to cell cohesion, or one determined by a host-defence mechanism.

Treatment Policy and Host Defence Considerations

It is a long-established principle that the treatment of localized breast cancer should also include an attack, either surgical or radiotherapeutic, on the regional lymph nodes because of the high incidence of microscopic involvement. With current mounting interest in the role of lymphoid tissue in reactions to foreign tissues and tumours, it is not surprising that concern has been expressed recently that surgical ablation or irradiation of regional nodes may reduce the natural resistance of the host against cancer, especially in early cases. On immunological grounds, Crile (1967) is opposed to treating clinically uninvolved axillary nodes. He claims better results following limited surgery for patients with stage 1 breast cancer, advocating simple mastectomy, or even local excision alone, for women with strictly limited clinical disease, and delaying axillary dissection until such time as node enlargement may appear. Bond (1967), from a retrospective analysis of many operable cases, concluded that irradiation after radical or simple mastectomy in patients with stage 1 disease reduces the survival rate, compared with surgery alone, by a "significant 9%." He assumed that this was due to breakdown of immunological control of the cancer by irradiation.

Hamlin (1968) has carried out a careful detailed analysis of histological features in the breast tumour and regional nodes which may be related to host resistance. In small groups of cases seen between 1935 and 1945 she found a greater 15-year survival rate among those treated by radical surgery alone, compared with surgery combined with irradiation. Unfortunately, the constitution of this material is uncertain, for after studying the histological sections "blind" Hamlin discovered that one-third of the patients in the initial series were lost to follow-up and, to make up the numbers, further cases had to be taken from later years. In the final analysis, involving 360 patients, 68 were excluded because death occurred within 15 years, apparently from unrelated disease.

Women with medullary breast cancer appear to form a special group of cases capable of high resistance against their tumour. What effect has axillary dissection and ancillary irradiation on their survival?

Results and Type of Treatment

Treatment for most patients with medullary breast cancer, as for our general cases, was by radical mastectomy with or without ancillary irradiation (Bloom and Richardson, 1957). Eighty-six per cent. of the medullary cases received this treatment, the remainder having local excision or simple mastectomy with or without radiotherapy. One stage 4 case was treated by irradiation alone (Table VI).

TABLE VI.—*Type of Treatment in the Medullary Breast Cancer Series*

Radical operation	29	86%
Radical operation + *x*-ray therapy	60	
Simple operation ± *x*-ray therapy	10	
Local excision ± *x*-ray therapy	4	
X-ray therapy	1	
	104	

The prognosis for women with medullary tumours is remarkably good, but apparently only if surgical treatment is radical. Thus the survival rate for 14 patients treated by local excision or simple mastectomy was extremely poor compared with cases treated by radical surgery, the majority in both groups also receiving postoperative radiotherapy (Fig. 10). The cases treated by conservative surgery did not appear to constitute a particularly unfavourable clinical group so far as age and stage distribution were concerned: eight cases were stage 1, three stage 2, and three stage 3. Eight out of 13 patients of known age were under 60. Ten cases had simple mastectomy and the remaining four had local excision. Ancillary radiotherapy was administered to 10 of the 14 cases. The results of radical surgery alone and combined with radiotherapy (Fig. 11) gave survival rates that are high and comparable in both groups.

Bearing in mind the contentions of Crile (1965, 1968) and of Bond (1967)—that particularly in cases with uninvolved nodes should care be taken not to interfere with host resistance by prophylactic node treatment—let us examine the effect of irradiation in cases where the axilla is known to be histologically free (Fig. 12). The survival rates in both treatment groups are equally high up to 10 years, after which the results may be rather better for cases receiving postoperative irradiation: note that the corrected survival following the combined treatment is practically 100%.

In a small but still more uniform group of patients—those with stage 1 grade III medullary breast cancer—the results again show (Fig. 13) that there is no evidence that survival is reduced by postoperative irradiation. On the contrary, survival

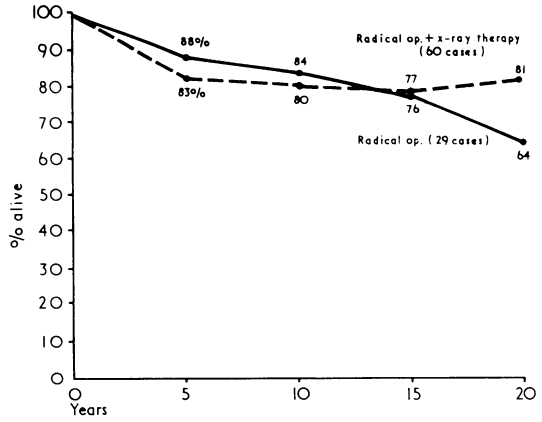

FIG. 11.—Corrected survival rates for patients with medullary breast cancer treated by radical mastectomy alone or with postoperative *x*-ray therapy.

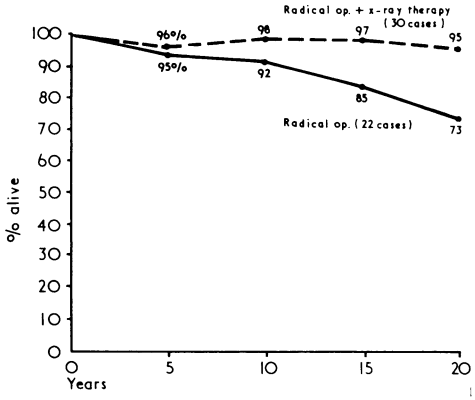

FIG. 12.—Corrected survival rates for patients with medullary breast cancer in whom the axilla is free (histological confirmation in 50 of 52 cases) treated by radical mastectomy alone or with postoperative *x*-ray therapy. Practically no deaths from breast cancer occur following the combined treatment.

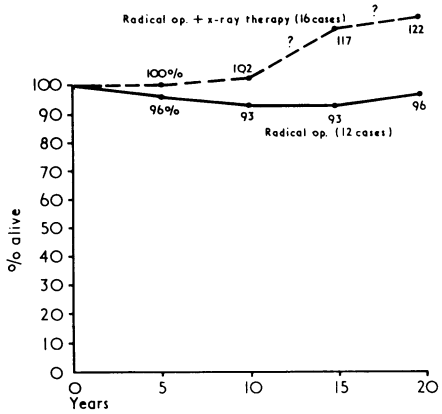

FIG. 13.—Corrected survival rates for patients with stage 1 grade III medullary breast cancer treated by radical mastectomy alone or with postoperative *x*-ray therapy. Is the apparent increase in normal life expectancy seen in the combined treatment group due to a sampling error or to a high degree of host resistance in these early cases affording protection not only against breast cancer but also against other diseases? (See text.)

rates for the group receiving radiotherapy are even greater than those expected in a general population of similar age and birth cohort distribution. This peculiar result could well be due to a sampling error in the small number of cases, since, taking the 20-year figures, the crude survival rate of 75% (12 out of 16 cases) does not differ significantly from the expected rate of 61% ($\chi^2=0.76$; $0.5>P>0.3$). On the other hand, it is tempting to speculate that the high degree of host resistance which may exist in these patients does protect against other tumours and perhaps also non-malignant disease, leading to a life-expectancy greater than for "normal" women. Thus it is concluded that neither axillary dissection nor irradiation appears to interfere with immune mechanisms so as to lead to a harmful effect in women with the medullary type of breast cancer.

Discussion

Though most of the evidence at present is circumstantial, it seems logical to adopt the concept of host resistance to cancer and to accept that this has an immunological basis related to lymphoid tissue. One aspect of the host reaction to breast cancer appears to be a lymphoid infiltrate associated with the primary tumour. A definite cellular reaction of this type is found in the so-called medullary carcinoma which has a remarkably good prognosis following radical treatment, even in the presence of axillary metastases.

In relation to the possible deleterious effects of *local* therapeutic measures against regional nodes in cancer patients, one should recall the experimental evidence which indicates that sensitized lymphoid cells leave the nodes within hours, or at most a few days, following antigenic stimulation, by which time the immune response has almost certainly become generalized. From Crile's (1965) work, for example, it seems that nodes in tumour-bearing rats need to be present for only about five days after contact with antigen for the immune response to be fully developed.

Since the doubling time for human breast cancer may vary from 20 to over 200 days it can be calculated that the time required for a tumour to reach only 1 cm. in diameter, based on 30 doublings, may vary from 23 months to 17 years (Gershon-Cohen *et al.*, 1963). Consequently, when a patient with breast cancer presents for medical advice the tumour has probably been present for at least a year, during which any immunological response against the tumour should certainly have become fully mounted and systemic; indeed, such a response may be declining or even completely exhausted as a result of increasing tumour activity. Thus how, at this late stage of tumour development, can *local* irradiation or surgical ablation of the regional nodes depress an immune response against cancer to a degree which proves harmful to the host? Cutler *et al.* (1969) drew attention to the superior survival of women with breast cancer treated by radical mastectomy in whom *bilateral* axillary nodes were palpable. This applied whether the homolateral nodes were histologically involved or not. Enlargement of negative nodes in these cases appeared to be related to considerable sinus histiocytosis, a histological manifestation of host resistance (Black and Asire, 1969). These authors suggest that the contralateral node enlargement is due to a *systemic* host reaction.

In animals the output of lymphocytes and the immunological responsiveness of regional nodes is not altered significantly following local irradiation with doses up to 2,000 r. This is due to the rapid repopulation of the depleted nodes by lymphocytes from the circulating pool (Hall and Morris, 1964; Benninghoff *et al.*, 1969). After several months, however, irradiated nodes tend to become depleted of cells and fibrosed.

The view expressed here that neither radiotherapy nor axillary nodes dissection appears to be harmful to patients with breast cancer rests chiefly on evidence found in a special and limited group of cases. It could be argued that the host reaction in women with medullary breast cancer is so well developed that these treatments are insufficient to reduce the immune response effectively; this does not exclude the possibility that with a lesser degree of host reaction local treatment may indeed be harmful, as suggested by Bond (1967), Crile (1967), and Hamlin (1968).

This latter view is unlikely to be correct since in selected early cases of breast cancer, without regard to special

histological type, radical radiotherapy and radical surgery have, in recent years, each given very good results. Rissanen (1969) found crude survival rates of 79% at five years and 71% at 10 years for 415 stage 1 cases of breast cancer treated solely by irradiation after local excision of the lump. In 121 cases with histologically negative axillary and internal mammary nodes, Urban (1964) obtained a five-year survival of 87% following an extended radical procedure in which all three regional node areas were dissected. From a cancer detection clinic, Gilbertson (1966) reported a five-year survival rate of 96% among 24 patients treated with radical surgery in whom the axilla was negative. In women with histologically negative but bilateral palpable axillary nodes due to sinus histiocytosis, the five-year and 10-year survival rates following radical mastectomy were 90 and 80% respectively (Cutler *et al.*, 1969). None of these results supports the concept of a significantly reduced host reaction to cancer in early breast malignancy as a result of radical surgery or irradiation.

Additional evidence that large volume irradiation by modern techniques, including the prophylactic treatment of regional lymph nodes, is not harmful in early cancer is found from the high survival rates recently reported for tumours such as seminoma testis, Wilms's tumour, and the reticuloses.

From the limited effect of immune responses on well-established tumours in experimental animals, any useful approach to immunotherapy is probably linked with conventional treatment and aimed solely at destroying residual tumour at the primary site or small distant metastases. Haddow and Alexander (1964) found that injections of irradiated autologous tumour failed to control the growth of a benzpyrene-induced fibrosarcoma in the rat. An *x*-ray dose of 2,000 r also had little effect, but irradiation and vaccine together produced definite tumour regression in half the animals. Though an effective host resistance may be present in women with medullary breast cancer, adequate local treatment of the primary tumour and regional lymph nodes appears to be necessary for longevity in this disease.

Despite the vast volume of experimental data concerning immunological aspects of tumour growth and development we are still far from applying such observations to the investigation and treatment of human cancer. In the meantime caution is required in trying to extrapolate animal data to man, and in interpreting results of orthodox treatment in retrospective studies involving heterogeneous groups of cases.

Though our study is admittedly a retrospective one, we have tried to examine uniform groups of cases classified by both clinical stage and histological grade. Recognizing the fact that the main material for this investigation concerns relatively few women with a special type of breast cancer, we could find no evidence that axillary dissection or postoperative irradiation harms patients with early highly malignant tumours in whom appreciable host resistance is considered to be present. On the contrary, we suggest that the remarkably high survival rates obtained for medullary breast cancer are a triumph of radical treatment in a situation where host resistance is high.

One may question the wisdom of rejecting radical treatment of breast cancer for lesser procedures on the present insufficient grounds that the former is harmful. It must be left to well-conducted clinical trials to establish the true value of conservative surgery and of preoperative or postoperative radiotherapy in the control of operable cases. Those responsible for designing such trials should consider carefully the possible danger of introducing so conservative an approach to treatment that the procedure becomes virtually inadequate.

Certain intriguing additional questions arise from this study concerning medullary tumours. Why do less than 10% of women with breast cancer have the changes associated with a high degree of host resistance? How can we induce or augment a natural host response in the remainder? By the time most patients present for treatment is the immune response already exhausted? Does the well-developed host resistance to breast cancer found in some 7% of cases extend also to other tumours and perhaps to non-malignant disorders? Helped by the immunologists we should now focus our interest on investigating the earlier cases of breast cancer being found by screening programmes. The immunological aspects of breast cancer are perhaps another reason for trying to reduce delay in women with this disease (Bloom, 1965).

Prospective breast cancer studies are needed to correlate host non-specific immune capabilities and also responsiveness to autologous tumour preparations with histological criteria such as nuclear grade and lymphoid reactions, and ultimately to relate these to prognosis. A start in this direction has been made by MacKay and Baum (1968) and also by Williams and Roberts (1968) in this country and by Stewart (1969) in Canada.

The method of correcting the survival rates is described in an appendix, which is available on application to the authors.

We are indebted to the medical staff of the Middlesex Hospital for kind permission to continue the study of breast cancer cases seen at that hospital, which constituted the material in our earlier reports on the subject of tumour grading. We are grateful to Professor R. A. M. Case and to Mr. Peter Payne for generous help with correcting the survival rates; to Miss Marjorie Martin, of the South Metropolitan Cancer Registry, for assistance in assembling the crude data; and to Miss Eileen Burton, of the Middlesex Hospital, for obtaining case follow-up information. We should like to express our thanks to Mrs. Judy Lay, of the Science Research Council's Atlas Computer Laboratory, for supervising the production by computer of the expected survival rates and to the University of London for meeting the cost.

The graphs are the work of the departments of art and clinical photography of the Royal Marsden Hospital.

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Haemolytic-uraemic Syndrome Treated with Heparin

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British Medical Journal, 1970, **3**, 188–191

Summary: Three children with the haemolytic-uraemic syndrome were treated with intravenous heparin. Peritoneal dialysis was required for two of them, one of whom died after 26 days of therapy. Renal biopsy specimens from the two survivors showed widespread glomerular disease, which appeared permanent in one case, but only occasional thrombi. It is suggested that heparin therapy, by preventing further intrarenal thrombosis, allowed the normal fibrinolytic mechanisms to remove previously formed thrombi.

Introduction

The haemolytic-uraemic syndrome, first described by Gasser *et al.* (1955), is characterized by acute haemolytic anaemia, thrombocytopenia, and uraemia. The mortality in the acute stage of the illness may be as high as 66% (Shinton *et al.*, 1964), but with modern management of fluid and electrolyte imbalance the prognosis should improve (Gianantonio *et al.*, 1964). With dialysis patients may now survive after prolonged oliguria (Sharpstone *et al.*, 1968). Heparin therapy has been advocated (Kibel and Barnard, 1964) on the grounds that the pathological changes in the kidneys resemble those found in the Schwartzman phenomenon, in which generalized microthrombi are observed (Verstraete *et al.*, 1965). Heparin appears to have improved the outcome (Table I). Below we present data on three children suffering from the haemolytic-uraemic syndrome whom we have treated with intravenous heparin in the past six months.

Case 1

An 11-year-old boy was admitted to the City General Hospital, Stoke-on-Trent, with a history of vomiting for two days. He had slight facial oedema and a blood pressure of 190/120 mm. Hg. He was anaemic, uraemic, and had thrombocytopenia; fragmented red cells and burr cells were present in a peripheral blood film. A diagnosis of the haemolytic-uraemic syndrome was made and heparin therapy was started. In view of the development of severe oliguria and a rising blood urea level, however, he was transferred two days later to the Children's Hospital. The results of further investigations (Table II) confirmed the diagnosis.

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TABLE I.—*Patients With the Haemolytic-Uraemic Syndrome Treated With Heparin (13 Additional Patients Treated With Heparin Were Reported by Gianantonio* et al. (1967), *but the Number of Survivors is Not Recorded).*

Authors	No. Treated	No. Surviving
Künzer and Aalam (1964)	1	1
Kibel and Barnard (1964)	1	1
Hitzig (1964)	4	3
Desmit *et al.* (1966)	1	1
Boen (1966)	1	1
Piel and Phibbs (1966)	3	2
Brain *et al.* (1967)	3	1
Habib *et al.* (1967)	3	2
Sharpstone *et al.* (1968)	2	2
Monnens and Schretlen (1968)	4*	2
Gilchrist *et al.* (1969)	8	7
Katz *et al.* (1969)	4	2
Gilchrist and Liebermann (1969)	2	2
Total	37	27

*One patient received streptokinase before heparin.

TABLE II.—*Laboratory Findings in Three Cases of Haemolytic-Uraemic Syndrome*

	Case I	Case II	Case III
Blood:			
Hb (g./100 ml.)	4·5	6·2	7·3
Recticulocytes (%)*	16	16	14·4
Platelets/cu. mm.	175,000†	38,000	95,000
Red cell morphology	Fragmented cells and Burr cells	Fragmented cells and Burr cells	Fragmented cells and Burr cells
Fibrin-degradation products (μg./ml.)‡ (Merskey *et al.*, 1966)	30	Not measured	27
Urea (mg./100 ml.)	450	315	324
Bicarbonate (mEq/l.)	16	23·5	11
Potassium (mEq/l.)	5·5	4·5	7·7
Urine:			
Protein (mg./100 ml.)	1,000	1,000	Anuric
R.B.C./cu. mm.	6	80	Anuric

*Maximum count recorded during the illness.
†He had already received heparin therapy.
‡Normal levels for our laboratory: mean 3·7 μg./ml., range 0-8 μg./ml.

Intravenous heparin therapy was continued, being given six-hourly in an initial dose of 8,000 units, the subsequent doses being adjusted to maintain the blood-clotting time between 20 and 30 minutes. He was transfused with 1,000 ml. of whole blood, and peritoneal dialysis was started. He developed congestive cardiac failure owing to increasing hypertension, which was treated with parenteral guanethidine and later oral bethanidine. His urine output steadily declined and he was completely anuric from the tenth day after admission. The next day he became delirious, three days later he had a generalized convulsion and thereafter he remained drowsy and confused. His blood urea fell steadily and was maintained around 100 mg./100 ml. by dialysis for eight hours a day. His platelet count remained above 100,000/cu. mm., except on two