THE FREQUENCY AND VARIATION OF MALIGNANT CELL AND TISSUE CHARACTERS AND THE FREQUENCY AND EXTENT OF INVASIVE GROWTH IN MAMMARY CARCINOMA.

A Survey of findings in 460 Breast Cancers.

by

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In making his diagnosis, it is the practice of the histologist to take note of certain characters which constitute, so to speak, his formula of malignancy. In general, the more prominent these characters and the greater their extent, the greater is the certainty regarding the fact of malignancy. It is but a further step to have a pronouncement made upon the degree of that certainty, which is equivalent, in a histological sense, to a judgement on the degree of malignancy. Special terms have been coined from time to time to express this judgement, such as anaplasia, de-differentiation and its obverse, differentiation, invasive growth and so on. The science of grading has, in recent years, taken on a special aspect because of its association with therapeutic procedure, and we may hope that a formula of malignancy will in time be achieved. Such a formula must obviously be based on probability and the more numerous the factors or characters which can be included in the formula, the closer to unity will be the probability fraction. In Murray's opinion, "no single structure or functional difference has been discovered which is peculiar to cancer... a combination of several differences, each in itself insufficient to account for the distinctive behaviour of malignant growth, might reinforce each other when present in unusual proportions" (1). Some of the characters used for
for the description of malignancy may, however, be so highly correlated that no addition to the probability concerned is obtained, but such characters are still worth recording, since it often happens that one or other character cannot be observed at all and the other then forms an efficient substitute. The degree of correlation of characters of malignancy is therefore itself a subject worthy of investigation.

In this study, I have endeavoured to make a detailed survey of cell and tissue characters in a large amount of malignant tumour material, with a view to determining their frequency and the extent to which they varied. My material has reference to one organ only, the breast, but malignancy of tissue has general characters irrespective of the site of tumour origin and "die Mamma ist die Amme der Geschwulstlehre".

Material

Tissue from 460 cases of malignant mammary tumour has been studied. The series is unselected in the sense that the cases are taken from routine reporting material received at the Laboratory of the Royal College of Physicians from a number of sources and the routine operative material from the Royal Infirmary, Edinburgh, only those cases being rejected which did not offer sufficient tissue for adequate examination.
Tumour tissue from metastases, tissue from male patients, from patients treated by pre-operative irradiation and autopsy material is not included in this series.

A considerable number of the cases have been studied in whole breast sections and the histological observations are, for the most part, based on appearances at the active growing edge of the tumour, where the nature of the extending malignant process is evident. This procedure is important when examining highly cellular growths, which, in their early stages, may show extensive intraductal malignant cell proliferation before infiltration. Such tumours, while still confined within cystic ducts, frequently produce cells of markedly anaplastic character; when they infiltrate the surrounding tissues, the cell type often becomes less atypical and so a truer estimate of their malignant potentiality is to be gained by observing them in an area of dissemination. Examination of the growing edge has also been found to eliminate, to a considerable extent, the variety of microscopical picture in any one tumour and therefore gives more reliable findings for histological comparison; it also avoids areas of degeneration usually evident in the older central parts of the growth.

The histological appearances noted were divided into two /
two main groups - I. the characters of the malignant cells and of the surrounding stroma, and II. the evidence of invasive growth. The observations are surveyed under the following headings:

I. **Cytological Characters**

1. Size of cell and nucleus; 2. Cytoplasmic staining reaction; 3. nuclear chromatism; 4. mitosis; 5. differentiation of (a) the malignant cell and (b) the malignant tissue; 6. degenerations of malignant cells and of stroma; 7. fibrosis and 8. lymphocytic cell accumulations.

II. **Evidence of Invasive Growth into**

1. Connective tissue; 2. lymph channels; 3. axillary lymph nodes; 4. blood vessels; 5. nerves; 6. the dermis; 7. the epidermis; 8. the pectoral fascia; 9. pectoral muscle; and 10. perinodal axillary tissues.

I. **Cytological Characters**

1. **Size of malignant cell and nucleus**

In some cases, the outline of the malignant cell is defined with difficulty; its boundaries are vague or the cytoplasm stains indifferently because granular or much vacuolated. The nucleus, in contrast, is almost always well-defined and it was thought its size
might serve as an index of the size of the cell if some relation could be established. Instead of measurement, I have estimated the size of malignant cell and nucleus in relation to that of other and normal cells observed in the mammary area. Normal mammary gland tissue shows epithelial cells which are fairly constant in size and the nuclear-cytoplasmic ratio in these cells was taken as the standard. Variations, however, occur in this tissue when involutionary and atrophic changes supervene and as this is especially apt to be the case at the very ages when cancer emerges, it was thought advisable to furnish in addition and, to some extent, as the chief object of comparison for nuclear size the small lymphocyte, the normal mammary cell nucleus being approximately the same size as that of the lymphocyte (fig. 1). The glandular cell, the red blood cell, the fibroblast and the endothelial cell were also observed in this connection.

An important point emerged early in the observations - the acquisition of the cancerous nature is, in almost all cases, associated with marked and definite changes in the morphology of the mammary cell, the most obvious of which is the production of a cell larger than the normal cell or the lymphocyte. In only a small minority of cases was the malignant cell or nucleus even as small as the glandular cell. The nuclei of the malignant cells were therefore divided into the following /
following 4 groups according to size - group I, nuclei 1 to 2 times the size of the lymphocytic nucleus; group II, 2 to 4 times this size; group III, more than 4 times this size and group IV, a mixed group, where variation in size was so marked that no one size predominated. The groups I, II and III may be said to correspond to the small, medium and large nucleus (figs. 2a and 2b, 3 and 4). Groups I, I+ and I− were noted but all three are included in group I, and so with groups II and III. Group IV, the mixed group, is shown in figs. 5a and 5b.

The association observed between size of cell and of nucleus is shown in the following table -

<table>
<thead>
<tr>
<th>NUCLEUS</th>
<th>I small</th>
<th>II medium</th>
<th>III large</th>
<th>IV mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>I small</td>
<td>173</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II medium</td>
<td>17</td>
<td>171</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>III large</td>
<td>0</td>
<td>2</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>IV mixed</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

These figures show a very definite correspondance between size of cell and size of nucleus. In the series counted, the nuclear groups show the following frequency distribution -

Group I /
In 17 cases, where cell size was indefinite, 15 showed a small nucleus and 2 a medium nucleus. The figures for the complete series of 460 cases are therefore:

- Small nucleus: 214 (47 per cent)
- Medium: 215 (47 per cent)
- Large: 15 (3 per cent)
- Mixed: 16 (3 per cent)

It should be emphasized that these size groups are necessarily somewhat arbitrary in their divisions. As will be evident in the drawings, malignant nuclei tend, within limits, to vary in size in the same tumour and a small nucleus might, by another observer, be placed in a 2-group, though comparison with a more or less consistently-sized cell such as the small lymphocyte makes the grouping more objective. A re-consideration of the two groups III (large) and IV (mixed) has suggested that it is probably more logical to combine them, as the large-cell growths are almost invariably markedly polymorphic (cf. figs. 4, 5a and 5b).

2. Cytoplasmic Staining Reaction

Variations evident in the staining of the cytoplasm may be due to differences in technique, but...
where, as in my material, a uniform method is employed by good technicians, variations are more likely due to actual differences in reaction than to accidental causes. Four types of staining have been observed - eosinophile, where the cytoplasm stains pink (the degree of staining in this group varied considerably); basophile, where it appears distinctly bluish; amphiphile, with staining intermediate between the two preceding groups, and anophile, where no distinct impression was gained. This last type includes cases which Delbet (2) described as showing "clear cytolysis" and others with a similar granular cytoplasm, largely unstained.

In the 460 cases, the following distribution was observed -

- eosinophile 227 (49 per cent)
- basophile 150 (33 . . . )
- amphiphile 31 ( 7 . . . )
- anophile 52 (11 . . . )

3. **Nuclear Chromatism**

It is usually stated that the nuclei of malignant cells are hyperchromatic, but neither the degree of chromatism nor its relation to the size of the nucleus is defined. The naked-eye hyperchromatic appearance of a malignant area in a stained section may often be explained by the proliferation and accumulation of cancer cells in that area, in comparison with /
with the sparse distribution of epithelium in normal glandular tissue, and this apparent hyperchromatism is evident when the individual malignant nuclei are ortho-chromatic or even hypochromatic. In these observations, I have taken as normal or ortho-chromatism the degree of chromatism usually evident in a normal glandular cell of the breast, without consideration of nuclear size. A large nucleus has quantitatively more chromatin than a smaller cell with similar staining, but an estimate of both chromatin and size would have involved unnecessary complications. In estimating chromatism in this series, the density of nuclear structure has been the criterion. In the fixation and preparation of tissue for microscopic examination, a certain degree of shrinkage of cells and nuclei is probably inevitable; this might produce what is interpreted as hyperchromatism, unless normal glandular cells, similarly affected, are also present in the area for comparison.

Variations in chromatism were divided into 4 groups and the following frequency observed -

- Hyperchromatic: 134 cases (29 per cent)
- Orthochromatic: 114 cases (25 per cent)
- Hypochromatic: 139 cases (30 per cent)
- Mixed group: 73 cases (16 per cent)

The /
The hyper-, ortho- and hypo-chromatic groups show surprisingly little difference in frequency; the group mixed, as in other characters, is a smaller one. The four types are shown in fig. 6.

Recent work by MacCarty (3) and others lays emphasis on the size of the nucleolus as a malignant character. This feature has not been specially studied in this series, which was too large for other than routine staining methods. These do not necessarily bring out the nucleolus as distinct from other nuclear structures, though in a considerable number of cases it is quite evident, as shown in fig. 7, c.

4. Mitosis

The frequency of mitotic figures in a malignant area is accepted as an index of proliferative activity and various methods of estimating this index are on record. As already mentioned, the study of whole breast sections has suggested that the nature of the malignant process is best observed at the periphery of the growth and the mitotic index in this series was therefore obtained by counting the number of mitoses in each of 10 high power fields at the growing edge, the median (middle) value of the 10 counts being taken as the index. In a small number of cases, ten peripheral fields were not available for observation, and in these other parts were studied, areas which showed degeneration/
degeneration or marked pyknosis being rejected. Malignant cells in lymph channels were not included, as growth in this position often appears different in character and comparison may therefore be less valid. All phases of mitosis were included (fig. 8); nuclear clumping due to appearances other than the prophase stage can usually be excluded in actively-growing tissue. Amitosis has not been allowed for, though it has been emphasized as a means of malignant cell increase by various writers. Maximov (4) considered that, although the constriction or segmentation of the nucleus which possibly indicates indirect division or amitosis is observed, there is no apparent evidence that, in human tissue, the cell itself divides as a result of nuclear fission. The multi-nucleated cell thus produced may, in tumour tissue, also be explained as a formation by fusion, and it was therefore thought advisable to exclude possible amitotic appearances from the mitotic count. At the high power magnification used, no nuclear count of any accuracy could be obtained in 140 cases; these included tumours with small malignant cells and hyperchromatic nuclei, some of which might or might not have been in prophase and a few old cases with indifferent staining. The material for count is, in this respect, "selected". No attempt was made to estimate the frequency of abnormal mitotic figures, though/
though these were not infrequently observed (cf. figs. 4 and 5).

The mitotic counts were graded as follows -

<table>
<thead>
<tr>
<th>Median count</th>
<th>No. of cases</th>
<th>Percentage (to nearest whole number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>71</td>
<td>22</td>
</tr>
<tr>
<td>1 - 2</td>
<td>72</td>
<td>22</td>
</tr>
<tr>
<td>2 - 3</td>
<td>89</td>
<td>28</td>
</tr>
<tr>
<td>3 - 4</td>
<td>62</td>
<td>19</td>
</tr>
<tr>
<td>4 - 5</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>5 - 6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6 - 7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>7 - 8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8 - 9</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>9 - 10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10 - 11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>11 - 12</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

320 100

No. of cases where no accurate count was possible 140

Total no. of cases 460

5. "Differentiation"

Differentiation, as a term applied to malignant mammary growth, is a rather ill-defined one. The presence or absence of differentiation is indicated, according /
according to some writers, by any features in the cancer cells which approximate to or markedly diverge from those observed in normal tissue, but in a narrower sense, interpretations of the term fall roughly into two groups, which concern (a) the morphology and function of the malignant cell and (b) the arrangement and architecture of the malignant tissue.

The following characters, accepted by various other workers as indicative of differentiation in malignant mammary growth, have been studied.

(a) Differentiation of the malignant mammary cell, as shown by

i. approximation to the normal mammary cell which lines the glandular structures, presumably a more or less columnar cell (MacCarty, Lewis and Geschickter et al.)

ii. functional or secretory activity, evident as cytoplasmic vacuoles with or without droplets of mucoid material (Greenough, Delbet, Hueper et al.)

(b) Differentiation of the malignant mammary tissue, as shown by

i. adenomatous arrangement of cells round an open space (Broders, Greenough);

ii. tubule formation, solid or hollow, in imitation of normal mammary ducts and acini (Reiman and Seabold, Patey and Scarf);

iii. squamoid or squamous changes (Delbet).
The absence of normal mammary cell cohesion - "cell isolation" - is regarded by some observers as an indication of marked lack of differentiation; this feature was noted in this series and the cases have been included in the group which showed none of the above signs of differentiation. The characters observed showed the following frequency -

<table>
<thead>
<tr>
<th>Character</th>
<th>No. of cases where observed</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. columnar cell</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>ii. cytoplasmic vacuoles</td>
<td>183</td>
<td>40</td>
</tr>
<tr>
<td>(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. adenomatous formations</td>
<td>106)</td>
<td>23)</td>
</tr>
<tr>
<td>ii. tubular formations</td>
<td>6)</td>
<td>1)</td>
</tr>
<tr>
<td>iii. squamoid changes</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>No differentiation, including</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the &quot;isolated cell&quot; growths</td>
<td>173</td>
<td>38</td>
</tr>
</tbody>
</table>

These characters are shown in figs. 9 - 21.

The total frequency of the various characters exceeded the total number of the series examined, as more than one feature occurred not infrequently in the same tissue (cf. fig. 9,e, with columnar cells in tubule formation). A comment seems necessary on the very small number of cases in which tubule formations were observed. At the periphery of the tumours, where the characters were, in general studied, malignant tubules which indicated duct or ductule cancer before invasion of the wall had occurred, were rarely seen and if present, were excluded from the count, as many workers do not accept as malignant, tumour cells before invasion.
invasion. Growth along lymph channels in tubular form at the growing edge was often seen, but for reasons already noted, was also excluded. Thus only the one case noted above showed malignant cells growing in tubule formation in the stroma, as in fig. 9,e. In probably all cases, adenomatous and tubular formations indicate the same tissue architecture sectioned in different planes and should therefore be considered together.

The time factor needs consideration in any estimate of the presence and influence of "differentiation" in malignant growth, but data are indefinite because dependent on the patient's memory and observation.

6. Degeneration of malignant tissue and of stroma

(a) Malignant tissue degeneration.

This feature was noted wherever it occurred in the tumour area, as the growing edge shows, in general, little evidence of cell destruction. Epithelial cell lysis is frequently observed in the lumen of ducts distended with tumour cells, when it may produce the appearance sometimes called comedo carcinoma; it may also be associated with extensive haemorrhage. Mucoid ("colloid") degeneration affects both epithelial and stroma elements and both forms are here noted together.

(b) Stroma degeneration.

Marked /
Marked hyalinization, extensive elastic tissue increase and myxomatous and mucoid changes are interpreted as degenerative appearances by various observers and their occurrence was noted in this series.

These degenerations were observed as follows -

- Extensive cell lysis, including "comedo cancer" cases
- Extensive haemorrhage
- Extensive hyalinization
- Extensive elastic tissue increase
- Mucoid changes in epithelium and stroma
- Myxomatous degeneration in stroma

More than one type of degeneration was often observed in the same tumour and the frequency is not stated as a percentage.

7. **Fibrosis**

I have restricted this term to signify active fibrosis, i.e., where proliferation of fibroblasts is evident, as quiescent fibrous tissue in a mammary area may indicate a phase of normal post-menopausal mammary involution. Active fibrosis is frequently seen in the centre of a malignant tumour and is then apparently reparative, resembling scar tissue, in an area damaged or destroyed by cancerous infiltration. The later contraction of such areas gives the characteristic naked-eye appearance of a scirrhoue carcinoma. Active fibrosis /
fibrosis is also found associated with malignant spread at the tumour periphery and elsewhere (cf. figs. 13 and 14); by some observers it is then considered a "defence factor" which inhibits tumour growth, but it has also been interpreted as a provision for support and nutrition and thus furthering rather than hindering malignant spread.

Active fibrosis was evident in larger or smaller areas in 291 cases in this series of 460 tumours, a frequency of **63 per cent**.

8. **Lymphocytic Cell Accumulations**

The significance of accumulations of lymphoid cells in malignant mammary tissue is, like fibrosis, an unsettled question, for there is much evidence both for and against the view that they indicate an immunity against cancer growth. The cell accumulations may be scattered diffusely through the tumour tissue or, more usually, are especially obvious at the periphery. They were evident in one or both positions in 311 of the 460 cases of the series, a frequency of **68 per cent**.

(see fig. 22)

II. Evidence /
II. Evidence of Invasive Growth into Mammary and Extra-mammary Tissues.

1. Connective tissue

The earliest stage of mammary carcinoma is evident as a malignant hyperplasia within the glandular structures (fig. 22). The next stage shows rupture of the duct walls and infiltration by the malignant cells of the periductal connective tissue. A further stage, invasion of the lymph channels, does not necessarily follow at once. In older subjects, where involutionary and atrophic changes in the mamma are associated with possibly extensive obliteration of the smaller lymph and blood vessels, the interval between transgression of duct walls and lymph stream invasion would appear to be considerable and large areas of infiltrated stroma may form palpable tumours which are detected and removed before the lymph stream is actually invaded.

No definite opinion regarding the stage of cancerous infiltration was arrived at in 32 cases of this series; in the remaining 428, a histological picture suggesting invasion of the connective tissue of the mammary area without evidence of lymph vessel involvement was observed in 66 cases, or 15 per cent. The microscopical appearance is seen in fig. 23.

2. Lymph channels /
2. **Lymph channels**

Lymph vessel invasion is of primary importance as a finding in malignant growth and the evidence which points to it needs critical examination. It is rare that the appearances which indicate lymph vessels - endothelial lining cells, the presence of valves and of scattered lymphocytes embedded in lymph in the lumen - are all observed in any one instance and other findings must in most cases be depended on to distinguish lymph vessels from connective clefts containing fibroblasts, or, on the other hand, from glandular structures or even from veins and capillaries. I have rarely observed the "perilymphatic fibrosis" described by Handley and which, if present, might have been of service in identifying the larger permeated lymph vessels at the periphery of the breast or in the pectoral fascia. The larger collecting trunks between breast and axilla seem indeed to have curiously inadequate walls, if judged by text-book descriptions. Mammary ducts can usually be distinguished from lymph channels by the cellular débris in their lumen, the more or less obvious basement membrane and the relation to other glandular elements, but these appearances do not always give clear guidance. In the mammary area, the blood vessels usually differ from lymph channels in the structure of their walls, but in the axillary tissue /
tissue, the larger lymph trunks which empty into the peripheral sinus of the nodes may have a considerable muscle content and interpretation is often difficult and not necessarily aided by the cells observed in the lumen (cf. figs. 24 - 30).

In this series, evidence of lymph vessel invasion was observed in 362 of the 460 cases. In 66 cases, as already noted, malignant spread had apparently not passed beyond connective tissue infiltration; in 32 cases, no definite opinion was arrived at.

The series thus showed:

- Lymph vessels invaded: 362 cases (85 per cent)
- ... not invaded: 66 cases (15 per cent)
- ... ? invaded: 32 cases

3. Lymph nodes in the axilla

As involvement of the lymph nodes in the axilla is an almost inevitable sequel to lymph vessel invasion of the mammary area in cases where malignant growth has extended beyond the early stages, the latter finding is, to a great extent, checked by examination of the axillary tissue. In a small proportion of cases, malignant cells in the lymph stream travel initially to nodes other than axillary; in a small number also, operation may remove the breast before cells actually in the lymph stream have reached the nodes, but the disparity in findings indicating involvement /
involvement of mammary lymph vessels and of axillary lymph nodes may also be due to accidents of sectioning.

The findings in the 460 cases studied were as follows -

Axillary lymph nodes invaded 274 (70 per cent)  
... ... not invaded 115 (30 ... ...)
No axillary tissue available 71 cases.

Lynham (4) places axillary lymph node invasion as high as 80 to 90 per cent in any routine series of mammary carcinoma.

The number of cases in my series in which no axillary tissue was available is considerable. It is accounted for by various causes, such as absence of palpable and/or visible lymph nodes in the axillary tissue submitted (most of these cases should probably be placed in the non-invaded group), omission by the surgeon to send axillary tissue for examination after a two-stage operation or absence of axillary tissue in cases where the age or condition of the patient dictated a modified breast resection, with or without subsequent axillary irradiation.

In the 389 cases where the lymph nodes gave a definite finding (274 positive and 115 negative), the invasion /
invasion or freedom of mammary lymph vessels and
axillary lymph nodes corresponded in 331 cases, a
percentage. This high correlation suggests that the
appearances interpreted as the presence or absence of
mammary lymph vessel invasion were, in the main, sub-
stantiated. Begg (14), on the other hand, observed
lymph vessel invasion in many of his series of 140
skin tumours in mice, but only 4 showed malignant
growth in the associated lymph nodes. The correlation
in mammary cancer needs emphasis, if the frequency
observed on my series be accepted. As already indic-
ated, axillary tissue is not always available for
microscopical examination, but if its invasion by
malignant cells can be as accurately deduced from
examination of the mammary tumour tissue as these
figures suggest, prognosis and therapy based on the
extent of malignant spread should consider lymph
cellular involvement in the breast tissues as a weighty
factor.

4. Blood vessels

It is the accepted teaching that carcinoma
is, in general, spread by the lymph stream and the
comparatively early invasion of the regional lymph
nodes is obvious evidence of this main route of dis-
semination. Considerable attention has, however, been
drawn
drawn in the more recent literature to the possibility and frequency of dissemination by the blood stream and appearances which supported this were therefore noted in this series. No structure was accepted as a blood vessel invaded by malignant growth until other possibilities had been ruled out. It is noteworthy that in every case in which the blood vessels were apparently invaded, there was also involvement of the lymph channels; some pictures indicated that malignant cells had erupted into the blood vessel lumen from the encircling perivascular lymph vessels, while in others, the malignant cells had infiltrated the muscle coats and thickened intima of partly sclerosed veins, which, in the planes sectioned, showed no accompanying lymph vessels. No arterial invasion was observed; the blood vessels involved were either capillaries, presumably venous, or veins. Invasion of the blood vessels is illustrated in figs. 31-42.

Instances of blood vessel invasion were divided into 3 groups -

<table>
<thead>
<tr>
<th>Description</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessels invaded in the breast only</td>
<td>75</td>
</tr>
<tr>
<td>axilla</td>
<td>42</td>
</tr>
<tr>
<td>breast &amp; axilla</td>
<td>21</td>
</tr>
<tr>
<td>apparently not invaded</td>
<td>302</td>
</tr>
<tr>
<td>? invaded (i.e. &quot;doubtful&quot;)</td>
<td>20</td>
</tr>
</tbody>
</table>

There were therefore 138 cases in which appearances interpreted /
interpreted as blood vessel invasion were seen, a frequency of 31 per cent, excluding the 20 doubtful cases. This unexpectedly high figure might suggest that more rigid criteria of blood vessel invasion structure and malignant involvement are necessary before this frequency can be accepted, especially as divergence of interpretation of the microscopical picture is evident from a study of the illustrations in the literature. The follow-up results in these cases showed, however, that in a considerable number where death had occurred with skeletal, pulmonary, abdominal or cerebral metastases, there was histological evidence, in breast or axillary tissue or both, indicating blood vessel invasion. The frequency observed may indeed be an underestimate, for while positive findings are of value, negative ones may be due to choice of the areas examined rather than to absence in the tissues of the evidence required.

5. **Nerves**

Pain is, in general, a late symptom in breast carcinoma and in many cases in this series its presence was associated with the encroachment of malignant tissue on nerve substance in the mammary area. In the majority of cases, this was shown microscopically by invasion of the perineural lymph channels, but all /
all stages of further involvement have been observed, even to destruction of the nerve fibres (figs. 43-45). Delbet (l.c.) noted that Paccinian corpuscles may be surrounded and actually invaded by tumour cells; no instance of such invasion was observed in this series, though corpuscles, surrounded or not by malignant cells were seen in a considerable proportion of the tumours examined in whole breast sections. Begg (l.c.) comments on the lack of evidence in the literature regarding nerve invasion in spontaneous mammary cancers in mice, though he himself observed peri- and endoneural malignant involvement in 18.5 per cent of a series of 140 skin tumours in these animals.

The findings in the 460 tumours in this series were:

- perineural invasion 53 cases
- peri- & endoneural invasion 17 ..
- no apparent invasion 329 ..
- no nerves observed in sections 21 ..

This shows a frequency of 70 (16 per cent) in the 439 cases where nerve tissue occurred in the sections, a finding comparable with Begg's figures of 18.5 per cent. As with other evidence of malignant spread, positive findings depend to a large extent on the selection of tissue for examination and this frequency may therefore be an understatement. In every case where /
where peri- or endoneural invasion was observed, the perivascular and periductal lymph channels were also involved by tumour growth.

The significance of neural invasion by malignant tissue, in relation to the formation of metastases in areas other than the axilla, is obvious and needs study in the light of later clinical findings in these cases.

6. The dermis

The dermis or true skin includes, in the mammary area, all the tissue superficial to the fatty layer lying on the corpus mammae. It may be invaded comparatively early by the expansion of a superficial tumour, either by the direct spread of cancer cells into the connective tissues below the epidermis or by malignant emboli reaching it along the suspensory ligaments. Another frequent line of spread is by way of the large periductal lymph channels which run to the subareolar plexus below the nipple (fig.30); the malignant cells by this route reach the smaller lymph vessels of the dermis, presumably by stasis and reversal of the lymph flow. In this series, invasion of the dermis and the epidermis were considered separately, as extensive involvement of the dermis is not necessarily associated with invasion and ulceration of the epidermal layers (figs 17, 35). The dermis was available for /
for examination in 354 of the cases and showed -

invasion 175 cases (50 per cent, where skin sectioned)
no invasion 179 (50 per cent)
no dermis in sections 106

7. **The epidermis**

Invasion of the epidermis was always found secondary to invasion of the dermis, except in a few early cases of Paget's disease of the nipple. In old patients, epidermal invasion and ulceration may be extensive and occur comparatively early, but otherwise this is a late finding and subsequent, in most instances, to marked malignant proliferation in the dermis (cf. figs. 35-46), with invasion of the lymph and even blood vessels.

Epidermal tissue in the mammary area was available for examination in 333 cases in the series and showed -

epidermis invaded 119 cases (36 per cent, where skin examined)
epidermis not invaded 214 .. (64 per cent)
no epidermis in sections 127

8. **The pectoral fascia**

Even when malignant growth arises deep in the breast, actual invasion of the underlying tissue, that is, of the fascia separating the corpus mammae from the pectoral muscle, may be a late development. It is, /
It is, in most cases, clinically evident by some degree of fixation, but where the malignant cells are found only in the perivascular fascial lymph vessels, this sign may be absent. The fascia is more frequently invaded by the progressive expansion of the tumour area. In this study, the criterion of pectoral fascia involvement adopted was the presence of malignant tissue definitely beyond the deep limits of any glandular structures, which, in involuting breasts, may be irregularly scattered in the increased deep fatty tissue. Invasion of the fascia both by the lymph stream and by continuous tissue spread from the tumour mass is included in the following figures, Tissue was available for examination in 332 cases. It showed

<table>
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<th>Description</th>
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<tr>
<td>Fascia invaded</td>
<td>116 cases</td>
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<tr>
<td>(35 per cent)</td>
<td></td>
</tr>
<tr>
<td>Fascia not invaded</td>
<td>216 ..</td>
</tr>
<tr>
<td>(65 .. .. ..)</td>
<td></td>
</tr>
<tr>
<td>No Fascial tissue available</td>
<td>128 ..</td>
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9. **The pectoral muscle**

Invasion of the pectoral muscle occurs in two ways, either by spread of malignant cells in the fibrous septa and their lymph channels or by penetration of the sarcolemma. Delbet notes these two means of spread, though he saw only one instance of the latter type. Both types of muscle invasion in this series /
series and their occurrence is considered together in
the following figures (see fig. 4/).

Deep muscle invaded 49 cases (15 per cent, where
observed)

... ... not invaded 284 ... (85 ... ... )

No muscle in sections 137 ... 

Willis (12), working on autopsy tumour material, found
that the pectoral muscle was "frequently invaded";
Wainwright (13) observed that it was involved in 60 per
cent of cases examined in whole breast sections, but
he included, on clinical grounds, cases where malignant
cells were found 2 mm or less from the muscle, as well
as those where actual penetration of the muscle had
occurred. My figures refer only to actual invasion.

10. **Perinodal axillary tissue**

The figures already mentioned regarding the
presence or absence of malignant tissue in the axill-
ary lymph nodes referred to invasion of the nodes them-
selves, but in the great majority of my sections, other
axillary tissue was available for examination and
tumour spread in these was also noted. The malignant
cells which reach the lymph nodes, early as emboli,
later possibly by continuous growth along the lymph
channels, proliferate first in the peripheral sinus
of the node and then gradually spread throughout the
lymphoid tissue of the medulla. Malignant growth out-
side /
outside the capsule of the node would seem to be a
definitely late occurrence and subsequent to consider-
able, if not almost complete replacement of lymphoid
tissue by cancer cells. Extension of tumour growth
outside the capsule of lymph nodes into the surround-
ing axillary fat has been observed both beyond the
hilum and beyond the convex surface where the afferent
lymph vessels enter the peripheral sinus of the node.
Perinodal axillary tissue was available for examina-
tion in 381 cases of the 460 examined and showed -

Axillary invasion beyond the nodes 132 cases (35 %)
No axillary invasion . . . . 249 . . (65 . . )
No perinodal tissue insections 79 . .

Summary of survey

I. Cytological characters

1. Size of nucleus - small, 47 per cent; medium,
47 per cent; large, 3 per cent; mixed size, 3 per cent.
The cell and nucleus corresponded in size in 84 per cent.

2. Cytoplasmic staining - eosinophile, 49 per cent;
basophile, 33 per cent; amphiphile, 7 per cent; ano-
phile, 11 per cent.

3. Nuclear chromatism - hyperchromatic, 29 per cent;
orthochromatic, 25 per cent; hypochromatic, 30 per cent;
variably chromatic, 16 per cent.

4. /
4. **Mitosis** - the median count (mitotic index), obtained in 320 of the total 460 cases, varied from 0 - 1 to 11 - 12, with a maximum (28 per cent) median count of 2 - 3.

5. **Differentiation** - characters interpreted in the literature as indicative of "differentiation" were observed, e.g. columnar malignant cells (5 %), cytoplasmic vacuoles (40%), adenomatous and tubular formations (24%), squamous and squamoid changes (10%) and absence of differentiation, e.g. cell isolation (30%).

5. **Cell and tissue degenerations** of various types, frequently more than one in the same tumour, were studied.

7. **Active fibrosis** occurred in 63 per cent in the series.

8. **Lymphocytic cell accumulations** occurred in 68 per cent in the series.

II. **Invasive growth** was observed as follows -

1. Into connective tissues only, 15 per cent.
2. .. lymph vessels also, 35 per cent.
3. .. axillary lymph nodes, 70 per cent.
4. .. blood vessels of breast, axilla or both areas, 31 per cent.
5. .. nerves, 16 per cent.
6. .. dermis, 50 per cent.
7. into epidermis, 36 per cent.
8. .. pectoral fascia, 35 per cent.
9. .. pectoral muscle, 15 per cent.
10. .. perinodal axillary tissues, 35 per cent.

References
Fig. 1. A, normal mammary gland cells; B, small lymphocytes; C, other stroma cells; M, malignant cells.

Fig. 2a. Small nucleus (Group I).

Fig. 2b. Small nucleus (Group I)

Fig. 3. Medium nucleus (Group II)

Fig. 4. Large nucleus (Group III)

N.B. Lettering for all figs.
A, normal glandular cells
B, small lymphocytes
C, other stroma cells
M, malignant cells.

NUCLEAR SIZE GROUPS
Fig. 5a. *mixed* nucleus (Group IV)

Fig. 5b. *mixed* nucleus (Group IV)

**NUCLEAR SIZE GROUPS**

Fig. 6

**NUCLEAR CHROMATISM**

A. Normal glandular cells
B. Small lymphoid cells
C. Other stroma cells
M. Malignant cells
Fig. 9. "Differentiation." a, f, cytoplasmic vacuoles.
b. vacuolated & non-vacuolated cells in same tumour.
c, d. adenomatous formations.
e. tubule formation with columnar cells.

Fig. 10. cytoplasmic vacuoles (cf. Fig. 9, a.)

Fig. 11. Solid tubules cut transversely (invading deep muscle)

"Differentiation" in malignant mammary tissue.
Adenomatous formations.

"pseudo-glandular" formations.

"Differentiation" in malignant mammary growth.
"DIFFERENTIATION" in malignant mammary tissue.
Fig. 18. Adenomatous structure in a recurrent nodule in skin.

Fig. 19. Adenomatous formation in a perivascular lymph vessel.
X: muscle in vein wall.

"DIFFERENTIATION" in malignant mammary growth.
Fig. 20. X, squamoid cells, Y, columnar cells

Fig. 21, a. Squamous change in a malignant lacrimation cancer.

Fig. 21, b. Squamous tissue with intercellular bridges and keratin formation.

"DIFFERENTIATION" in malignant mammary tissue.
Fig. 22. Malignant growth in ducts before invasion. X, lymphocytic cell accumulations.

Fig. 23. Malignant growth in duct (d) with invasion of connective tissue (c)

Invasive growth in malignant mammary tissue.
Fig. 24. Invasion of lymph vessels(+) in circum-mammary fat.

Fig. 25. Invasion of small lymph vessel.(1)

Fig. 26. Invasion of small lymph vessels(+) in circum-mammary fat.

Invasion of lymph vessels in malignant mammary tissue.
Fig. 27. Invaded lymph vessels (l) and stroma (c)
in Scirrhous carcinoma.

Fig. 28. Invaded lymph vessel (l) and stroma (c)
in papillary adenocarcinoma (P).

Fig. 29. Invaded lymph vessels in corpus mammae (x).

Fig. 30. Invaded lymph vessels of subareolar plexus (l). m. nipple muscle.

Invasion of lymph vessels in malignant mammary tissue.
Fig. 31. Invasion of vein.

Fig. 32. Invasion of vein.

Fig. 33. H.P. of cells in vein (fig. 32)

Fig. 34. Invasion of vein (same vessel, in transverse and oblique section)

Fig. 35. Invasion of vein

**INVASION OF VEINS** in malignant mammary tissue.
Fig. 36. Invaded vein, with thrombus and overgrowing endothelium.

Fig. 37. Invasion of blood capillaries in dermis, at x and y.

Fig. 38. Invasion of vein in centre of axillary lymph node.

INVASION OF BLOOD VESSELS IN BREAST AND AXILLA
Fig. 39. Invasion of blood vessels in a lactation breast cancer, rapidly fatal.

Fig. 40. Invasion of veins in axillary fat. X, endophlebitis, with no tumour cells.

Invasion of blood vessels in breast and axilla.
Fig. 41. Invasion of vein in axillary fat.

Invasion of Blood Vessels in Breast and Axilla
Fig. 43. Invaded nerves in axilla (autopsy).

Fig. 44. Invaded and partially destroyed nerves in axilla (autopsy).

INVASION of NERVES (advanced malignant growth).
Fig. 45. Invasion of a large nerve in axilla (brachial plexus, autopsy) with destruction of fibres.

Fig. 46. Invasion of epidermis

Invasion of NERVE and EPIDERMIS in malignant mamma.
Fig. 47. Invasion of pectoral muscles (P) and dermis (D) in advanced mammary carcinoma.
THE FREQUENCY AND VARIATION OF MALIGNANT CELL AND TISSUE CHARACTERS

AND

THE FREQUENCY AND EXTENT OF INVASIVE GROWTH IN MAMMARY CARCINOMA.

A Survey of findings in 460 Breast Cancers.

By

E.K. Dawson.

M.A., M.B.
METASTATIC TUMOUR OF THE BREAST

With the Record of a Case.

E. K. Dawson.
M.A., M.B.
Metastatic Tumour of the Breast

Virchow's statement that almost all those organs which show a strong tendency to develop primary malignant tumour are seldom the site of secondary tumour growth finds confirmation in a study of mammary cancer. Recorded cases of metastatic tumour in the mamma are rare and, except when the breast involvement is part of a terminal generalised malignant dissemination, their acceptance demands convincing histological description or illustration.

Though the breasts are possibly affected by metastatic tumour in the terminal stages of many cases of malignant disease, it is apparently unusual for the mammary tissues to be investigated as part of a routine autopsy examination unless there was evidence in vivo of mammary invasion. It is therefore impossible to assess with any accuracy the actual frequency of such invasion; on the other hand, one cannot accept tumour in the breast as necessarily metastatic, when it forms part of a generalised malignant dissemination. Discussion of "metastatic mammary tumour" is therefore confined to those recorded cases where clinical and microscopical data point, more or less conclusively, to primary growth in another organ or tissue. Other groups /
groups of cases need, however, brief mention.

(a) Mammary involvement in generalised malignancy.

It is noteworthy that few cases are on record. Sanderson (1855), Arnott (1869), Legg (1878), Handley (1907) and Tod (1929) noted metastatic tumour in one or both breasts as a terminal manifestation of skin or ocular malignant melanomata. These tumours were, in general, pigmented and therefore truly secondary, though in some cases they involved the mammary skin as part of an extensive subcutaneous tissue spread rather than the substance of the breast itself. It is interesting to note that, at a time when these pigmented growths were considered sarcomata, Arnott believed that "they should be classed with the true cancers".

(b) Statistical and other references to metastatic mammary tumours.

In a collected series of 292 primary cancers of the cervix uteri, Schroeder (1887) found secondary invasion of the breast in 3 cases. Wells (1919), at a meeting of the American Association for Cancer Research, mentioned a case, seen at autopsy, of "extensive carcinoma of the thyroid gland with both adrenals, both mammary glands and both ovaries extensively involved by metastases". Petzold (1923), in a survey of necropsy material at Kiel for the years 1914 - 18, noted 2 secondary breast cancers in 140 malignant cases, one from /
from a primary gastric, the other from a uterine growth; the latter showed extensive spread, with invasion of both lungs, pleurae and retroperitoneal lymph nodes. No histological descriptions or illustrations are presented in these references. An exhaustive search of the literature would probably reveal other similar cases.

(c) Bi-lateral mammary tumours.

The criteria for distinguishing primary bi-lateral mammary tumour from metastatic growth in the second breast raise many clinical, anatomical and histological points. Billroth (1911) considered that, as metastatic mammary tumour originating elsewhere than in the other breast is so rarely observed, it can hardly be compared with bi-lateral malignant growth. In a series of 266 autopsy cases of breast cancer, with 33 showing bi-lateral tumour involvement, Török and Wilhelshöfer (1880) were unable to decide whether the condition was a true metastasis in the second breast or a local extension of the primary disease or a simultaneous new growth. It is probable that many of the cases described as "primary bi-lateral" are actually metastatic in one of the breasts, especially when the second tumour appears after the removal of an earlier /
earlier growth, but the clinical and microscopical data presented are frequently insufficient to decide the relation of the two.

(d) **Localised mammary involvement in blood and similar diseases.**

Tumour in the breast may result from the arrest and proliferation in the mammary tissues of cells from the circulating blood. These are not metastatic tumours in the ordinarily-accepted sense, though the clinical appearance in several recorded cases suggested malignant deposits. McWilliams and Hanes (1912) described, in a woman of 33 years with axillary lymph node enlargement, bi-lateral mammary tumours which were diagnosed as lymphosarcoma but later proved to be "incidents in a generalised leucaemic process". A somewhat similar case was reported by Simon (1912) of an apparently malignant mammary tumour in a girl of 16 years, associated with a typical myeloid leucaemia. Similar leucaemic tumours in the breast are recorded by Trevithic (1903) and others and Ziegler mentioned "pseudo-leucaemic granuloma" in the female breast. All such mammary "tumours" are metastatic growths only if we extend the connotation of "tissue" or "organ" to include the circulating blood.
In addition to the cases which fall into one or other of these four groups, there have been recorded with some detail a number of breast tumours described as secondary to primary malignant development elsewhere, that is, metastatic in the usual sense. Their main features are summarized in the following table. (see next page)

It is difficult to accept some of these cases as true metastatic mammary tumours. Only in four (cases 3, 5, 7 and 10 in the table) are histological illustrations presented and these, especially in the "sarcoma" cases, are not always convincing. On the evidence submitted, the growths in cases 4, 6, 7 and 9 are apparently truly secondary in the mamma, the primary site in each of these being the gastric mucosa. Case 7 (Moutier and Marre's) is specially convincing, with good clinical and autopsy notes and illustrations.

Record of a new case.

The following case is considered to be one of a metastatic, not a primary tumour of the mamma. The available clinical and autopsy data are meagre, but the tissue submitted for microscopical examination provided striking histological pictures of the distribution/
<table>
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<tr>
<th>No.</th>
<th>Author and Date</th>
<th>Sex + Age of Patient</th>
<th>Primary Tumour in</th>
<th>Histological Diagnosis</th>
<th>Metastases in</th>
<th>Metastases in Elsewhere</th>
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<td>1</td>
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<td>M. 45</td>
<td>Liver</td>
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<td>F. 30</td>
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<td>F. 65</td>
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<td>+</td>
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<td>7</td>
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<td>F. 51</td>
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<td>“Granulcar carcinoma”</td>
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<td>+</td>
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<td>8</td>
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<td>Stomach</td>
<td>“Lymphoscarcoma”</td>
<td>+</td>
<td>-</td>
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<td>9</td>
<td>Stahr 1923</td>
<td>M. 46</td>
<td>Ovaries</td>
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<td>10</td>
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<td>F. 16</td>
<td>Ovaries</td>
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distribution and path of spread of the malignant cells. These mucus-containing, signet-ring cells, considered as originating in the gastric mucosa, stand out in contrast to the tissues of the invaded organs and define the structure and distribution of the lymph vessels they have entered. The sections described form part of a large amount of material collected for a study of the microscopical anatomy and topography of lymph vessels, with special reference to those of the mammary and axillary areas and the case seems worthy to put on record as illustrating an unusual form of malignant tumour dissemination, in which the cells are apparently circulating in the lymph stream without forming obvious deposits.

Clinical history. A woman of about 25 years of age, who had recently given birth to a child, had not regained her health and came under observation as "an obscure case of indigestion and wasting of a few weeks' duration". There was no symptom other than slight indigestion and though the loss of weight suggested carcinoma, there was no evidence of definite malignant growth except an enlarged lymph node on the thoracic wall of the left axilla. Before death, which occurred shortly after admission to hospital, the enlarged lymph node was excised and sent to this Laboratory for diagnosis.

Autopsy /
Autopsy confirmed the tentative diagnosis of gastric disease and showed an ulcerated carcinoma of the stomach. There was no ocular evidence of tumour in any other organ. The breasts showed the normal physiological hypertrophy of pregnancy and lactation. Both mammary glands, the pancreas, one ovary and the lymph nodes adjacent to these organs, with portions of the stomach and intestine were sent for histological investigation.

**Histology**

**Stomach.** The tumour in this organ gives histological evidence of being the primary focus of the malignant disease and shows a proliferative growth in the mucosa (fig. 1) with ulceration. The tumour involves the whole thickness of the stomach wall to the serous coat, though the latter, in the area submitted, is not invaded. Malignant cells are present in the lymph vessels of the mucosa itself, in the muscularis mucosae and in the submucosa (fig. 1, x). There is a diffuse carcinomatous infiltration of the muscle coats (figs. 2 and 3), invasion of the nerves and of the myenteric plexuses lying between the layers of gastric muscle fibres (figs. 4 and 5). The type of tumour cells varies but is, in most parts, the typical mucus-containing signet-ring cell characteristic of many carcinomata of the digestive tract.

**Intestine /**
A lymph node removed with the ovary (exact location not noted) shows almost complete replacement by tumour growth.

Axillary lymph node. This node, removed from the left axilla before the death of the patient, shows extensive replacement of lymphoid tissue by malignant growth. The distended peripheral sinus is filled with signet-ring cells (fig. 11), the varied size and morphology of which are shown in fig. 12. Afferent and efferent lymph vessels show emboli of similar, more or less detached malignant cells (fig. 14) and there are appearances in the thickened capsule which point to invasion of blood vessels (fig. 22). In the substance of the lymph node are scattered groups of non-mucinoid malignant cells lying among those of the mucus type (fig. 13).

Right and Left Breasts. Tissue from both mammae shows invasion of practically the entire lymph vascular system by malignant cells of the same mucinoid type. While the other organs examined also show this form of secondary extension, the main interest of this case lies in this unusual occurrence in the mammae. Several important points are illustrated by the histological examination.

1. The hypertrophy of the mammary lobules, consequent on the recent pregnancy (fig. 15).
2. Evidence of lymph vessel distension, even when the channels contain no malignant cells (fig. 16) and a suggestion of the actual increase of lymph vascularity, associated with functional (pregnancy and lactation) activity. This has an obvious bearing on the facilitation of malignant cell spread in mammary tumours emerging during reproduction and supports the clinical evidence of the high malignancy of such growths.

3. The participation of lymph vessels of all sizes in the malignant cell spread.

4. The distribution of invaded lymph channels, large and small, entirely in the interlobular connective tissue (fig. 16). The position of the invaded vessels is partly periductal, as is evident near the larger ducts (fig. 17), partly perivascular (figs. 18 and 19); their distension by tumour cells allows of their being followed for considerable distances in either position. No lobule is itself invaded, though in some areas lymph vessels at the periphery of lobules show malignant cell contents (figs. 20 and 21).

5. The wall of the mammary lymph vessels shows no structure beyond an endothelial cell lining. Round the largest interlobular vessels filled with tumour cells a slight connective tissue condensation is suggested, but there is no evidence of "perilymphatic fibrosis".
Valves are apparent in lymph vessels of all sizes (figs. 20 and 21, v). No muscle coat is seen in the lymph vessels of the mammae or of any of the other organs examined, but a variable muscle content is found in the wall of some afferent and efferent channels observed near the various lymph nodes.

6. There is a striking absence of fibroblastic activity and of chronic inflammatory cell accumulations in the mammary stroma in response to the presence of the malignant cells.

7. Many of the channels containing tumour cells and lymphocytes also show considerable numbers of red blood cells (fig. 19, ro), but, although malignant invasion of veins is suggested both in the primary tumour and in the axillary lymph node (fig. 22), the blood-containing vessels in the breast are, in my opinion, lymph rather than blood vessels, as judged by their structure and distribution.

**Discussion**

The special interest of this case lies, as already mentioned, in the type of tumour spread. It appears that the cancer cells are moving in the lymph stream through the various organs without giving rise to obvious tumour nodules.

The origin of the tumour seems quite definitely to be the stomach, which shows tissue and lymph vessel invasion.
invasion extending from ulcerated mucosa almost to the serous coat. Involvement of the other organs is entirely a lymph vessel carcinosis. Willis (1934) has found that carcinoma of the stomach may produce almost body-wide dissemination of this type, though in cases where the gastric tumour forms mucus-containing malignant cell deposits in the ovary, metastases in other organs are rare. The coincident involvement of breast, ovary and pancreas from a primary gastric growth is apparently very unusual, as no other recorded case has been traced.

The limited number of organs sent for microscopic examination makes the path of spread from the primary tumour uncertain. Appearances in the pancreas suggest invasion from the coeliac lymph nodes, into which it normally drains, by reversal of the lymph flow, as there was no evidence of continuous spread from the stomach and the pancreas shows only a marginal, and therefore presumably early lymph vessel carcinosis, without destruction of the glandular tissue. In the ovary, the preservation of the normal size and shape of the organ, the absence of malignant cells on or near the germinal epithelium, the limitation of tumour tissue to the lymph channels, the distension of the sinus between cortex and medulla and the apparent movement of cancerous emboli outwards from this plexus towards the more superficial cortical /
cortical tissue all suggest metastatic invasion of the ovary by retrograde lymph flow from the neighbouring malignant lymph node rather than a transcoelomic transplantation, a suggestion strengthened by the integrity of the gastric serosa. Whether the malignant tissue in the ovary be considered a true Krukenberg tumour need not be discussed here.

Evidence for the metastatic nature of the bilateral mammary involvement lies in -

(a) Carcinogenesis in the gastric mucosa.
(b) The non-participation of the glandular tissue of the breasts in any hyperplastic or neoplastic activity and the absence of any primary tumour appearances.

The lobules which hypertrophied during pregnancy already show slight involution, possibly from disuse, possibly also from pressure by the cancer-distended lymph channels; the ducts are either quiescent or show only slight lining-cell proliferation with desquamation.

(c) The type of malignant cell, a mucus-containing, signet-ring cell similar to that formed in the primary gastric growth, is evident in all the secondarily-invaded organs, including the mammae. The mucinoid ("colloid") cell met with in certain types of primary mammary carcinoma indicates, in my opinion, a second-
secondary degenerative change and not, as here, a primary malignant cell formed elsewhere and carried in the lymph stream to the mammary tissue.

(d) The limitation of the tumour cells in the mammary area entirely to the lymph channels indicates a spread throughout rather than a genesis within the organs.

The age of the patient, a young woman of about 25 years and the increased lymph vascularity and distension associated with pregnancy may explain the rapid and extensive mammary lymph vessel carcinosis in this case. Stasis in the lymph channels, combined with extensive malignant replacement of axillary lymph nodes without obvious tumour formation in the mamma, suggests that in this organ, as in pancreas and ovary, the path of tumour invasion was by retrograde lymph flow from the axilla, subsequent to invasion and blockage of supraclavicular lymph nodes from the gastric growth. This path of mammary invasion was well demonstrated in the progressive clinical picture described in Moutier and Marre's case, where supraclavicular nodes, axillary nodes, thoracic skin and mammary tissues were invaded, in this sequence. Virchow observed supraclavicular lymph node involvement in 4 per cent of a series of gastric cancers.
cancers and Willis found cervical nodes, most frequently the left supraclavicular, invaded in 7 of 41 gastric cancers, a much higher percentage. A routine examination of the cervical lymph nodes in any series of gastric tumours, whether clinically enlarged or not, would throw light on the frequency of malignant spread to the axillary and mammary tissues; it would also be helpful in defining the structure and distribution of the lymph vessels in these areas, where they might be made prominent by malignant invasion, associated with the stasis and vascular distension of a reversed lymph flow.

The type of malignant cell observed in the different organs and its variety of size and morphology are seen in fig. 23 and the other illustrations; it is noteworthy that definite mitoses were found only in tumour cells of non-mucinoid type observed in the primary growth and in several areas in the lymph nodes (cf. fig. 13 and 23,F) and not in the mucinoid cells circulating in the lymph stream.

Summary.

Metastatic mammary tumour is apparently a rare occurrence. Ten recorded cases are summarized and a new one, with the primary growth in the stomach, is described. This tumour, of mucus-containing, signet-ring /
ring cell type, showed extensive lymph vessel carcinosis in both mammae, ovary and pancreas, without the formation of obvious metastatic deposits in these organs; the associated lymph nodes were largely replaced by tumour.

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Fig. 1. Gastric Tumour (primary growth), with invaded lymph vessels (x) in muscularis mucosae and submucosa. x60.

Fig. 2. Gastric Tumour, with malignant invasion of muscle coats. x60.

Fig. 3. Gastric Tumour, with malignant invasion of muscle. x300.
Fig. 4. Gastric Tumour, with malignant invasion of nerve (N)  x 300.

Fig. 5. Gastric Tumour, with malignant invasion of myenteric plexus (P) and nerve (N)  x 300.

Fig. 6. Pancreas, with lymph vessel carcinosis (semi-diagrammatic)
Fig. 7. Lymph vessel (x) between cardiac lymph node (left) and pancreas (right, not shown) invaded by tumour. X60.

Fig. 8. Ovary, with lymph vessels of plexus (x) between cortex (c) and medulla, invaded by tumour. X60.

Fig. 9. Ovary, invaded lymph vessel (cf. Fig. 8, x) showing wall and contents. X300.

Fig. 10. Ovary: small lymph vessels in cortex, with malignant cells and lymphocytes. X400.
Fig. 11. Axillary Lymph Node: peripheral sinus (ps) and medulla (m) invaded by tumour. x 60.

Fig. 12. Axillary Lymph Node: tumour cells (signet-ring) in peripheral sinus. x 300.

Fig. 13. Axillary Lymph Node: tumour cells of non-mucinoid type in medulla. x 300.

Fig. 14. Axillary Tissue: afferent lymph vessel invaded by tumour. x 300.
Fig. 15. Mamma: pregnancy hypertrophy of glandular tissue, and invaded lymph vessels (x). x60.

Fig. 16. Mamma: distended interlobular lymph vessels with tumour cell emboli. x60.

Fig. 17. Mamma: duct (d) and invaded periductal lymph vessels (x). x60.
Fig. 18. Mamma: small arterial loop (A) with invaded perivascular lymph vessels (X), interlobular invaded channels (X').

Fig. 19. Mamma: part of arterial loop (A) of Fig. 18, with perivascular lymph vessels (X) containing tumour and red blood cells (RC).}

Fig. 20. Mamma: lymph vessel (X) with tumour cells and valve (V) at periphery of lobule (L).
**Fig. 21.** Mamma: invaded lymph vessels (x) with valve (v) at periphery of lobule (L).  
\[x \times 300.\]

**Fig. 22.** Vein in thickened capsule of malignant lymph node, with tumour cells in lumen and muscle wall.  
\[x \times 100.\]

**Fig. 23.** Types of Tumour Cells in the invaded organs, compared with normal blood and tissue cells at same magnification (A).  
B. in stomach (primary tumour);  
C. in pancreas;  
D. in ovary;  
E. in mammary;  
F. in axillary lymph node (m, mitosis).
METASTATIC TUMOUR OF THE BREAST

With the Record of a Case.

by

E.K. Dawson.
11.

DRAWINGS OF PATHOLOGICAL MAMMARY TISSUE
ILLUSTRATIVE OF A METHOD OF TUMOUR RESEARCH.

by

S. K. Dawson
M.A., M.B.
These drawings are a selection from a series of over 120 illustrations made from routine material received from the Pathology Department of the Royal Infirmary and from the Histological Department of the Royal College of Physicians Laboratory, Edinburgh.

They represent the preliminary stage of the method used in an investigation of mammary tumours, in an attempt to correlate clinical, anatomical and microscopical findings in benign and malignant growth with the methods and end-results of treatment.

The operation material received is sectioned in a plane which passes through the nipple and the palpably greatest diameter of the tumour area and a rapid pencil or wash drawing is made of the cut surface, to indicate the anatomy of the new growth and its relation to the breast and surrounding tissues. If this plane does not also pass through obviously invaded areas in the axilla, the axillary tissues are sectioned serially to locate the presence of actually involved or "suspicious" lymph nodes. If necessary, the tissue is fixed for some days and the cut surface levelled for drawing by binding to a large sheet of glass. The areas subsequently chosen and prepared for microscopical examination are indicated on the drawing or on a diagram of it, in order that the macroscopical and microscopical /
microscopical pictures of the same areas may be compared. In cases which, from their clinical history or anatomical features, suggest particular histological interest, a whole-breast section is prepared, in addition to the routine smaller sections of selected areas.

The numbers on the drawings, where inserted, indicate the position and extent of tissue prepared in small sections.
Mrs. S. act. 47
Small defined Scirrhous Cancer. 1, 2, 3. Areas sectioned. Radical operation.

Mrs. S. act. 46
Typical Scirrhous Cancer - axilla invaded.
Miss T. aet 73. Large haemorrhagic Cancer—duration 5 yrs.
Miss M. aet: 51

Palliative operation for large ulcerated Carcinoma.
Tumour Area, with Invasion

Remains of nondescript tissue in tumour area.

Areas 1, 2, 3 sectioned for micro-

Examination:

1. Axillary node

2. Regional lymph node

3. Axillary lymph node
Mrs. R. aged 77

Remains of glandular tissue in a fatty breast

Simple Amputation (because of Age)

Mrs. V. aged 83
Advanced Cancer replacing Mammary Tissues. Palliative operation, for ulceration.
Benign Mammary Tumour [Fibroadenomatosis] in Male Subjects.

Gynecomazia

(Sections prepared included the entire corpus mammæ).
Tumour

Normal Mammary Tissue

Tumour

Pectoral Muscles

Axillary Fat + Lymph Node
First breast treated in a
Mrs. J. H. aet. 52 Bi-lateral Carcinoma. Full interstitial Radium therapy
followed by amputation
Mrs. C. aet. 53.
Palliative operation.

Large (whole area) sections made, in addition to 6 small ones.
Curious 'bosselated' skin invasion and ulceration (....)

of A + B (surface view)
Carcinoma with Pregnancy (8½ months)

Mrs. H. aet. 42
NOCYh 0.
Mammary Tissue Carcinoma with Lactation
Malignant Axillary Lymph Nodes
Pectoral Muscles
Tumour
Normal Mammary Tissue
Carcinoma with Lactation
Lactating Breast with Carcinoma (no skin or deep muscle included)

Lactating Breast, with Carcinoma (M) and normal tissue (G)

Whole breast sections of malignant breasts.
(Small sections were also prepared.)
Fig. A. [15th operation tissue] Right mamma. Plane of tissue section for B.

Fig. B. Cut surface of tissue. Fig. A. Right mamma.

Fig. C. 16th operation (simple mastectomy) - Right mamma.

Figs. A-F. Case of ?self-mutilation, producing successive "lumps" of haemorrhage into fatty tissue. Multipara, age 33.
Fig. D. Left breast. x—x plane of tissue section. Fig. E. x
Y—Y

Fig. E. Left breast. (cf. plane x—x, Fig. D)
Fig. F. Left Breast. (cf. plane Y-Y, Fig. D).

Showing small sterile abscess, and haemorrhages with venous thrombosis extending into deep muscle.
DRAWINGS OF PATHOLOGICAL MAMMARY TISSUE

ILLUSTRATIVE OF A METHOD OF TUMOUR RESEARCH.
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Papers in MSS.


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(Illustrations by the Writer.)

1936.