

# Lobular Carcinoma of the Female Breast

## Report of 73 Cases

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ONLY a small group of cases of infiltrating lobular carcinoma of the breast have been reported<sup>8</sup> since Foote and Stewart<sup>3,4</sup> described, named and illustrated this relatively uncommon, though distinctive, form of mammary cancer in women. Godwin,<sup>5</sup> Haagensen,<sup>6</sup> Miller and Kay,<sup>8</sup> and Newman<sup>10</sup> have presented cases showing the transition from *in situ* lobular to infiltrating lobular carcinoma, but there have been no papers detailing how frequently the often innocuous appearing residual lesions of *in situ* lobular carcinoma of the breast are found in mastectomy specimens once invasion of the stroma has taken place. Histologic evidence of antecedent, residual, *in situ* lobular carcinoma was found in 72 of 73 cases of infiltrating lobular carcinoma of the female breast seen at the George Washington University Hospital and is reported here.

### Selection of Material

The 73 cases that comprise the data for this paper were selected by examining *all* slides from *all* cases of carcinoma of the breast seen at the present George Washington University Hospital from April 1948 through August 1, 1965.

The slides from 1,436 cases of carcinoma of the female breast were studied. Forty cases which showed *only in situ* lobular

carcinoma in the biopsy or mastectomy specimens or both were excluded from the present study, 32 of these having been reported previously.<sup>10</sup> Two included cases (28 and 66) had been presented as Cases 3 and 18, respectively, in the 1963 paper.<sup>10</sup> Case 10 of the original *in situ* group<sup>10</sup> was reported recently.<sup>2</sup> These 73 cases, then, were culled from 1,396 cases of carcinoma of the female breast and represent 5.2 per cent of the total cases of breast cancer seen at the George Washington University Hospital. In the preliminary survey of the 1,396 cases, 142 having either a terminal duct and/or lobular pattern were set aside for further review. This group was then restudied in much greater detail and 73 representing a "pure" group of infiltrating lobular carcinomas were selected for this report. This "pure" group was established by excluding those cases in which the terminal duct elements contributed a major component to the tumor. If there was duct formation in areas of stromal invasion, or if the single cell feature was not the most prominent element in either the breast tissue or nodal metastases (where positive nodes were found), the case was excluded from the final "pure" grouping. If the bulk of the infiltrating tumor was of terminal duct origin, even though *in situ* lobular and infiltrating lobular carcinoma were also present, the case was also excluded. We recognize that the point at which a terminal duct becomes a lobule is highly

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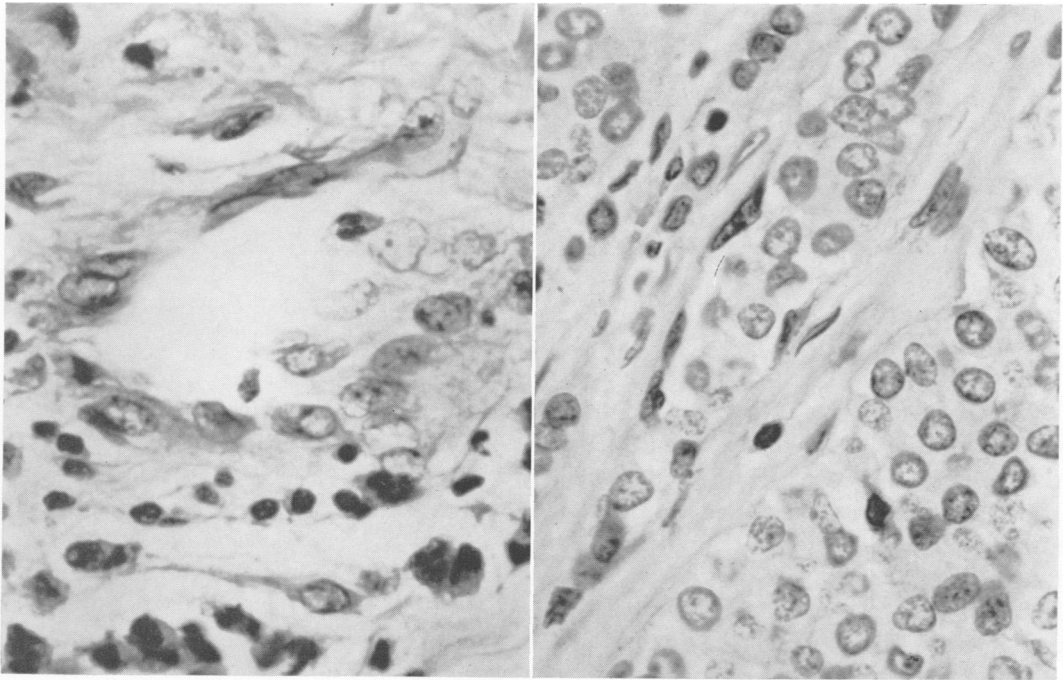


FIG. 1. Case 37. Vascular invasion in patient with negative axillary nodes who died of disseminated infiltrating lobular carcinoma.  $\times 610$ .

FIG. 2. Case 48. Vascular invasion in patient with negative axillary nodes.  $\times 610$ .

subjective and somewhat arbitrary, but we were attempting to set up as "pure" a group of cases representing the *single cell pattern* of infiltrating lobular carcinoma as was possible. Using these highly rigid criteria, the original group of 142 cases with a prominent terminal duct or lobular pattern or both (10.2%), was reduced to the 73 cases that comprise the data for this paper (5.2%). Except for a few photomicrographs emphasizing specific points, we do not intend to repeat the descriptions and photomicrographs already available in the literature<sup>2-7, 10, 13</sup> for both *in situ* lobular and infiltrating lobular carcinoma. These cases represent 70 patients (three bilateral "pure" infiltrating lobular carcinomas) plus four additional patients who had second primaries of duct type, for an overall incidence of second primaries in this series of 10 per cent.<sup>12</sup> All patients are Caucasian except four (Cases 10, 12, 63, 65). Thirty-five cases involved

the right breast, 37 involved the left breast and in one case of a submitted slide (Case 53), the side was not stated.

#### Pertinent Data and Findings

The average age of these patients is 48.3 years as against an average age of 45 years for the patients with no invasion.<sup>10</sup> Ages ranged from 29-83 years (see discussion). Twenty-one patients were menopausal or post-menopausal, 52 were pre-menopausal. Thirty-seven patients had positive axillary nodes, 36 had negative nodes in mastectomy specimens. Eighteen of 37 cases with positive axillary nodes are dead (one double primary with positive nodes in each axilla, Cases 45 and 55); one patient died of a second primary carcinoma of the stomach (Case 9). Thirty-one of 36 cases with negative axillary nodes are free of disease as of August 1, 1965. Two patients had bilateral infiltrating lobular carcinomas with negative axillary nodes on each side (Cases

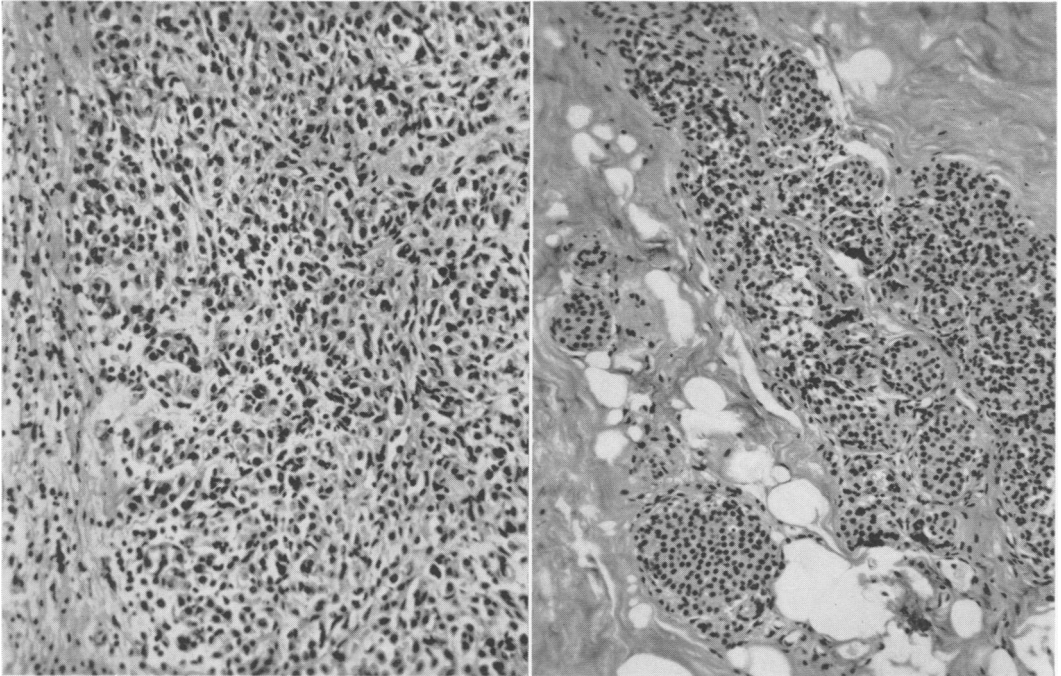


FIG. 3. Case 29. Infiltrating lobular carcinoma, left breast.  $\times 112$ .

FIG. 4. Case 29. Biopsy of right breast taken at time of left mastectomy. *In situ* lobular carcinoma.  $\times 98$ .

29, 36; Cases 42, 56). Eighteen of 37 cases with positive axillary nodes are alive (17 NED). Five of thirty-six cases with negative axillary nodes in mastectomy specimens are dead, emphasizing the value in terms of prognosis of an extended search for vascular invasion when reporting carcinoma of the breast where axillary nodes are negative.

#### Discussion

The finding of areas of residual *in situ* lobular carcinoma in 72 of 73 cases of "pure" infiltrating lobular carcinoma in mastectomy specimens, once stromal invasion has occurred, indicates that a "let's wait and see" attitude toward these innocuous-appearing, "early" lesions in breast tissue is not justified. Based on this study of 1,396 cases of breast cancer, lobular patterns of female breast cancer occur more frequently than reported previously.<sup>8</sup> This disparity may be attributed to differences

in sampling of breast cancer (including peripheral beds), in the number of random sections from all quadrants and in the detail with which one studies this material. Also, the concept of lobular carcinoma as a distinctive form of female breast cancer may still not be appreciated or accepted by many pathologists and surgeons despite its delineation by Foote and Stewart.<sup>3, 4</sup> A large volume of material must be examined to appreciate the transitions between *in situ* and infiltrating lobular carcinoma.

We are satisfied that when *in situ* lobular carcinoma is diagnosed treatment should be prompt and vigorous to forestall the ravages of invasive cancer. Therapy for this lesion, once confirmed by permanent section (hazards of frozen section diagnosis have been detailed by Stewart,<sup>18</sup> Newman<sup>10</sup> and Benfield, Jacobson and Warner<sup>2</sup>), should consist of a modified simple mastectomy plus a random biopsy

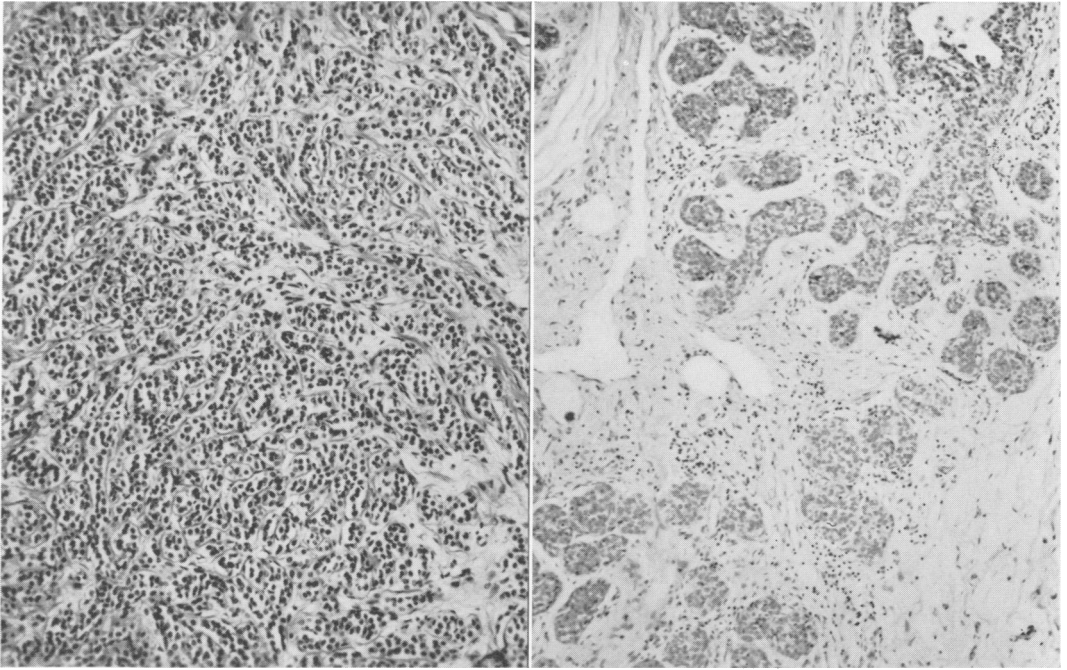


FIG. 5. Case 36. Infiltrating lobular carcinoma of right breast, 13 months after original biopsy. See Figure 4 above.  $\times 98$ .

FIG. 6. Case 66. Biopsy right breast 1960 showing *in situ* lobular carcinoma. No evidence of invasion in biopsy or mastectomy.  $\times 63$ .

of the upper outer quadrant of the opposite breast at the time of mastectomy. All breast tissue plus low-lying, adjacent, level I nodes should be removed but the pectoral muscles left intact. If the biopsy is positive the procedure should be repeated on the second breast; if the biopsy is negative, periodic follow up by means of mammography and thermography, as well as manual examinations, is recommended. The use of the modified simple mastectomy obviates the need for additional surgery if a small focus of invasion is found in the mastectomy specimen since the closest drainage area would already have been removed.

When invasive cancer has been proved by frozen section at biopsy, a classical Halsted-Meyer radical mastectomy is per-

formed. If on permanent section the tumor is infiltrating lobular carcinoma and shows extensive areas of *in situ* lobular carcinoma, we recommend a mammogram of the remaining breast. If a suspicious area is found we suggest biopsy of that site. If the mammogram is negative, we suggest a random biopsy of the upper outer quadrant, thereafter following the same procedures outlined for the *in situ* lesion.

Once invasion of the stroma has taken place the sequence of events is essentially similar to that of the more frequent types of duct carcinoma. This has been emphasized previously by Stewart.<sup>13</sup>

As with duct carcinomas, younger patients fared poorly.<sup>12</sup> Those with many positive nodes invariably did poorly (though occasionally a "long-term" survival is seen

FIG. 7. Case 66. Biopsy of "nodule" at lower inner end of right simple mastectomy scar 4 years after operation. Thought to be a neuroma or a suture granuloma. Note residual breast ducts plus *in situ* and infiltrating lobular carcinoma.  $\times 105$ .

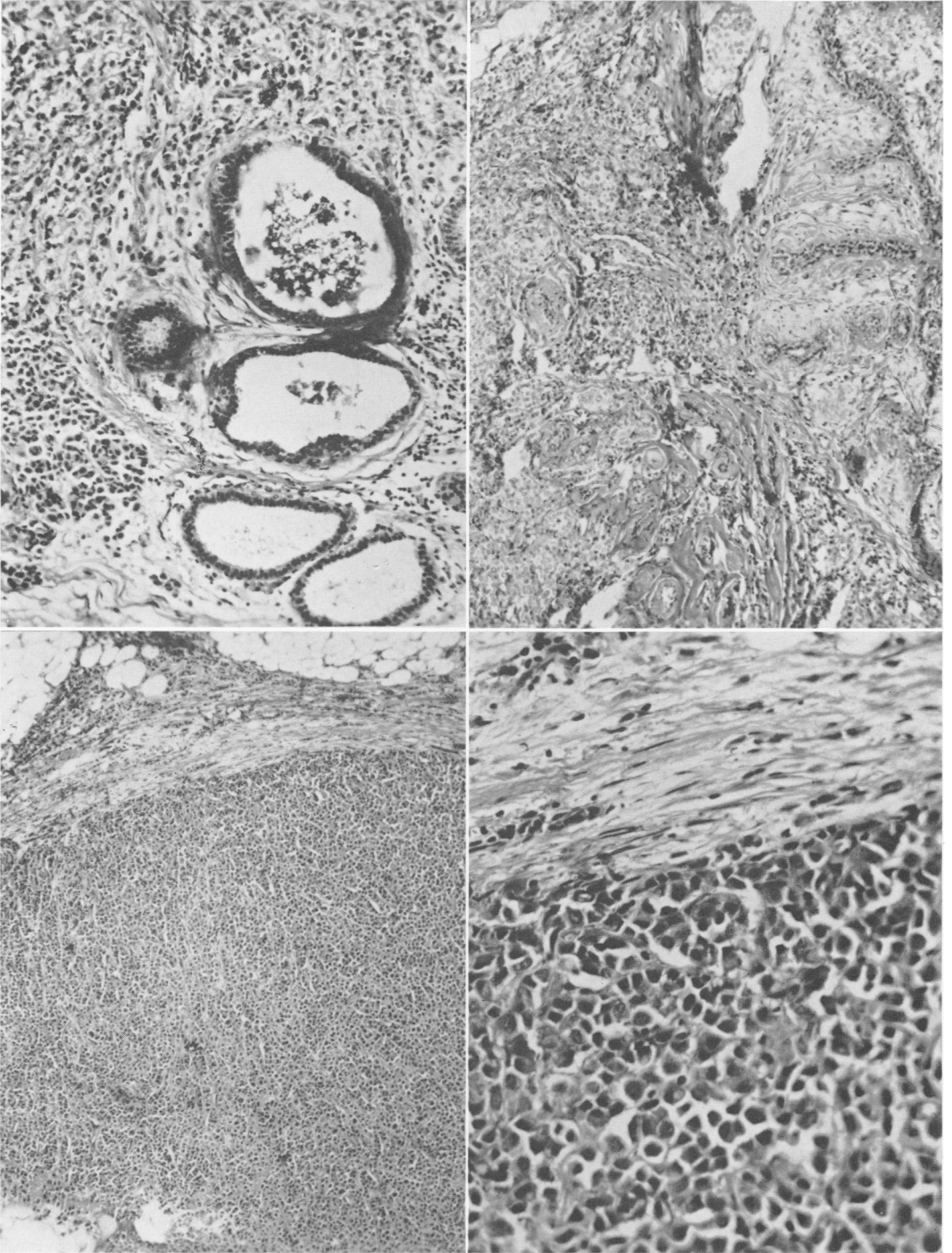


FIG. 8. Case 66. Focus of residual breast tissue (including small fibroadenoma) with *in situ* and infiltrating lobular carcinoma in "nodule" from end of mastectomy scar.  $\times 63$ .

FIG. 9. Case 66. Right supraclavicular node and adjacent fat showing metastatic lobular carcinoma breast.  $\times 50$ .

FIG. 10. Case 66. Higher power showing single cell pattern in node sometimes mistaken for reticulum cell sarcoma.  $\times 255$ .

TABLE 1. *Infiltrating Lobular Carcinoma Breast Showing Residual in Situ Lobular Carcinoma*

Case	Initials	Age @ Mast.	Side	Axillary Nodes	Follow-up*	Comment
1	M. N. L.	49	R	+ 3/28	NED '65	17 yr. survival with positive nodes.
2	M. E. P.	55	L	- 0/18	NED '65	17 yr. survival.
3	R. T.	66	R	+27/33	DOD '51	Died 20 months after mastectomy.
4	J. T.	49	L	- 0/19	NED '65	16 yr. survival. 3 separate distinct masses found in breast.
5	M. C.	72	R	+ 5/21	DOD '51	Died 2 yr. after mastectomy. See text for discussion of age and terminal duct involvement.
6	E. R.	42	R	+ 1/20	NED '65	16 yr. survival with positive node.
7	G. W.	43	R	- 0/20	DOD '59	Died 9 yr. after mastectomy. Extensive vascular and nerve invasion present.
8	L. E.	39	L	- 0/21	NED '65	15 yr. survival.
9	R. H.	42	L	+10/21		Developed histologically verified new primary of stomach. Death due to abdominal spread of 2nd carcinoma.
10	F. B.	32	R	+ 6/10	DOD '53	2½ yr. survival post-mastectomy.
11	J. W.	40	R	+19/22	DOD '52	9 month survival post-mastectomy.
12	S. E. C.	73	R	+ 6/20	DOD '51	6 month survival post-mastectomy.
13	M. G.	47	L	+ 1/9	NED '65	13 yr. survival with positive node.
14	E. G.	39	L	+15/26	DOD '54	19 month survival post-mastectomy.
15	J. H. W.	46	R	- 0/12	NED '65	12 yr. survival.
16	H. Mc.C.	43	R	+ 2/22	DOD '56	3¼ yr. survival post-mastectomy.
17	D. D.	45	L	- 0/15	NED '64	12 yr. survival.
18	C. T.	37	L	- 0/30	DOD '63	9 yr. survival post-mastectomy. Extensive vascular invasion found.
19	L. C.	40	L	+ 1/26	DOD '58	5 yr. survival post-mastectomy.
20	N. S.	44	L	+20/29	DOD '60	6 yr. survival with many nodes positive.
21	M. F.	47	R	+ 3/33	NED '65	11 yr. survival with positive nodes.
22	T. M.	42	L	+ 1/29	NED '65	11 yr. survival following first primary. Developed new breast primary; infiltrating duct carcinoma with fibrosis on right 2 yrs., later in 1956. 9 yr. survival since 2nd primary.
23	P. S.	42	R	- 0/18	NED '65	11 yr. survival.
24	G. R. F.	48	L	- 0/11	NED '65	10 yr. survival.
25	A. I.	44	R	+ 4/20	DOD '64	9½ yr. survival with positive nodes.
26	H. B.	48	L	- 0/17		Lost to followup. NED when last seen.
27	G. A.	52	L	- 0/25	DOD '65	9 yr. survival post-mastectomy. Vascular invasion present.
28	H. McD.	45	L	- 0/21	NED '65	This is Case 3 of series reported in <i>Ann. Surg.</i> , 157: 1963. Included because patient seen with infiltrating lobular carcinoma 40 months after initial diagnosis.
29	N. M. LaG.	46	L	- 0/18	NED '65	9 yr. survival following first primary. In situ lobular carcinoma found in right sided biopsy. Developed infiltrating terminal duct and lobular carcinoma on left 13 months later—see Case 36.

\* NED—No evidence of disease; DOD—Dead of disease; LWD—Living with disease.

We wish to thank Miss Marianne O'Brien, Medical Records Section, Warwick Cancer Clinic, for tracing all the patients used in this study. Only Cases 26 and 53 were lost to follow up. Case 53 was a submitted slide with no clinical data available.

TABLE 1.—(Continued)

Case	Initials	Age @ Mast.	Side	Axillary Nodes	Follow-up*	Comment
30	A. A. R.	57	L	— 0/25	NED '65	9 yr. survival post-mastectomy. Thought to be plasma cell mastitis on frozen section.
31	S. P.	43	R	+17/37	DOD '60	3½ yr. survival post-mastectomy.
32	K. K.	45	L	+ 2/10	DOD '58	2 yr. survival post-mastectomy.
33	E. M.	44	L	— 0/23	NED '65	9 yr. survival.
34	E. N.	36	R	+ 9/18	DOD '60	3½ yr. survival post-mastectomy.
35	J. I.	29	R	+18/30	DOD '57	6 month survival post-mastectomy.
36	N. M. LaG.	47	R	— 0/23	NED '65	2nd primary infiltrating terminal duct and lobular carcinoma 13 months after 1st side. Case 29 above. 8 yr. survival following 2nd primary.
37	T. K.	57	R	— 0/17	DOD '62	5 yr. survival post-mastectomy. Vascular invasion present.
38	E. P.	38	R	— 0/20	NED '65	8 yr. survival.
39	M. St.	65	R	+ 4/15	DOD '58	14 month survival post-mastectomy. Positive supra-clavicular node found at time of mastectomy.
40	D. J.	46	R	+ 3/18	NED '65	8 yr. survival with positive nodes.
41	M. Sa.	56	L	— 0/17	NED '64	7 yr. survival.
42	S. W.	45	R	— 0/19	NED '65	7 yr. survival since first primary. Developed new primary on left 3 yrs. later—see Case 56.
43	M. Gi.	69	L	— 0/16	NED '65	7 yr. survival.
44	M. K.	69	R	+ 4/18	NED '65	7 yr. survival with positive nodes.
45	M. C.	45	R	+29/29	DOD 4/21/64	Survived 6 yr. with all nodes positive. Developed 2nd primary on left. Case 55 below.
46	F. R.	39	L	— 0/18	NED '65	6½ yr. survival since first primary. Developed 2nd primary on right in 1964. Infiltrating duct carcinoma with fibrosis. 1½ yr. survival since 2nd primary.
47	M. S.	49	L	+ 6/15	NED '64	5½ yr. survival. NED when last seen in 1964.
48	M. Kr.	51	L	— 0/18	DOD '65	6½ yr. survival post-mastectomy. Vascular invasion present.
49	R. S. H.	51	R	— 0/14	NED '65	6 yr. survival.
50	H. R. M.	48	L	+ 3/15	NED '64	6 yr. survival with positive nodes.
51	O. W.	45	L	+11/16	NED '65	6 yr. survival with many positive nodes.
52	K. B.	41	L	+ 1/12	NED '65	6 yr. survival with positive node.
53	E. P.	46		— 0/8		Submitted slide. Side not known. Lost to followup
54	M. J. S.	39	R	— 0/22	NED '64	5½ yr. survival. NED when last seen in 1964.
55	M. C.	47	L	+22/22	DOD 4/21/64	2nd primary. Also infiltrating lobular carcinoma lived 47 months; all nodes positive on both sides. See Case 45.
56	S. W.	49	L	— 0/13	NED '65	See Case 42—2nd primary. 4 yr. survival following 2nd primary.
57	S. Wh.	43	R	+17/18	LWD. '65	4 yr. survival post-mastectomy. Had extensive abdominal involvement when explored for "appendicitis." Metastatic carcinoma in appendix.
58	E. S.	41	L	+ 2/19	NED '65	4 yr. survival with positive nodes.
59	A. F.	46	R	— 0/28	NED '64	2 yr. survival. NED when last seen in 1964.

TABLE 1.—(Continued)

Case	Initials	Age @ Mast.	Side	Axillary Nodes	Follow-up*	Comment
60	J. H.	83	R	— 0/12	NED '65	3 yr. survival. Oldest patient in series.
61	V. P.	31	R	— 0/22	NED '65	3 yr. survival.
62	M. P.	50	L	— 0/18	NED '65	3 yr. survival.
63	Y. S.	41	L	— 0/10	NED '65	2 yr. survival.
64	M. Sh.	63	L	+ 5/22	NED '65	2 yr. survival with positive nodes.
65	N. D. C.	49	L	+ 2/22	NED '65	2 yr. survival with positive nodes.
66	M. L.	41	R			This is Case 18 of series reported in <i>Ann. Surg.</i> , <b>157</b> : 1963. Had simple mastectomy. 4 yrs. later developed nodule at lower end of scar which proved to be residual breast tissue showing infiltrating lobular and residual <i>in situ</i> carcinoma. Positive supraclavicular node excised. Treated with radiation to supraclavicular area and axilla. Developed additional skin recurrence in scar in Aug. 1965.
67	J. M. G.	78	R	+ 1/20	NED '65	This is the only case in the series in which <i>in situ</i> lobular carcinoma could not be demonstrated in the material available. Areas of intraductal carcinoma demonstrated in terminal ducts.
68	E. H.	50	L	— 0/31		Too recent to evaluate.
69	H. L.	48	L	— 0/24		Too recent to evaluate.
70	V. W.	56	R	+16/19		Too recent to evaluate.
71	E. T.	51	L	— 0/30		Too recent to evaluate.
72	R. B.	47	R	— 0/19		Too recent to evaluate.
73	B. B. L.	49	R	+ 1/18		Too recent to evaluate.

as in Cases 45 and 55). Patients with negative nodes usually fared well, though on occasion they died of disseminated disease. In five such cases (7, 18, 27, 37, 48) it was possible to demonstrate vascular invasion (Fig. 1, 2). This finding of vascular invasion has been noted at other sites in recent years, notably lung and bowel, and has assumed increasing importance in surgical pathology.

Several patients showing a more rapid evolution of infiltrating lobular from antecedent *in situ* lobular carcinoma can be added to those already documented. Case 28 (Case 3 in the original series<sup>10</sup>) has remained free of disease for 3 years since the original report. Case 29 had infiltrating lobular carcinoma of the left breast (Fig. 3). At operation, biopsy of the right breast showed *in situ* lobular carcinoma (Fig. 4).

Thirteen months later she presented with a palpable mass and a frozen section showed infiltrating carcinoma. Right radical mastectomy was performed (Case 36, Fig. 5). She has remained free of disease to date. Case 42 had an infiltrating lobular carcinoma on the right, but no biopsy of the left side was done at operation. Three years later, she appeared with a mass on the left side (Case 56) which also showed infiltrating lobular carcinoma with negative nodes; she has remained well to date.

The most interesting case in terms of the evolution and progression of *in situ* lobular to infiltrating lobular carcinoma is Case 66 (Case 18 in the earlier series<sup>10</sup>). *In situ* lobular carcinoma was seen on biopsy (Fig. 6) and simple mastectomy was performed. There was no evidence of invasion in any of the many slides prepared



from the biopsy specimen. Exactly 4 years later she returned with a "nodule" at the lower aspect of her mastectomy scar. This was excised locally under the impression that it represented an "involuting" suture granuloma or a "neuroma." It proved to be residual breast tissue which showed infiltrating lobular carcinoma as well as residual foci of *in situ* lobular carcinoma (Fig. 7) plus a small fibroadenoma (Fig. 8). She later developed a positive supraclavicular node which was excised (Fig. 9, 10).<sup>\*</sup> She was treated with irradiation to the supraclavicular area and axilla and developed an additional skin recurrence in August 1965. While it is possible that we missed a focus of invasion in our examination of the original mastectomy specimen, it seems more likely that the source was previously unexcised breast tissue at the lower end of her mastectomy scar. This suggests a not uncommon hazard in performing mastectomy—the difficulty in removing all breast tissue. Haagensen<sup>6</sup> has emphasized this problem.

It is apparent that the evolution of infiltrating lobular carcinoma need not take as long as suggested by prior reports.<sup>5, 6, 8</sup>

Though the majority of patients are premenopausal and menopausal, the presence of some elderly patients can best be explained by the occasional case in which the decision as to site of origin (terminal ducts or lobules) is difficult to make—or by assuming the persistence of areas of *in situ* carcinoma for long periods beginning in the premenopausal period. In this series there are eight patients 65 years or older (Cases 3, 5, 12, 39, 43, 44, 60, 67). Case 67 was the only patient in whom *in situ* lobular carcinoma could not be identified in the material available for study. She did, however, show foci of in-

traductal terminal duct carcinoma, though the infiltrating component consisted of the single cell pattern of lobular carcinoma. As Stewart said, "Cancers of the breast simply do not adjust their growth patterns to the requirements of rigid coding."<sup>13</sup>

### Conclusions

We believe that earlier recognition and treatment of *in situ* lobular carcinoma will forestall the development of some events described in this series. We hope that this study will end the artificial separation of *in situ* lobular carcinoma of the breast from its later infiltrating form and that surgeons will treat this disease as a continuum, appreciating the high incidence of bilaterality.<sup>1, 2, 8, 10, 12</sup>

We have not discussed multicentricity, "paired" organ sensitivity, or "field" phenomena, but our review of 1,436 cases of breast cancer convinces us that multicentric origin is the *usual* mode of growth for all types of breast cancer<sup>11</sup> and reflects a biologic phenomenon common to human cancer at all sites (see Ref. 9 for an excellent recent discussion).

### Summary

All slides from 1,436 cases of carcinoma of the breast seen at the George Washington University Hospital since April, 1948, were examined. Forty cases showing *only in situ* lobular carcinoma are *not* included in this paper, 32 of these having been presented previously.

In an initial survey of the material, 142 cases having terminal duct or lobular component or both were separated from 1,396 cases of carcinoma of the breast (10.2%). These cases were re-examined, and by rigid and stringent criteria, 73 cases representing "pure" infiltrating lobular carcinoma were established. This is probably the largest group of infiltrating lobular

<sup>\*</sup> We wish to thank Dr. William J. Jaffurs, Pathologist, Columbia Hospital for Women, Washington, D. C., for allowing us to use this slide. Figures 9 and 10 were prepared from this material.

carcinomas reported to date, and represents about 5% of the cancers examined in this series.

In 72 of these 73 cases, histologic evidence of "early," antecedent, *in situ* lobular carcinoma was found. Once invasion of breast stroma has taken place, the sequence is similar to that in the more frequent carcinomas of duct origin. Patterns of lobular carcinoma of the breast occur more frequently than previously supposed.

Recommendations for treatment, depending on whether the tumor is non-infiltrating or infiltrating, are discussed. Additional cases of progression from *in situ* lobular to infiltrating lobular breast cancer are presented.

Residual *in situ* lobular in 72 of 73 cases of "pure" infiltrating lobular carcinoma of the female breast indicates that they form a continuum. When diagnosed it should be treated promptly to forestall (where possible) the sequence of events reported in this paper.

#### Acknowledgments

Earl Newcity, Chief, Photographic Laboratory, the George Washington University School of Medicine, prepared the photomicrographs.

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