Virchows Arch [Pathol Anat] (1981) 393:75–91

Virchows Archiv A
© Springer-Verlag 1981

Mononuclear Stromal Reactions in Mammary Carcinoma, with Special Reference to Medullary Carcinomas with a Lymphoid Infiltrate

Analysis of 108 Cases

R. Bässler*, A.M. Dittmann, and M. Dittrich
Institute of Pathology, Städt. Kliniken Fulda, D-6400 Fulda, Federal Republic of Germany

Summary. One hundred and eight breast carcinomas were investigated to determine the frequency and intensity of mononuclear stromal reactions in different types of breast cancer, including the cytopathology of the lymphoid stroma in medullary carcinoma. The mononuclear infiltrates were analysed microscopically in the invasive area of the carcinoma and in the surrounding connective and fat tissue. The results were correlated and investigated statistically by different tests.

1. Invasive breast cancer shows slight or medium mononuclear stromal reactions in the marginal zones of the tumors in 61.6%. In 19.2%, infiltrates of the surrounding tissue were absent, and in 19.2% the cell reactions were strong. The values agree with investigations in the literature which give average values for lack of infiltration of 22.3%, for slight or medium degree reaction, 62.2% and for strong reaction 15.4%.

2. It can be seen by comparison of the different types of carcinoma, that medullary carcinoma with lymphoid stroma is significantly different from all other types. These cannot be further differentiated by the degree of infiltration because there is a relatively homogenous distribution of average values.

3. Intensive stromal reactions are not only a sign of immunological defense reactions but may also be induced by necrosis and metaplasias. We found positive correlations between the degree of malignancy of the syncytial cords of the medullary carcinoma and their circumscription.

4. Medullary carcinomata are subclassified in three types: 1. Medullary carcinoma with lymphoid stroma, a circumscript tumor surrounded by capsule-like connective tissue. 2. Atypical medullary carcinoma with irregularly developed lymphoid stroma and incomplete capsule. 3. Medullary components in invasive ductal carcinoma with circumscribed shape.

* Dedicated as a mark of friendship and respect to my teacher in honour, Professor Dr. H. Bredt, of his 75th birthday

Offprint requests to: Prof. Dr. R. Bässler, Pathologisches Institut der Städt. Kliniken Fulda, D-6400 Fulda, Pacelli-Allee 4, Federal Republic of Germany

0340-1227/81/0393/0075/$03.40

5. The lymphoid stroma of medullary carcinoma shows a different density and pattern. Lymphocytes tend to form round infiltrations whereas plasma cells occur in band formations. In the surroundings of the tumors lymphocytes predominate, while in the center of the carcinoma plasma cells and mixed infiltrations are observed. The prognosis is favorable. From the reported results it is concluded that immune reactions occur in and around the tumor and in the regional nodes, or in the blood, but these hostreactions can only be analysed when it is possible to determine tumor-specific-antigens in the carcinoma.

Key words: Breast cancer – Stroma reaction – Medullary breast cancer – Subclassification

Introduction

This paper details histopathological, cytological and statistical investigations carried out to establish how frequently there is a mononuclear cell infiltrate in the stroma around the different types of mammary carcinoma, the intensity of the reaction and the characteristic cytopathological features of the infiltrate around medullary carcinoma. Our objective was to establish the histological features that allow the quantitative and qualitative assessment of the immune reaction to mammary tumors.

The mononuclear stromal reaction around tumors has been known for decades as "small cell infiltration", was thought to be associated with destructive tumour growth or an accompanying inflammatory reaction. It was first given importance in the assessment of the prognosis by McCarty (1922) and Sistrunk and McCarty (1922). Böhmig (1930) in his investigations into the part played by the mesenchymal elements of tumours recognised 3 types of stroma: the "stroma" of the tissue in which the tumour grows, the stroma of the tumour itself and the surrounding stroma, i.e., the reaction to the tumour. This latter includes the so-called "small cell reaction" around the periphery of the neoplasm, which is assumed to be a local defense reaction or immune reaction.

The question of defense reaction identifiable on histological criteria was re-examined by Black et al. in the years 1953 to 1973. They identified a) the lymphocytic stromal infiltrate around tumours b) the perivenous infiltration c) the sinus histiocytosis of the axillary lymph nodes. Their conclusion was that the small cell infiltration was dependent on the tumour as well as on the nature of the host tissue and that it was a non-specific local defence reaction or manifestation of immunity.

These cellular reactions around the carcinomas as well as in the tumour stroma (medullary carcinomas with lymphoid stroma, Moore and Foote 1949) have been regarded by some as giving a more favourable prognosis (Black et al. 1963, 1969) while others have been skeptical. Kister et al. (1969), Champion et al. (1972) and Flores et al. (1974) found them to be of no prognostic value. Recent studies by Heidenreich et al. (1979) using immunological surface markers of lymphocytes and histological variables in cases where the tumours were staged clinically, also failed to show any correlation between the immunological findings, histological criteria and prognosis.

Materials and Methods

1. Analysis and Statistical Evaluation of the Momonuclear Stromal Reaction Surrounding the Carcinomas. Operation specimens from 78 cases of mammary carcinoma from the years 1975 and 1976 were examined by a quantitative cytological method. Any specimens that were not well preserved at the margin or that did not include a sufficiently wide margin around the tumour were rejected. Sections were stained by HE, PAS and van Gieson-Resorcin. Tumours were classified, according our own histological classification (Bässler 1978) into:

a) invasive ductal and invasive lobular carcinomas ($n = 30$);

b) intraductal carcinomas ($n = 30$);

c) invasive carcinomas with special types of differentiation ($n = 18$).

Counts were done using a Visopan (Reichert) projection-microscope with a magnification of 25×. To facilitate counting and to standardise the area counted a home made grid was used, made from a sheet of transparent plastic measuring 6.25 × 6.25 cm, divided into 16 squares, each 15.6 × 15.6 mm. It was fixed to the projection screen. The area was equivalent to a piece of tissue 16 × 50 × 50 µ, equivalent to 200 × 200 µ. Lymphocytes were counted in a field at the margin of the tumour measuring 100 × 200 µ and in an adjoining field of fibrous and fatty tissue of the same size. Ten large fields (200 × 200 µ) were selected at random per case (Fig. 1).

Evaluation: For every case the mean value, the standard variation, the variance, and the 95% confidence limits were calculated. The mean values were compared using the t-test and the significance of the findings was assessed (Dittmann 1979).

2. Statistical Evaluation of the Investigations Into the Lymphoid Stromal Reactions in Medullary Carcinomas. Material from 30 cases of medullary carcinomas with lymphoid stroma was available. Sections were prepared from both the central part of the tumour and from an area outside of the core of the tumour after staining by HE, van Gieson-Resorcin, PAS, Methylgreen-Pyronine and o-Toluidine. The point countin method of Chalkeley (1943) was used to estimate the proportional volumes. Ten different areas were counted, both at the centre of the tumour and next to the tumour margin. Lymphocytes, plasma-cells, pyronin positive cells and mast cells were counted separately before estimating the mean values for the numbers of lymphocytes and plasma cells. Out of a total of 30 cases examined 22 could be properly assessed. The individual results and the mean values are tabulated (Dittrich 1980).

In view of the small number of areas sampled the results were evaluated by the Wilcoxon test for differences between pairs. Our aim was to establish whether the distribution pattern of the infiltrating cells was statistically significant. The evaluation was carried out for both lymphocytes and plasma cells.

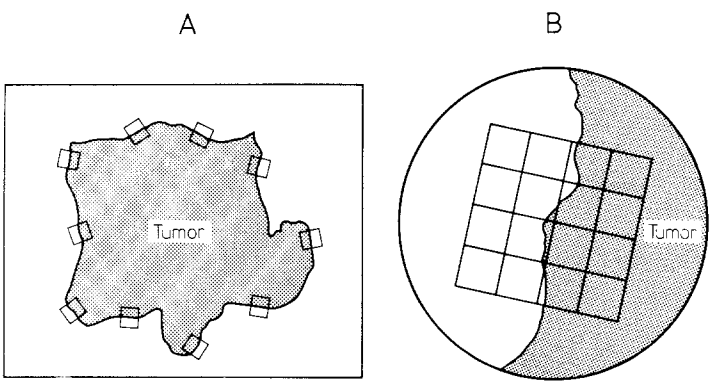

Fig. 1 a, b. Schematic representation of method of counting mononuclear cells at periphery of tumour. **a** Tumour with drawing of 10 fields. **b** Tumour margin with grid, half over tumour, half over adjoining stroma

Results of the Quantitative Investigations of the Mononuclear Stromal Reactions

1. Mean Values for Lymphocyte Numbers at the Margin of Different Types of Tumour

Calculation of the coefficient of variation established that it was usually high in relation to the mean value, thus excluding a Poisson type of distribution. This indicates that there is sometimes a lot of scatter between the n_a points. In view of this more reliable results can be obtained by calculating the mean values by taking the square root of the actual numbers counted. The results for the mean value $\bar{x}$, the standard deviation s and the average error of the mean value are shown in Table 1 for each type of tumours with n cases.

2. Comparison of Mean Values (t-Test) and Evaluation

It is clear from the results obtained that medullary carcinomas with a lymphoid stroma form a separate group. All the other types of tumour differ from this with regard to marginal lymphocytic infiltration.

Tumours other than medullary carcinomas do not form a homogeneous group. Attempts to classify them by their mean values (Table 2) for round cell infiltration, according to the numbers of lymphocytes present, did not give results that were statistically significant.

3. Distribution of Cell Concentrations (%)

To give a better picture of the lymphocytic infiltration around tumours, the following procedure was adapted with regard to the mean value of $\bar{x}_a$ but without reference to the histological classification –

Table 1. Number of lymphocytes in mammary carcinoma (see text)

Tumour classification		Mean value		Standard deviation	Mean error[a]
Group	Type		$\bar{x}$	S	$\frac{S}{\sqrt{n}}$
A = invasive ductal and lobular	solid-scirrhous	10	5.8505	1.9556	0.6184
	small cell-	10	3.6987	1.2470	0.3943
	mixed	10	4.9897	2.0530	0.6492
B = intraductal	comedocarcinoma	10	4.3343	1.1945	0.3777
	cribriform	10	4.5849	2.2283	0.7047
	papillary	5	2.3903	1.0877	0.4864
	mixed type	5	3.0860	0.8037	0.3594
C = special differentiation	mucinous	8	2.4118	0.4578	0.1618
	medullary with lymphoid stroma	10	11.5244	2.1599	0.6830

[a] Mean value = $\bar{x}$, Standard deviation = s, Average error of mean value = $\frac{S}{\sqrt{n}}$

Table 2. Average number of lymphocytes, based on the mean value $\bar{x}$ for the area counted

Medullary carcinoma with lymphoid stroma	11.52
Solid – scirrhous carcinoma	5.85
Mixed forms of invasive duct carcinoma	4.98
Cribriform – solid carcinoma (intraduct carcinomas)	4.59
Comedocarcinoma	4.53
Small cell (lobular) carcinoma	3.70
Mixed types of invasive intraduct carcinoma	3.09
Mucinous carcinoma (Colloid carcinoma)	2.41
Papillary carcinoma	2.39

Table 3. Percentage distribution of cases according to the density of the lymphocytic infiltrate. (x_a = mean value for number of lymphocytes)

x_a	0–5	6–50	51–
	no lymphocytic infiltrate 19.2%	slight to moderate infiltrate 61.6%	heavy infiltrate 19.2%

$\bar{x}_a \leq 5$: no lymphocytic infiltration
$6 \leq \bar{x}_a \leq 50$: slight to moderate lymphocytic infiltration
$\bar{x}_a \geq 51$: heavy lymphocytic infiltration

This gave the following percentages: no lymphocytic infiltration 19.2%, slight to moderate infiltration 61.6%, heavy infiltration 19.2% (see Table 3).

2. Quantitative Cytological Investigations of the Lymphoid Stroma of Medullary Carcinomas

After cytomorphological identification cells were counted in a predetermined area and the numbers for each area were recorded. The values obtained varied between less than 10 to more than 250 per field. The mean values were calculated for the different fields for each carcinoma, for both lymphocytes and plasma cells. In 12 cases mainly lymphocytes were found in the central part of the tumour, in two cases there were roughly equal numbers of lymphocytes and plasma cells while in 10 cases plasma cells outnumbered lymphocytes. Adjoining the tumour margins lymphocytes were in the majority in 20 cases, while in 2 cases there were about equal numbers. In 14 our of 22 cases there was a distinctly higher lymphocyte concentration at the tumour edge than at the centre, however plasma cells showed a higher concentration at the centre of the tumour. In order to study the cell concentrations in the infiltrate further they were classified, according to site, for cases with 50 to 100 cells. No connection could be established between the density of the infiltrate and the diameter of the tumour or the age of the patient.

By applying the appropriate statistical tests it could be demonstrated that there was a significant increase in the frequency with which *lymphocytes were more numerous at the tumour edge and plasma cells more numerous at the tumour centre.* It can be accepted that in medullary carcinoma of the breast there is *a definite pattern for the distribution of the cellular infiltrate.*

Discussion

1. Histopathology of the Mononuclear Stromal Reaction

As a rule, in mammary carcinoma, round cell infiltration is noted at the periphery, in the area where the growing tumour is surrounded by connective tissue and fat. Histopathological investigations establish that this infiltrate is slight or moderately severe in the majory of breast carcinomas and that it is absent in 19.2% of cases. By the application of statistical methods it can be established that medullary carcinoma with a lymphocytic stroma forms a homogenous group, unlike all the other histological types of breast tumours. The group with heavy lymphocytic infiltration includes medullary carcinomas with lymphoid stroma and a few invasive duct carcinomas as well as intraduct carcinomas with an unusually marked stromal mononuclear reaction. The latter resembles lymph nodes and occasionally even includes germinal centres. In the case of intraduct carcinomas (non-invasive and invasive), the cellular infiltrate accompanies the ducts in the circumductal stroma, sometimes as a mixture of lymphocytes and plasma cells, or there may be a very dense cellular infiltrate completely surrounding the ducts (Fig. 3). If some normal glandular acini survive in an area infiltrated by a carcinoma then it is usual for the round cell infiltrate to be very heavy in the area where the acini are and for it to cover them completely. The quantitative studies done on 78 mammary carcinomas are in substantial agreement with the work of Schiødt (1966) reporting on 303 carcinomas and the work of Fisher et al. (1975) who did a visual assessment on 1000 invasive mammary carcinomas.

The grading we used to assess the density of cellular infiltration was established from preliminary studies (Fig. 2), it was then used to make more valid comparisons. When comparing the results obtained by authors using different methods it is apparent that there is substantial agreement on proportions of tumors in the group without any cellular infiltrate and the group with a light or moderate infiltrate. In the group with a marked cellular infiltrate there is a significant difference between the findings of von Schiødt (1966) and our own, which are approximately twice as high as his (Table 4).

The findings show that on average 22.3% of mammary carcinomas show no mononuclear cell infiltrate in the zone of tumour proliferation, 62.2% a slight or moderate infiltrate and 15.4% an intense mononuclear cell infiltrate. It was not possible to relate different types of carcinoma or groups of tumours to the intensity of the cellular infiltrate. Carcinomas with no stromal reaction included some from the large group of invasive ductal carcinomas (papillary carcinomas) and special types of differentiation, such as mucinous carcinoma. The second group, with slight or moderately heavy cellular infiltrate, includes the majority of invasive and non-invasive ductal and lobular carcinomas.

A heavy cellular infiltrate was noted in medullary and circumscribed carcinomas (Fig. 4) and only rarely in invasive duct carcinomas or in tumours with necrosis.

It follows that the intensity of the mononuclear stromal reaction is an indication of an immunological reaction to a growing tumour and that it is influenced by local factors in the tumour. These include necrosis and metaplasia, although extensive necrosis can occur without any lymphocytic infiltration (Schiødt 1966). A further

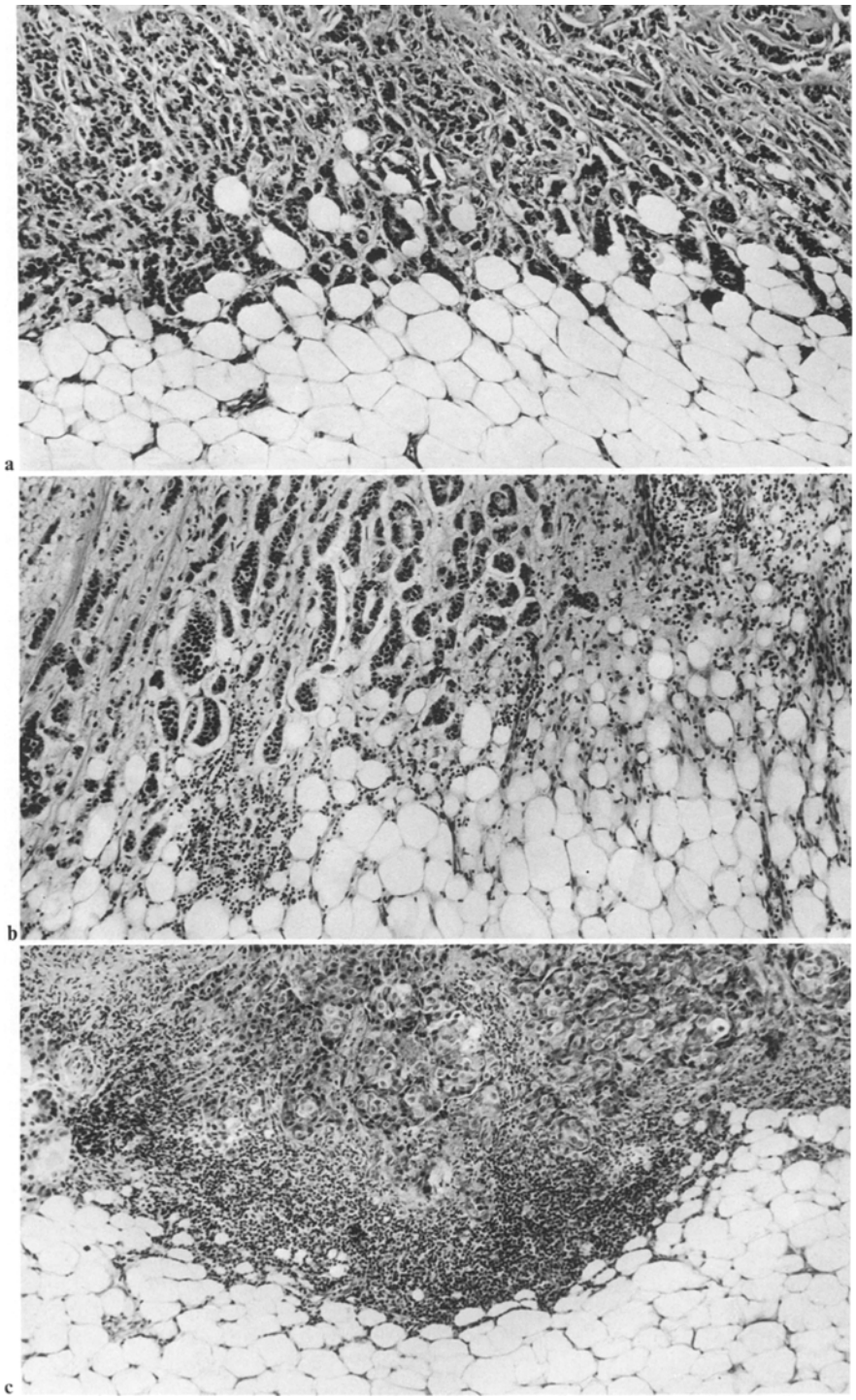

Fig. 2a–c. Tumour margins of invasive ductal carcinomas lacking any mononuclear infiltrate. (**a**) With slight infiltration (**b**); marked infiltration (**c**); in the surrounding of a medullary part of a tumour. Formalin, Paraffin, HE, Magnification ×160

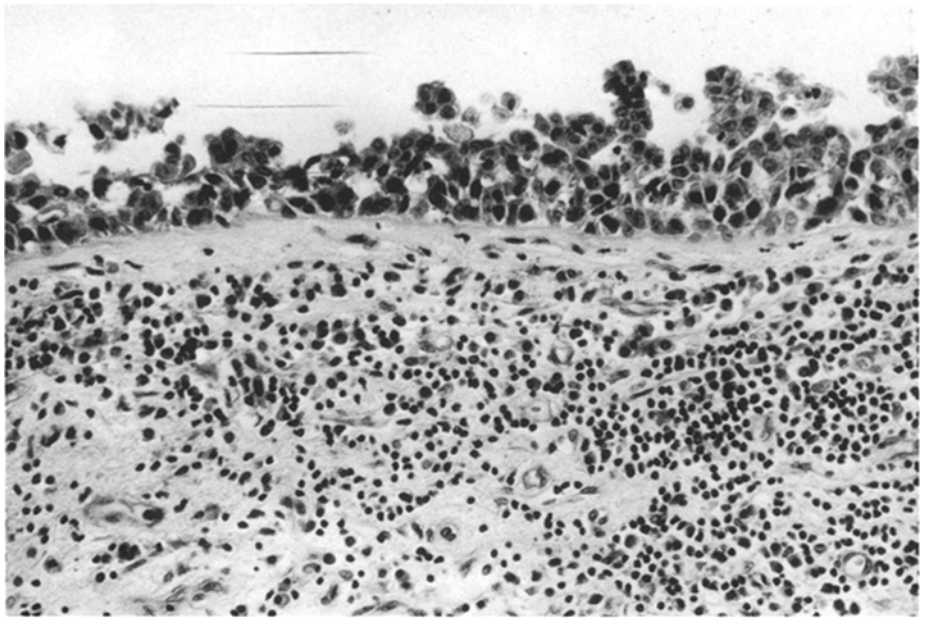

Fig. 3. Heavy lymphoplasmocytic infiltrate around a non-invasive intraduct carcinoma. Formalin, Paraffin, HE, Magification ×220

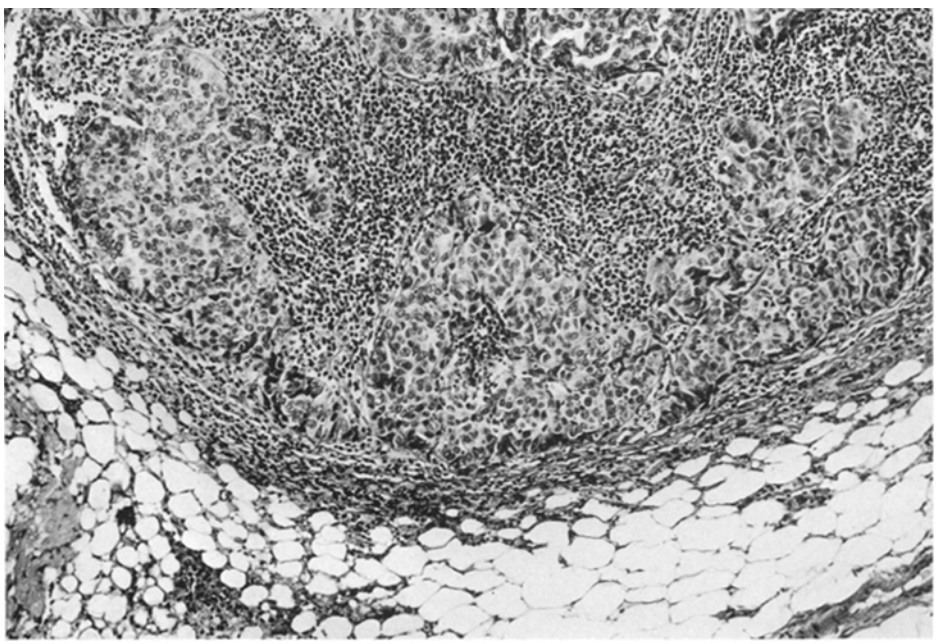

Fig. 4. Field including margin of circumscribed medullary carcinoma with lymphoid infiltrate (Type I) and connective tissue capsule. Formalin, Paraffin, HE, Magnification ×140

Table 4. Percentage distribution of invasive mammary carcinomas according to density of lymphocytic infiltrate

Author	no lymphocytic infiltration	slight to moderately severe infiltration	heavy infiltration
Schiødt	23%	67%	10%
Fisher et al. (1975)	24.2%	58%	17%
Our own findings	19.2%	61.6%	19.2%
Average	22.3%	62.2%	15.4%

correlation noted by von Fisher et al. (1975) was the marked stromal infiltrate in large, circumscribed carcinomas of high grade malignancy (G 3; NG 1) (Black et al. 1955), occurring between the ages of 20 and 45, particularly in negroes. The above criteria apply particularly to medullary carcinomas, their high grade of malignancy appears to be the cause.

Cytomorphological Studies show that the infiltrate surrounding the tumour is composed predominantly of lymphocytes, or of mixed mononuclear cells. It is rare to find plasma cells predominating (Fig. 6, 7b). A mixed cellular infiltrate is also common in intraduct carcinomas (Fig. 3). According to Schiødt (1966) infiltrates were lymphocytic in 53% of cases, mixed in 29% and plasmacytic in 18%. The figures given by Fisher et al. (1975) are – lymphocytic infiltrate 46.7% mixed 26.7%, but plasmocytic in only 0.4% of cases. A further 2% had macrophages and granulocytes. Apart from the marked difference in the percentage of the plasmacytic infiltrate, there is good agreement.

Immunological Differentiation of the lymphocytes in invasive carcinomas by immunohistological methods was carried out by Schoorl et al. (1976). They found a predominance of T-lymphocytes. In intraduct carcinomas, however, there was a predominance of B-lymphocytes. Further studies of the subpopulations of lymphocytes were carried out by Howell et al. (1978). They reported 52% T-lymphocytes and 17% B-lymphocytes, in malignant tumours and 58% T-lymphocytes and 15% B-lymphocytes in benign tumours. These percentages are said to reflect the percentages present in the peripheral blood.

Mast cells in the stroma of tumours were investigated by Higuchi (1930), Simpson (1950), Hieronymi (1954), Fisher and Fisher (1965) and Leuschner (1969) as it was supposed that serotonin might influence the growth of tumours. These authors found an increase in the number of mast cells in the area where tumour and surrounding connective tissue meet and Fisher et al. (1965) proposed, on the basis of experimental work, that this might represent a defensive reaction. Hamlin (1968) found no positive associations.

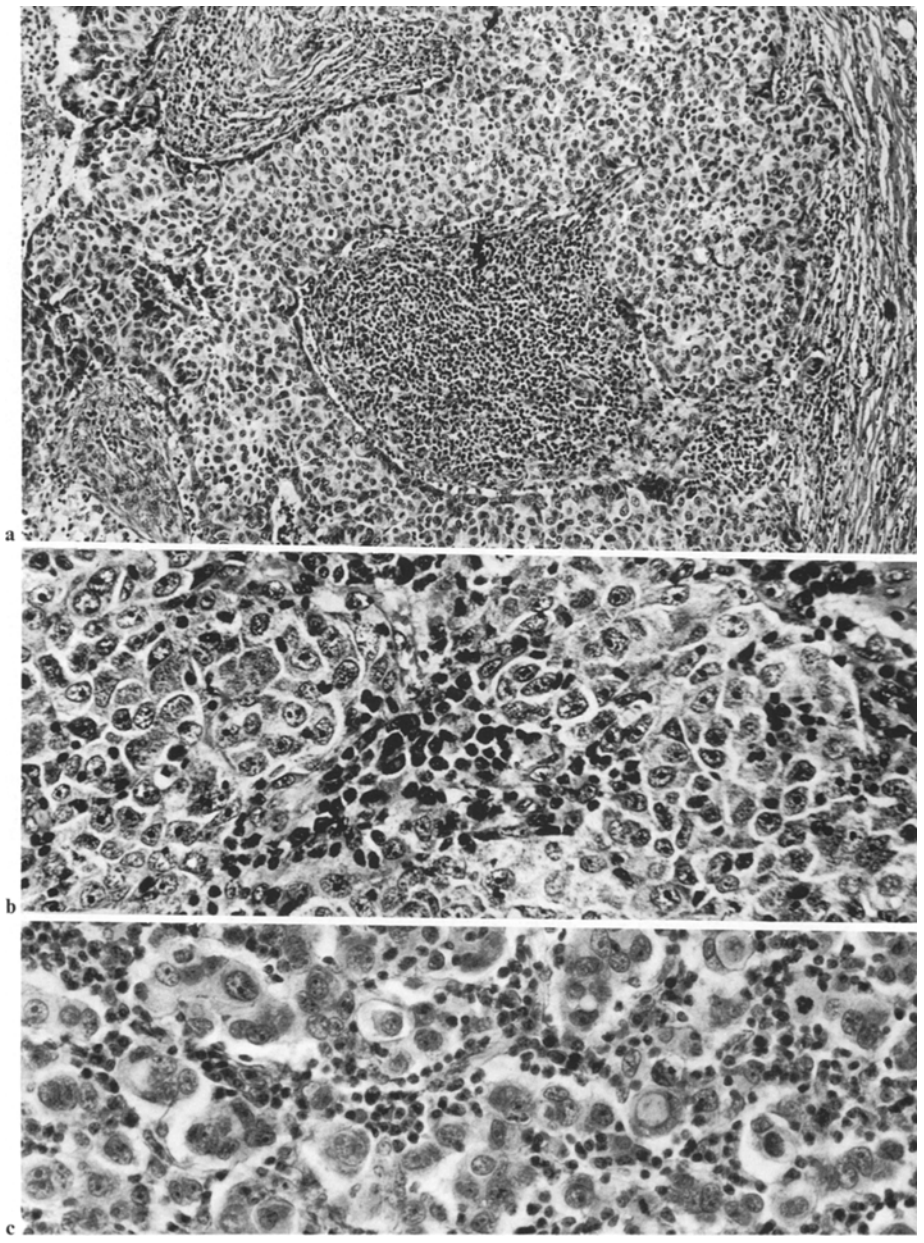

Fig. 5a–c. Medullary carcinoma lymphocytic stromal reaction showing differences in the appearance of the infiltrate. **a** Syncytial tumour with sharply demarcated lymphocytic infiltrate. **b** Focal collections of predominantly plasma cells. **c** Diffuse infiltration with separation of tumour cells into isolated groups and single cells. Formalin, Paraffin, HE, Magnification 140, ×220

Fig. 6. Medullary carcinoma with only a slight fibrous tissue reaction with a predominently plasma cell infiltrate that forms a cord-like pattern within the tumour parenchyma. Formalin, Paraffin, Methylgreen-Pyronine, Magnification ×40

2. Histopathology and Cytology of the Lymphoid Stroma of Medullary Carcinomas and Their Classification

An analysis of 30 medullary carcinomas shows that they constitute about 7% of all breast cancers. The mean diameter of the medullary carcinomas for the whole series wa 3.2 cm; if axillary nodes were present this rose to (n = 9) : 4.22 cm. The average age of the women was 54,3 years. (Ridolfi et al. 1977; Bässler 1978; Azzopardi 1979).

The lymphoid infiltrate completely fills the spaces between the groups of tumour cells and occasionally forms a follicular pattern with small germinal centres. Primary tumours can resemble lymph node metastases in some cases (Fig. 4). It is usual for the lymphoid infiltrate to extend from the tumour into the surrounding connective tissue and fatty tissue. In between the group of tumour cells that form band-like structures the lymphoid infiltrate has a sharp edge and in the case of predominantly lymphocytic infiltrates forms broad complexes and rounded foci (Figs. 5a, 7a, 9). Plasma cell infiltrates, or mixed infiltrates with plasma cells, form band-like structures (Figs. 6, 7b). The density of the infiltrates varies. In medullary carcinomas with the haviest infiltrate, groups of tumour cells and single tumour cells may be separated from each other by the infiltrate (Figs. 5b, 5c, 9).

Quantitative assessment of the different elements of the cellular infiltrate shows a distinct difference in composition when comparing the tumour centre with the tumour margin. This difference is statistically significant. In 20 out of 22 cases studied a prevalence of lymphocytes was found near the edge of the tumour, in two

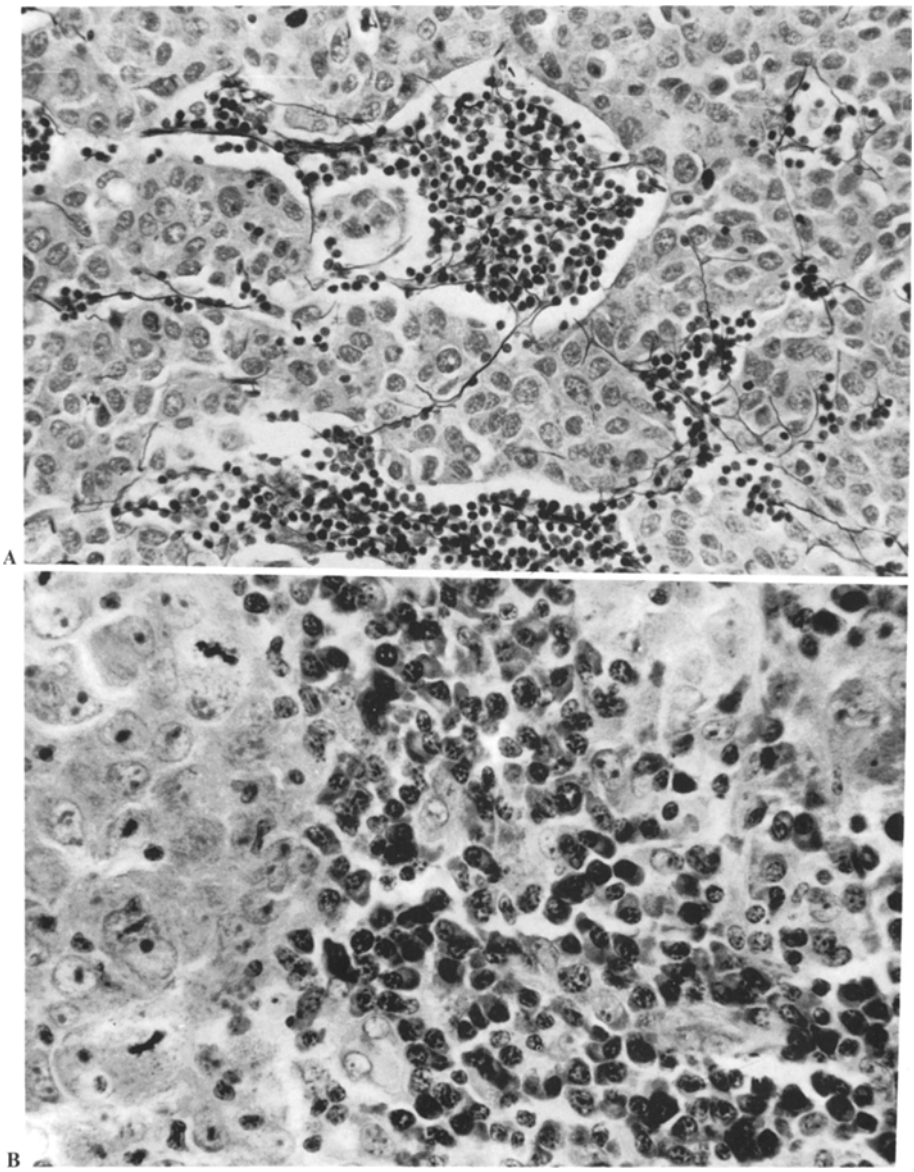

Fig. 7. A Medullary carcinoma with a lymphocytic infiltrate and loose fibrous tissue network where the infiltrate is and within the tumour parenchyma. Formalin, Paraffin Gomori / Neutral red Magnification ×230. **B** Plasmacytic infiltrate showing well defined margins, in the central part of the tumour. Formalin, Paraffin, Giemsa, Magnification ×310

cases were equal numbers of lymphocytes and plasma cells in this area, while in the other tumours there was a preponderance of plasma cells at the tumour centre. This predominance was associated with the formation of a complete pseudocapsule which delineated the tumour as a rounded bosselated or pushing type structure. This agrees with the term "circumscribed carcinoma" introduced by Haagensen

Table 5. Subclassifiation of medullary carcinoma of breast

Criteria	Type I Typical medullary carcinoma with lymphoid stroma	Type II Atypical medullary carcinoma with lymphoid stroma	Type III Medullary components in an invasive ductal, circumscribed carcinoma
Presence of pseudocapsule	++	±	−
Structure of tumour	uniform medullary	medullary (>75%)	medullary in part (<75%)
Tumor edge	well circumscribed	well circumscribed	parly circumscribed
Lymphoid infiltrate	+++	+ − ++	±
Intraduct and glandular components	−	+	+
Histologic grading	3	3/2	2/3
Nuclear grading	1	1/2	2/1
Lymph node secondaries 1–3 nodes[a]	14%	24%	23%
10 year survial[a]	84%	74%	63%

[a] Ridolfi et al. 1977

(1971). By noting the presence of a medullary structure in tumour and the appearance of the connective tissue at the margin of the carcinoma *three types* of carcinoma can be recognised; their histological characteristics and their prognosis are given in Table 5.

Types of medullary breast cancer:

1. *Typical medullary carcinoma with lymphoid stroma* that is cricumscribed and has a connective tissue (pseudo-)capsule.

2. *Atypical medullary carcinoma* with non-homogeneous lymphoid stroma and incomplete (pseudo-)capsule.

3. *Medullary components in invasive ductal carcinomas;* these tumours are often polycyclic or circumscribed.

The above classification shows that type I is characterized by three features:

1. a macroscopic rounded, circumscribed tumour,
2. a marked diffuse lymphoid stroma
3. a high nuclear grading of the epithelial elements (NG 1 according to Black).

The criteria are incomplete in the case of type II, tumour shape and nuclear grading are similar to type I (Fig. 9). They have a higher frequency of axillary metastases (more than 4 nodes: Fisher 1977; Ridolfi et al. 1977). Type III is an invasive ductal carcinoma that includes medullary elements. Some are circumscribed, or have a dense mononuclear infiltrate. Only two of the criteria of type I are present, but in a partial form only. Ridolfi et al. (1977) designated these tumours "non-medullary infiltrating ductal carcinomas".

3. Prognostic Implications of the Mononuclear Stromal Reaction in Medullary Carcinomas

The findings of Schiødt (1966) and Fisher et al. (1975) and our own observations show that dense mononuclear infiltrates are usually associated with tumours of

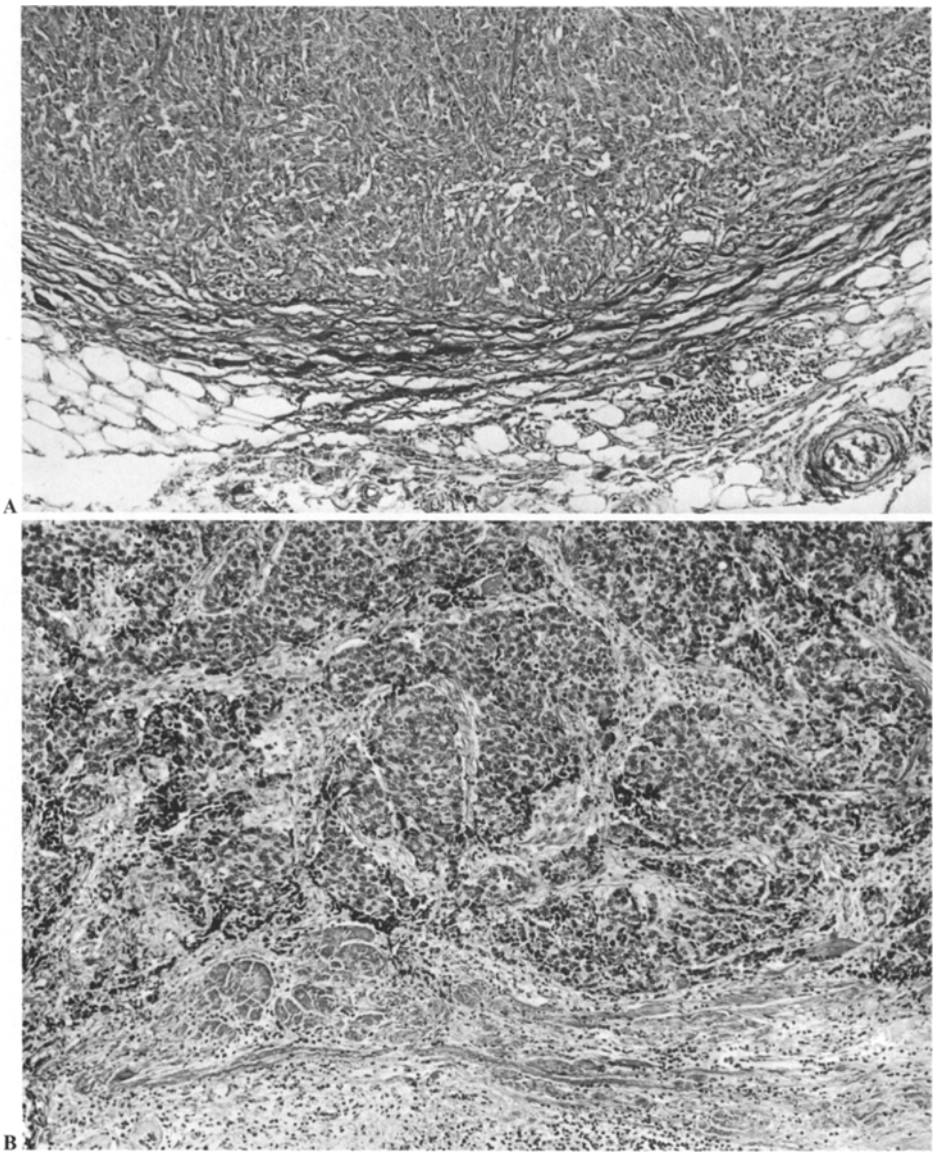

Fig. 8. **A** Outer edge of medullary carcinoma with lymphoid stroma Type I. Complete pseudocapsule formation. **B** Outer edge of atypical medullary carcinoma (Type II). It shows a clearly defined edge with little round cell infiltration in the manner of circumscribed carcinomas (Type II). Formalin, Paraffin, Elastic/van Gieson, HE, Magnification ×140

high grade malignancy, as confirmed by our study of medullary breast cancer. The dense capsule formed in medullary carcinoma of type I are a manifestation of a special stroma reaction that makes recognition of the type on naked eye examination. The studies of Ridolfi et al. (1977) have shown that the 10 years survival for medullary breat cancer with a lymphoid stroma (type I) is 84%, for

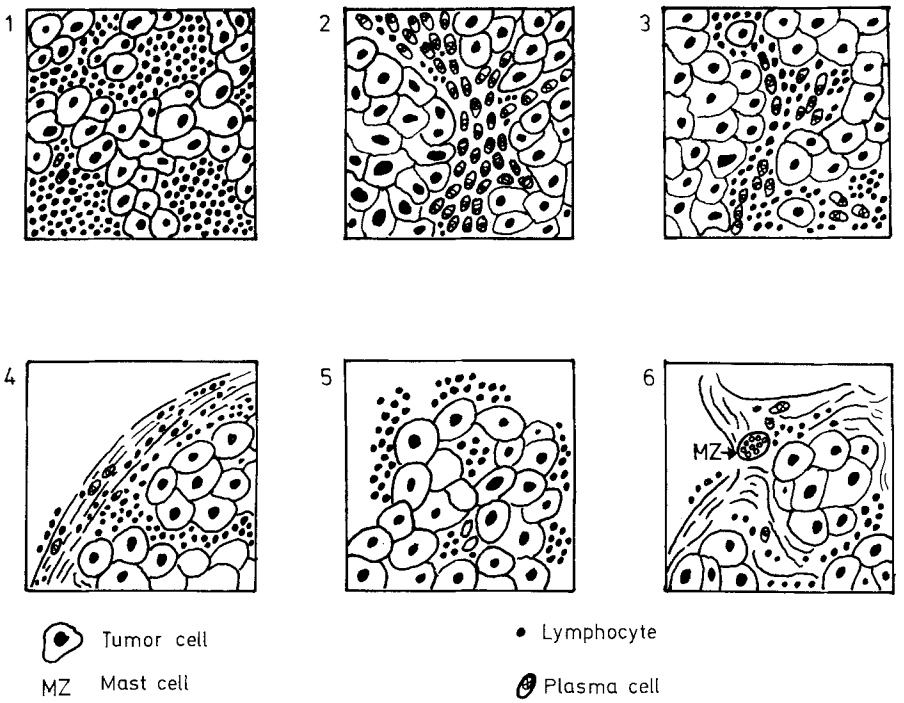

Fig. 9. Schematic representation of the shape of the cellular infiltrates and surrounding connective tissue. 1. Predominantly lymphocytic infiltrate showing a nodular, rounded type of distribution. 2. A mainly plasmacytic infiltrate showing a predominantly cord-like arrangement. 3. A mixed cellular infiltrate. 4. Connective tissue capsule around circumscribed medullary carcinoma, it is infiltrated by some lymphocytes and plasma cells (type I). 5. Margin of medullary carcinoma without any attempt at capsule formation (Type II). 6. Tumour with areas showing a medullary structure (Type III), there is some patchy condensation of connective tissue and infiltration by small numbers of mast cells (MZ)

atypical medullary carcinoma (type II) is 74%, and for the socalled non-medullary invasive ductal carcinoma (type III) 63%. In all three types deaths occured in the first five years after treatment. The above authors also esablished a connection between density of the cellular infiltrate and the 10 year survival, this also applied to the number of plasma cells present.

The Frequency of Axillary Lymph Node Metastases is not significantly lower in medullary breast cancer than in invasive ductal carcinoma, although there is a significantly better survival rate (Ridolfi et al. 1977). Our investigations show that axillary metastases were present in 43% of cases. In 9 cases of medullary carcinoma the mean diameter of the primary tumour was 4.22 cm. In 6 out of 9 cases one or two nodes were involved and the infiltrate at the centre of the carcinoma was composed predominantly of plasma cells. In 3 cases more than 4 lymph nodes were involved.

Even today, following intensive and manifold immunological studies of the mononuclear stroma reactions in breast cancer, there is no satisfactory interpretation of the findings. Dense lymphoplasmocytic infiltrates within the stroma of tumours are often clearly correlated with the degree of maligancy. The

relatively favourable prognosis could be due to cellular or humoral immunological defense mechanisms. Minor degrees of mononuclear infiltration, or the complete lack of a reaction suggest an absence of, or a weak antigenicity of the tumour, or possible the presence of blocking humoral factors. Only the isolation of tumour specific antigens will resolve the problem.

References

Alderson MR, Hamlin J, Staunton MD (1971) The relative significance of prognostic factors in breast carcinoma. Br J Cancer 25:646–656

Azzopardi JG (1979) Problems in breast pathology. WB Saunders Cp, London Philadelphia Toronto

Bässler R (1978) Pathologie der Brustdrüse. In: Spez pathologische Anatomie, Bd 11. Springer, Berlin-Heidelberg-New York

Berg JW (1956) Sinus histiocytosis: a fallacious measure of host resistance to cancer. Cancer 9:935–939

Berg JW (1971) Morphological evidence for immune response to breast cancer. Cancer 28:1453–1456

Black MM (1973) Human breast cancer. A model for cancer immunology. Isr J Med Sci 9:289–299

Black MM, Asire AA (1969) Palpable axillary lymph nodes in cancer of the breast. Cancer 23:251–259

Black MM, Kerpe S, Speer FD (1953) Lymph node structure in patients with cancer of the breast. Am J Pathol 29:505–517

Black MM, Leis Jr HP (1972) Cellular responses to autologous breast cancer tissue. Cancer 28:263–273

Black MM, Oper SR, Sperr FD (1955) Survival in breast cancer cases in relation to the structure of the primary tumor and regional lymph nodes. Surg Gynecol Obstet 100:543–551

Black MM, Speer FD (1958) Sinus histiocytosis of lymph nodes in cancer. Surg Gynecol Obstet 106:163–175

Black MM, Speer FD, Opler SR (1956) Structural representations of tumor-host relationships in mammary carcinoma Biologic and prognostic significance. Am J Clin Pathol 26:250–265

Böhmig R (1930) Das Krebsstroma und seine morphologischen Reaktionsformen. Beitr Pathol Anat 83:333–382

Champion HR, Wallace IWJ, Prescott RJ (1972) Histology in breast cancer prognosis. Br J Cancer 26:129–138

Cutler SJ, Black MM, Mork T, Harvei S, Freeman C (1969) Further observations on prognostic factors in cancer of the female breast. Cancer 24:653–667

Cutler SJ, Black MM, Goldenberg IS (1963) Prognostic factors in cancer of the female breast I. An investigation of some interrelations. Cancer 16:1589–1597

Dittmann AM (1979) Form und Häufigkeit lymphocytärer Randreaktionen bei verschiedenen Typen des Mammakarzinoms. Ein pathohistologischer Beitrag zur Tumorimmunologie. Inaug Diss Marburg

Dittrich M (1980) Beiträge zur Pathomorphologie der Formen des medullären Mammakarzinoms. Inaug Diss Marburg

Fisher E, Fisher B (1965) Role of mast cells in tumor growth. Arch Pathol 79:185–191

Fisher ER, Gregorio RM, Fisher B (1975) The pathology of invasive breast cancer. A syllabus derived from findings of the National Surgical Adjuvant Breast Project. (Protocol No 4) Cancer 36:1–85

Flores L, Arlen M, Elguezabal A, Livingston SF, Levowitz BS (1974) Host tumor relationships in medullary carcinoma of the breast. Surg Gynecol Obstet 139:683–688

Haagensen CD (1971) Diseases of the Breast, 2nd ed. WB Saunders, Philadelphia

Hamlin HM (1968) Possible host resistance in carcinoma of the breast. A histological study. Br J Cancer 22:383–401

Heidenreich W, Jagla K, Schüssler J, Börner P, Dehnhard F, Deinhardt J, Kalden J, Peter HH, Deicher H (1979) Immunological characterization of mononuclear cells and morphological findings in patients with mammary carcinoma. J Cancer Res Clin Oncol 95:65–74

Hieronymi G (1954) Über das Vorkommen und Verteilung saurer Mukopolysaccharide in Geschwülsten. Frankf Z Path 65:409–434

Higuchi K (1930) Die Gewebsmastzelle in der Mamma. Folia Haematol (Lpz) 40:401–414

Howell A, Snaala A, Ling NR (1978) Host cells in human breast tumours. Br J Cancer 38:185

Kister SJ, Sommers SC, Haagensen CD, Friedell GH, Cooley E, Varma A (1969) Nuclear grade and sinus histiocytosis in cancer of the breast. Cancer 23:570–575

Leuschner U (1969) Über die Lokalisation von Mucopolysacchariden und Mastzellen in skirrösen Karzinomen der Mamma. Acta Histochem 34:126–137

MacCarty WC (1922) Factors with influence longevity in cancer. A study of 293 cases. Ann Surg 76:9–12

Moore OS, Foote FW (1949) The relatively favorable prognosis of medullary carcinoma of the breast. Cancer 2:635–642

Ridolfi RL, Rosen PP, Port A, Kinne D, Miké V (1977) Medullary carcinoma of the breast. A clinicopathologic study with 10 year follow-up. Cancer 40:1365–1385

Schiødt T (1966) Breast carcinoma. A histologic and prognostic study of 650 followed-up cases. Munksgaard, Copenhagen

Schoorl R, de la Riviére AB, von dem Borne AEG, Feltkamp Vroom TM (1976) Identification of T and B lymphocytes in human breast cancer with immunhistochemical techniques. Am J Pathol 84:529–544

Sistrunk WE, MacCarty WC (1922) Life expectancy following radical amputation for carcinomaa of the breast a clinical and pathological study of 218 cases. Ann Surg 75:61–69

Accepted April 8, 1981