CLINICAL, HISTOLOGICAL, AND SCINTIGRAPHIC STUDIES OF

THE AXILLARY LYMPH NODES IN PATIENTS WITH OPERABLE

BREAST CANCER

BY

R.B. Black, M.B., M.S., (Adel.), F.R.A.C.S.

University Department of Surgery,
The Queen Elizabeth Hospital,
Woodville,   South Australia.

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Table A. Clinical details and 'superstaging' results of 172 patients with operable breast cancer.

Figure A. Histological features of lymph node 'reactions'.

Table B. Retrospective histological review of nodes excised at mastectomy from 172 patients.

SUMMARY

It is surprising that there remain so many areas of controversy concerning the axillary nodes in breast cancer. There is disagreement on the value of palpation for clinical staging; on the importance of certain histological 'reactions'; on the need if any to determine the nodal status before operation; and, on how many nodes should be removed.

This thesis is the result of three investigations on axillary lymph nodes directed at these and related matters. All three projects were initiated during a year's study leave in 1979. Further evaluation and assessment of the data proceeded during 1980.

A.   The first arose because of my involvement in the follow-up patients after mastectomy. All such women had been carefully assessed and documented with respect to clinical stage, and also to a series of investigations to detect occult metastases ('superstaging' tests). 172 women had been followed for over two years. Histological sections of all nodes excised were reviewed, with respect to (a) the size and number of nodal metastases and (b) the node 'reactions' of sinus histiocytosis lymphocyte predominance and germinal centre predominance.

B.   In the second project a modified technique of axillary lymphoscintigraphy was developed using Technetium labelled Antimony Sulphide colloid. Although this agent had been used in other regions of the body to detect nodal metastases there had been only one previous study of the axillary nodes, and in that investigation it was claimed to be effective in the diagnosis of breast cancer.

SUMMARY cont.

C.   The third project was concurrent with, but arose from, the
other two. A detailed dissection, mapping, measurement and histological
assessment of axillary nodes was undertaken in 50 women undergoing mas-
tectomy and axillary node sampling. In an attempt to correlate
histological features with scintigraphic appearances, a larger sample
of nodes was dissected than had been excised from patients in Study A.
As a result it was possible to obtain original data on the sizes of
lower axillary lymph nodes, whether 'reactive', metastatic or normal
(unstimulated). The site of all nodes was also defined, and inferences
could be made as to the size at which axillary nodes become palpable.

        The findings were as follows :

1.   Careful clinical assessment is of fundamental importance in
predicting recurrence.

2.   Node histological appearances are no better (in a small node
sample) unless features other than metastases are taken into account.

3.   Sinus histiocytosis and lymphocyte predominance are favourable
features, lymphocyte depletion and germinal centre predominance are
unfavourable. Micrometastases are of little consequence.

4.   'Superstaging' tests are valueless except in a small, selected,
group where nuclear bone scanning may have predictive value.

5.   Axillary lymphoscintigraphy cannot diagnose breast cancer.

6.   Axillary lymphoscintigraphy, however, is accurate in the
diagnosis of prognostically significant lymph node metastases in 9 out
of 10 patients.

7.   A size range of all types of nodes in the axilla has been
defined.

SUMMARY cont.

8.   The site of such nodes has also been determined - germinal
centre predominance is commonly found close to the primary tumour
(as are metastases). Nodes showing other features are not.

9.   For nodes to be palpable they usually contain metastases,
and are 1g weight and/or 1.5 cm in diameter or more.

10.   Palpable, suspicious, nodes and impalpable nodes are well
correlated with the presence or absence of metastatic deposits (79%,
68%).

11.   Palpable, non suspicious, nodes do not confer prognostic
advantage. Nor do they predominantly show 'favourable reactions'.

In addition the appendix contains computer data, showing :

12.   That tumour cellularity is an important prognostic index, and

13.   That oestrogen receptor content may need modification if its
level is to be used as an index of prognosis, and that

14.   Precise knowledge of the number of nodes containing deposits may
also be extremely important, even when obtained from a small node
sample.

Findings 2, 6, 7, 8, 9, 12, 13 and 14 represent new information.
Findings 1, 3, 4 and 10 confirm and amplify some previous work, though
they are at variance with others. Findings 5 and 11 refute the single
previous paper on each topic. Areas of controversy are discussed,
especially those publications whose results are apparently at conflict
with the results in this thesis.

EXPLANATION OF THESIS

The thesis is divided into 8 chapters, and an appendix. This last contains the bulk of the raw data together with computer analysis and illustrations of node reactions and scans. The background to the studies are in Chapter 1. It is not extensive as previous work in the field of projects B and C (in Summary) is negligible. The dissatisfaction with clinical assessment of nodes is examined and several questions are raised.

Chapters 2 to 6 are self-contained descriptions of five studies embodied in the three major projects outlined in the Summary. Three of the chapters are modifications of published work. (Black et al 1980 a, b, 1981).

In Chapter 2 the value of clinical staging is confirmed and 'superstaging' is rejected as an index of early recurrence. Nodal biopsy is shown to be important. In particular sinus histiocytosis and lymphocyte predominance are confirmed as advantageous features; but germinal centre predominance is not. Micrometastases are shown to be much less grave findings than gross metastases. Computer analysis (in the appendix) amplifies these findings showing that metastases in a single node are less serious than deposits in more than one. It also indicates that tumour cellularity may be an additional independent prognostic factor - a new finding.

In Chapter 3 lymphoscintigraphy is investigated as a diagnostic test for breast cancer. Even after basic and extensive modifications which allow for more interpretable scans, there is shown not to be any difference between scans obtained in benign (11 patients) and malignant breast disease (68 patients).

EXPLANATION OF THESIS cont.

In Chapter 4 the same technique is examined for its ability to predict the presence of nodal metastases in the axilla. In the 90% of scans which were interpretable, prediction of gross metastases was very reliable - 5 out of 6 clinical misclassifications being corrected by the scan findings.

Chapter 5 contains a clinico-pathological correlation of node assessment in nearly two hundred patients, the retrospective series from Chapter 2 and a prospective series of 50 patients who had a larger sample of nodes excised. The correlation with respect to nodal metastases was surprisingly good - reflecting no doubt the careful and strict criteria for clinical assessment - 79% for those with clinically suspicious nodes, and 68% for those with impalpable nodes. In nearly half of the 32% misclassified in the latter group, the metastases were only microscopic. Such a correlation provides the basis for the useful prognostic index of node palpation in Chapter 2. In addition sinus histiocytosis and lymphocyte predominance were commoner in impalpable nodes, but were uncommon in patients whose palpable nodes were thought to be benign. This was the first occasion in which this group's histological node status had been evaluated. Also new was the demonstration that the larger node sample from the prospective series had identified more sinus histiocytosis, lymphocyte predominance, lymphocyte depleted, and fatty nodes but not more nodes with metastases (gross or microscopic) or germinal centre predominance.

In Chapter 6, perhaps for the first time, the 'geographical' site of 'reactive' nodes was identified. Sinus histiocytosis and lymphocyte predominance were shown to occur higher in the axilla than

EXPLANATION OF THESIS cont.

germinal centre predominance and metastases; lymphocyte depleted and fatty nodes were also found proximally. This provided the explanation for the higher yield of sinus histiocytosis, lymphocyte predominance etc. in the prospective series. A detailed range of lymph node sizes (weight and diameter) was defined. All 'reactive' and metastatic 'classes' of nodes were (as a group) larger than unstimulated nodes though there was considerable overlap, and the difference between the diameter of sinus histiocytosis and unstimulated nodes was not significant statistically. Finally it was concluded, from an assessment of the sizes of nodes in those whose nodes were palpable, that the limit of palpability is of the order of 1.5 cm diameter and/or 1g in weight. Even so 'reactive' nodes exceeding those limits were more often than not impalpable.

Chapter 7 places in perspective the results of the preceding five chapters. Work published previously, or during the course of these studies, is analysed. Four particular areas of controversy are examined : (1) the dissatisfaction with node palpation on the one hand and the allegedly favourable group with benign node enlargement on the other; (2) the 'protective' nature of some node reactions, notably sinus histiocytosis and lymphocyte predominance; (3) the previous (possibly spurious) results with 'diagnostic' lymphoscintigraphy; and, (4) the early enthusiasm with 'superstaging' tests and the findings of an 'additional source of nodes' in the axillary tail of the breast. In addition the complementary information from the computer analysis is discussed with respect to prognostic factors in operable breast cancer. The relationship between tumour cellularity, oestrogen receptor status and prognosis is examined.

The conclusions in Chapter 8 are the answers to the 8 questions raised in Chapter 1.

DECLARATION

The work in this thesis has not been presented for the award of any other degree or diploma in any University. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is given in the text.

(R.B. BLACK)

Adelaide. April 1981.

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ACKNOWLEDGEMENTS cont.

The responsibility for the conduct of all projects, the interpretation of data, and the conclusions drawn are entirely mine.

The thesis is dedicated to my wife Tania, for her encouragement, support and forbearance.

CHAPTER I

A BACKGROUND TO THE AXILLARY NODES IN BREAST CANCER

The aims of the studies in this thesis were to investigate certain areas of controversy concerning the axillary lymph nodes in patients with operable breast cancer. In spite of the fundamental role of node palpation in all methods of clinical staging, the significance of palpable lymph nodes has been regarded by different authorities with emotions varying from near complete faith on the one hand to total disillusionment on the other. Yet there has been little interest or enthusiasm in developing methods to determine before operation whether nodal metastases are present or not. Many clinicians had relied entirely on pathological information after mastectomy; others had supplemented this with investigations for occult metastases, or 'superstaging' tests. Some had suggested that prognostic (and hence therapy-planning) information should be based entirely on the number or size of histologically determined nodal metastases, others were more impressed with the value of one or other form of 'reaction' in the nodes. There appeared furthermore to be little information as to whether nodes in the axilla are normally palpable, what size they might be, or what node 'reaction' might be encountered in normal individuals.

A wide spread reappraisal of the importance of lymph node information (clinical, histological, radiological etc.) was called for. The opportunity for me to do this arose during 1979 while on study leave in Edinburgh where a large number of patients with operable breast cancer were being treated and/or followed after carefully documented preoperative assessment.

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

1.   <u>THE LYMPH NODE AS AN ORGAN OF CLINICAL INTEREST</u>

Considering their small size and apparent homogeneity it would seem at first surprising that so much clinical interest should be directed toward the collections of lymphoid tissue called lymph nodes or glands. Almost as soon as the novitiate medical student enters the <u>anatomy</u> dissecting room he is confronted with the problem of identifying these structures. He is introduced to the concept of spread of disease to such organs, and in particular to the spread of breast cancer to the nodes in the axilla. If he is lucky enough, or diligent enough in his dissection, he may find a few nodes in the axilla. A few years later he is introduced to the fact that palpation of such organs constitutes a fundamental part of the routine <u>physical</u> <u>examination</u> of patients. He is surprised to learn that enlargement of such organs occurs commonly, and that such palpable enlargement is often taken by the clinician as presumptive evidence of disease, especially malignant disease.

With such a fundamental and persuasive introduction to lymph nodes, it would come as a surprise for him subsequently to realise that palpation of nodes, and the interpretation of their palpability, is a matter of disagreement, surrounded by controversy or trapped in misunderstanding. There has been no exhaustive study to define clearly the <u>size and palpab-ility</u> of normal nodes in different regions of the body. Very little objective data is available in standard textbooks of anatomy and surgery - none for example in Aird (1950), Johnston and Whillis (1956), Love (1959), Allen (1970), Nardi and Zuidema (1972), Schwartz (1974), Illingworth and Dick (1975), or Clain (1980). Maximow and Bloom (1957), state that nodes vary 'from 1 to 25 mm in diameter'. Goldsmith (1977) suggests that they 'vary in size from a few millimetres to more than a centimetre',

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

while Basmajian (1975) more colourfully states that they vary in size

'from a pin's head to an olive'.

Both Allen (1970) and Goldsmith (1977) agree that, within the

axilla, the central group are the largest and 'most often clinically

palpable'. Wilson (1979) suggests that nodes '5 mm in diameter can

frequently be palpated in the normal axilla'.

No technical or experimental data are given to support any of

these claims.

Many of the <u>terms used</u> to describe changes in lymph nodes have

been imprecise. <u>Histologically</u>, the term 'lymphadenitis' may be quite

inaccurate (Symmers (1966), while even the term 'reactive hyperplasia'

carries the suggestion that the changes are a reaction to some intrinsic

or extrinsic agent which is beneficial and/or protective. In recent

years a variety of new terms has been introduced - again without

precise definition and/or acceptance. Changes suggested to be of a

'<u>reactive</u>' type include <u>sinus histiocytosis</u> (Black et al 1953, Black

and Speer 1960), <u>germinal centre predominance</u> (Syn. follicular or

germinal centre hyperplasia) and <u>lymphocyte predominance</u> (Syn. paracortic-

al hyperplasia, Tsakraklides et al, 1974). Some nodes are <u>unstimulated</u>,

that is they show none of these features and are therefore presumably

'normal'. Others contain considerable quantities of fat. Yet others

are fibrotic, Syn. '<u>lymphocyte depleted</u>' (Tsakraklides et al 1974) or

'exhausted' (Black and Speer 1960). I propose in general to use the

terms underlined above though in some cases these may not have been

the ones used by the author concerned.

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

Which of these also are normal ? In an autopsy study of
487 subjects Tsakraklides and his colleagues suggested that most of
these 'reactions' may be found occasionally in a normal population
(Tsakraklides et al 1975). Germinal centre predominance, however,
was commoner in children and young adults; lymphocyte depletion was
a feature of old age; and, lymphocyte predominance was found mostly in
neonates. It is highly questionable, however, whether the study should
be taken as a normal reference range, though at present it is the only
authoritative attempt at such a definition. It should be noted that,
within the study population, many of the subjects had died of
malignancy or, in the case of adolescents and young adults, from the
complications of drug addiction. Similar qualifications may be made
about the conclusion by Black and Speer (1958), who found only 2-3%
of cases with significant sinus histiocytosis in an autopsy/biopsy
study of 321 cases. The strict 'normality' of the control group must
be placed in considerable doubt.

Thus with some nodes it is difficult to say whether they are
normal or not. Symmers (1966) puts it this way : 'It is impossible to
distinguish sharply between normal states of functional activity in
lymph nodes and pathological changes .... a normal node in the strict-
est sense .... unaffected by exogenous influences .... is unknown after
the end of foetal life'. Perhaps this evades the issue a little. It
is certainly possible to identify some obviously pathological states -
acute, necrotizing, or chronic lymphadenitis, Tuberculous, Syphilitic,
and Lepromatous, disease (Symmers, 1966) and metastatic cancer. These

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are undoubtedly pathological.

The clinical term most often used is <u>lympadenopathy</u>. It implies that a node has been assessed by palpation as abnormal - it is undoubtedly palpable and presumably pathological. Which of the 'reactions' described above is lymphadenopathic in the sense that it may cause nodes to become palpable ? If 'reactions' are normal, then '<u>lymphadenomegaly</u>' might be a better term (Gormly and Benveniste, 1980), but even this (meaning strictly enlargement of lymph glands) makes the inherent assumption that the normal range of lymph node sizes is known. <u>Clearly the question of whether palpable lymph nodes are reliable</u> <u>determinants of disease is an important one.</u> Nowhere is this question more important than in the assessment of patients with breast cancer.

2.   <u>CLINICAL STAGING OF BREAST CANCER</u>

Assessment of the anatomical extent, or of the nature and degree of the spread, of breast cancer is a fundamental clinical exercise referred to as 'staging'. The palpability or otherwise of ipsilateral lymph nodes is used in all staging classifications. (See Table 1.1). The Manchester classification placed patients in Stage II if axillary nodes were palpable on the side of the breast lesion, while the Columbia, New York classification placed them in Stage B (Haagensen, 1974). In the U.I.C.C.[*] (1974, 1978) classification patients were also classed as Stage II (N_1) if such nodes were palpable. In any series of patients with breast cancer the prognosis of

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* Union Internationale Contre le Cancer (International Union against Cancer)

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patients classified Stage I (or A) is usually better than those class-ified Stage II (or B). In spite of this, it is not universally agreed that attempts to stage patients in this way is of proven benefit.

TABLE 1.1

<u>CLINICAL STAGING CLASSIFICATIONS</u>

SYSTEM	STAGE	DEFINITION
Manches-ter	I	Growth confined to the breast.
	II	Ditto, plus palpable mobile node(s).
	III	Skin involvement beyond the growth; fixity of growth to muscle or fascia.
	IV	Fixation of axillary nodes and/or of tumour to chest wall, supraclavicular, contralateral or dis-tant metastases.
Columbia N.Y.	A	No skin oedema or ulceration, chest fixation, or axillary node involvement.
	B	Ditto except axilla clinically involved (not fixed and less than 2.5 cm diameter).
	C	Any one of 5 grave signs, limited skin oedema; skin ulceration; solid fixation; axillary nodes >2.5 cm; nodes fixed.
	D	All others : 2 or more of above; extensive oedema or skin nodules; inflammatory carcinoma; arm oedema; metastases.
U.I.C.C. (1974)	T_0	No primary tumour palpable.
	T_1	Tumour 2 cm or less; a without, b with fixation to fascia or muscle.
	T_2	Tumour 2-5 cm; a & b as above.
	T_3	Tumour more than 5 cm; ditto.
	T_4	Extension to chest wall or skin.
	N_0	Impalpable homolateral nodes.
	N_{1a}	Mobile nodes, not considered to contain growth.
	N_{1b}	Mobile nodes considered to contain growth.
	N_2	Fixed nodes.
	N_3	Supraclavicular or infraclavicular nodes or arm oedema.
	M_0	No distant metastases.
	M_1	Metastases, including skin beyond breast.
	I	T_{1a} or b; N_0 or N_{1a}; M_0

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TABLE 1.1

<u>CLINICAL STAGING CLASSIFICATIONS</u> cont.

SYSTEM	STAGE	DEFINITION
U.I.C.C. (1974) cont.	II	T_0, T_{1a} or $_b$; N_{1b}; M_0; T_{2a} or $_b$; N_0, N_{1a} or $_b$; M_0
	III	Any T_3 or T_4 with any N; M_0. Any T with N_2 or N_3; M_0
	IV	Any T; any N; with M_1.
U.I.C.C. (1978)	T.N.M.	Unchanged from 1974.
	I, II, IV	" " "
	IIIa*	*T_{3a} or $_b$, N_0, N_{1a} or $_b$; M_0
		Any $T_{1, 2, 3}$; N_2; M_0
	IIIb	Any $T_{1, 2, 3}$; N_3; M_0
		T_4; any N : M_0

* In the Edinburgh surgical management, referred to subsequently, only the first class of Stage III a was deemed operable. That is, the size of the primary tumour did not render the patient inoperable in the absence of other advanced features.

In Edinburgh 20 years ago McNair and Dudley (1960) assessed the ability of their senior colleagues to distinguish between the above two lymph node categories. It should be realised that, at that time in Edinburgh, it was uncommon for patients with breast cancer to have nodes removed at mastectomy - simple mastectomy with radiotherapy was the rule for patients with operable disease (McWhirter, 1955). McNair and Dudley selected 62 normal women and asked two observers to record their findings in the axillae. Both felt nodes in over half the patients, but in 34 of 124 axillae (27%) there was disagreement as to which axilla had the palpable nodes ! Curiously enough there was more disagreement in slim patients than in obese ones. In another part of their study 5 clinicians examined 10 patients (20 axillae) 4 of whom had some form of breast disease. The 5 examiners agreed that the nodes were palpable in 48% of observations whether there was breast pathology or not.

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However, there was disagreement in 35% and 30% of these groups.
Furthermore, one examiner thought 20% were abnormal, while another
assessed 73% as abnormal.

They concluded from this interesting and illuminating
study : 'It seems unlikely that clinical classification of breast
carcinoma by examination of axillary lymph nodes has any part to
play in the management of the disease. The use of axillary lymph
nodes for this purpose (clinical staging) is seen to be valueless
and misleading'. This conclusion was perhaps too sweeping a
generalisation; what the study had shown was that there was
disagreement between observers. However, the disagreement occurred
in subjects, the majority of whom were normal. It might have been
more reasonable for them to conclude that palpation in breast cancer
was valueless if their subjects had been patients with breast cancer.
But support for this somewhat depressing attitude would appear to
have been found - from the same city, Edinburgh - and promoted in
recent authoritative reviews (Carter 1976, Wastell 1978).

Wallace and Champion (1972) from Edinburgh reported on the
proportion of patients with breast cancer classified Stages I and II
who had node metastases confirmed histologically following mastectomy.
Of 174 women treated for breast cancer 55 patients had palpable lymph
nodes (Stage II). Pathologically only 45% of these had confirmed met-
astases, whereas 26% of those classified Stage I (impalpable nodes) had
confirmed lymph node metastases. Furthermore, the difference in survival
between clinical Stages I and II was not significantly different. There
was, however, a significant difference in survival between those who were

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pathological Stages I and II. The experience of others in correlating clinical and histological assessment of node metastases is listed in Table 7.1, Chapter 7. In most the correlation was not as poor as that experienced by Wallace and Champion.

3.   <u>'SUSPICIOUS' OR 'NOT SUSPICIOUS' PALPABLE AXILLARY NODES</u>

In the Manchester staging of breast cancer, no fundamental attempt was made to indicate whether palpable nodes might or might not be felt to contain metastases. Ten years ago Cutler and his colleagues reported on the follow-up of 1,210 patients with breast cancer who had been assessed pre-operatively as to whether palpable lymph nodes were thought to be 'suspicious' or 'not suspicious' of metastases (Cutler et al, 1970). They showed that there was a small group of 70 patients with palpable, not suspicious, lymph nodes who had a prognosis which was not only better than those with palpable suspicious nodes, but better even than those with impalpable nodes. Axillary metastases were histologically confirmed in 40% of patients whose nodes were not suspicious compared with 85% in those with suspicious palpable nodes.

This finding, which does not appear to have been confirmed, has now been recognised in the U.I.C.C. classification of clinical staging (Table 1.1) in which patients are classified N_{1a} if palpable nodes are felt not to be suspicious, and N_{1b} if metastasis is suspected. Their findings, and especially that there were patients in this favourable group who sometimes had bilateral palpable nodes (there were 19 only in this sub-classification) may have contributed to the

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inference that 'reactive' nodes might have some protective, immuno-
logical role in patients with breast cancer. The precise,

histological basis for this benign and apparently favourable enlarge-
ment (or palpability) of lymph nodes has not been defined, though

Black and Asire (1969) found more sinus histiocytosis in patients

with bilateral palpable nodes than in patients with impalpable nodes.

(See Chapter 7).

It might be thought that Cutler's findings would help to

explain the poor correlation between node palpability and metastatic

involvement in Wallace and Champion's report. However, in this latter

series even those patients with uninvolved but palpable nodes did not

have a better prognosis than patients with impalpable nodes. The

5 year survival rate from this series was 75% in those with impalpable

nodes compared with 54% in those with palpable (but pathologically

negative) nodes.

Although Haagensen (1957, 1974), like Cutler, also subdivided

his patients with palpable nodes according to whether metastases were

or were not suspected, the survival data of the two subgroups is not

distinguishable in his publications. Other large series have not

included a group with palpable, not suspicious, nodes (e.g. Atkins et

al, 1972, Johnstone 1972, Roberts et al 1973, Hamilton et al 1974,

Lacour et al 1976, Schottenfeld et al 1976, Co-operative Breast Cancer

Study Group 1978, Langlands et al 1979).

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4.   CLINICAL, PATHOLOGICAL, OR 'SUPER' STAGING ?

The clinical stage of patients with breast cancer is dependent upon assessment of three components in the U.I.C.C. (1974, 1978) classification. (Table 1.1). The primary tumour size (if measurable) constitutes the 'T' part of the equation, to which is added the node status 'N', and the presence of any detectable metastases 'M'. From the above considerations, it can be seen that there might be some concern as to the validity of the 'N' part of the classification.

Such concern would not be justified if nodes were regularly excised at mastectomy for subsequent pathological or histological assessment. This would enable each patient to be correctly assigned to histological (metastatic) node status. Appropriate therapy could then be given, and prognosis assessed in comparable (histologically staged) groups. However in recent years there has been a trend towards more conservative operations in patients with carcinoma of the breast. Such is the trend that excision of one or more lymph nodes is by no means standard practice in Britain (e.g. Hamilton et al 1974, Murray et al 1976) though radical excision of lymph nodes has been favoured in North America (e.g. Johnstone 1972, Schottenfeld et al 1976).

The confirmation of axillary metastases has been used in many cases as a guide for subsequent radiotherapy. More recently, confirmed lymph node metastases have been used as a criterion for inclusion of patients in trials of adjuvant chemotherapy (Fisher et al 1975a, Bonadonna et al, 1976). It is of course questionable, whether

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examination of a small sample (rather than the majority) of axillary nodes would enable a patient to be classified accurately.

It was in an attempt to overcome some of these difficulties that a project was started in Edinburgh in 1973 (Cant et al 1975, 1977, Forrest et al 1976), in which a very meticulous and <u>detailed study of the axillary tail</u> of the breast, together with adjacent lymph nodes was undertaken. This was performed in all patients undergoing mastectomy for cancer, and was supplemented by a series of <u>investigations ('super staging')</u> designed to search for the presence of occult metastases in bone, liver and brain.

The early results of this study were quite encouraging (Cant et al, 1975). Of the first 45 patients studied, nodes were identified in 90% when both the axillary tail of the breast and adjacent areas of fatty, axillary, tissue were searched for lymph nodes independently. The latter search was made by the surgeon at the time of mastectomy. Nodes adjacent to the breast but not in the axillary tail were designated 'pectoral nodes'. In only one case was one of these nodes invaded by a metastasis when the axillary tail nodes were negative. The implication was that the axillary tail alone would provide adequate material for lymph node assessment in a substantial proportion of cases. However, when the first 60 cases were reviewed, only 36 (60%) had nodes identified in the axillary tail (Cant, 1977).

The 'super staging' investigations (described in detail in Chapter 2) also appeared to be encouraging. Twenty-two (44%) of

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50 women had positive tests and 42% had positive nodes (Cant et al, 1977). There was no correlation between those with positive nodes and those with positive 'super staging' investigations. It was felt that both tests, i.e. the histological examination of the nodes and the 'super staging' tests would be independently predictive of the likelihood of early recurrence (Cant, 1977). At early follow-up of the 33 patients with 'suspected metastases', 11 had recurrent disease, whereas there was no recurrent disease amongst the 17 patients in whom metastases had not been suspected. However, in this early analysis the patients classified as having 'suspected metastases' included not only those with positive 'super staging' tests, but also those with positive nodes. The 'super staging' tests were not shown to have a prognostic significance which was independent of the node classification. These findings are considered further in Chapter 7.

More recently these patients, together with subsequent patients having the above battery of tests have been evaluated (Forrest et al, 1979). At this analysis it was shown that the presence of positive tests (super staging) alone was of no prognostic value, the rate of subsequent recurrence being almost identical in those with positive tests and in those with negative tests. These findings raise some fundamental questions. Were the 'super staging' investigations completely valueless or were some of the tests of some predictive value ? Was the clinical evaluation (staging) of the patient (which had been carefully assessed in the group of patients, but had not been analysed) of value in predicting the prognosis of this group ?

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

Could the clinical and pathological evaluation be used as a prognostic guide in spite of (a) the small node sample, and (b) the suggestion that node palpation was of negligible value ? The answers to these important questions are investigated in Chapter 2.

5.   <u>PRE-OPERATIVE DETERMINATION OF AXILLARY NODE STATUS</u>

The difficulty and controversy regarding the clinical assessment of node status has been referred to above. Not only does the ability to predict node metastases vary from report to report, but even in the best of hands a significant number of patients who are thought clinically to have node metastases are found to have them free of disease (from 15% - 65% in the above two series). Furthermore there is a substantial proportion of patients with impalpable nodes (from 24% - Atkins et al 1972 - to 47% - Haagensen 1957) who are shown subsequently to have nodal metastases. Even the above ranges of correlation take no account of technical differences in pathological examination. Some pathologists will cut serial sections of most nodes, some a single section from the largest; some will find a median of 7 nodes in a radical mastectomy specimen, others 28 (Fisher and Slack 1970).

In most cases it will not be of great importance to be certain of the pre-operative node status, as nodes will be excised at mastectomy for histological assessment. However, if simple mastectomy alone is practised (Murray et al 1976) or - in 40% of cases - if the axillary tail alone is examined (Cant 1977) nodes will not be available for microscopic examination. Under these circumstances, it might be preferable to have a technique which would predict the likelihood of

CHAPTER 1 : A BACKGROUND TO AXILLARY NODES cont.

lymph node metastases before operation. Such a test would be applied
if the treatment of patients differed depending whether or not lymph
node metastases were present. The distinction today is only made after
mastectomy. A rational treatment innovation might be to give pre-
operative adjuvant therapy to patients who have a high risk of lymph
node (and more distant) metastases. Various techniques for preoperat-
ive investigation of lymph nodes have been tried, but none has become
standard practice.

Kalisher (1975) evaluated xeroradiography as a means of
investigating axillary nodes. Although he was able to demonstrate
axillary nodes in a proportion of patients, he did not feel that
negative X-rays could exclude the presence of axillary metastases.
Furthermore, he found it 'impossible to distinguish inflammatory
from malignant nodes'.

One of the most reliable methods of obtaining information
on nodal pathology is lymphangiography (or lymphadenography), a
technique which is well established in the lower limbs for the
investigation of abdominal lymphoma. The technique is also described
for the upper limb and axilla (Hultborn et al 1970, Kinmonth 1972).
It has been used in the investigations of post-mastectomy oedema, and
of skin tumours, notably melanoma (Browse, 1972) as well as in breast
cancer. It has also been used to assess the completeness of axillary
dissection at mastectomy (Kendall et al 1963, Hultborn et al, 1974).
However, it is not an easy technique for patient or investigator and
is subject to some difficulties in interpretation because of the

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

similarities between the appearances of metastases and fatty defects
(Kinmonth, 1972). Extravasation is also common (Browse, 1972).

In what is perhaps a unique experience, a Hungarian group
has studied axillary node drainage of the breast by '<u>direct mamma-
lymphography</u>' (Kett et al 1970, Kett and Lukacs, 1974). In this
technique, lymphatics in the breast have been cannulated after
outlining them with patent blue dye in a way similar to that used
in the limbs. This group has studied the normal lymph drainage of
the breast in 32 patients with benign disease (Kett et al, 1970) and
also the changes in lymphatic flow that occur as metastatic deposits
gradually replace the axillary nodes. They correlated X-ray appear-
ances with nodal appearances after mastectomy (Kett and Lukacs, 1974)
and were able to identify nodal deposits as small as 2 mm diameter (Kett
et al, 1970). They found that lymphadenography via the arm was
inaccurate (Kett and Lukacs, 1974) but neither they nor Kinmonth (1972)
have provided figures to show what correlation could be achieved.

However, the earlier experience of Kendall and his
colleagues gave some measure of the precision of the technique
(Kendall et al, 1963). They studied 9 patients prior to modified
radical mastectomy (Patey and Dyson, 1948). All except one were
suspected, on lymphangiography, to have nodal metastases.
Histologically nodal deposits were confirmed in only 6. One of the
false positive results in fact was in a patient with a benign lump.
These authors felt that their experience of 6 out of 8 correct did
not justify the general introduction of preoperative lymphangiography.

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

The above investigations suggest that, though of great theoretical and academic interest, lymphangiography is somewhat impractical for a patient who is about to undergo mastectomy.

A more practical type of investigation is <u>lymphoscintigraphy</u>. The technique has been reviewed recently by Zum Winkel and Hermann (1977). It has been used to demonstrate nodes in a number of sites including the axilla, the internal mammary chain, and the inguinal region. In their review they stated that changes in the lymphoscintiscan may occur as a result of normal anatomical variations and from pathology. Decreased activity may occur in obstructed lymphatics or nodal metastases. They allude to other changes in what is referred to as 'lymphadenitis'. Earlier studies mostly followed the injection of radioactive colloidal gold ^{198}Au (Turner-Warwick 1959, Kazem et al 1969, Hultborn et al 1970, 1974, Bechyne and Dienstbier, 1976). However, this agent gives a quite unacceptable radiation dose, especially to the injection site, which may receive up to 1,000 rads.

Latterly a more acceptable agent has been developed, viz ^{99m}<u>Technetium labelled Antimony Sulphide colloid</u> (^{99m}Tc A.S.C.). Using this agent Ege (1976, 1977, 1978, 1979) has now performed over 2,000 examinations of the <u>internal mammary nodes</u> in patients with various conditions, including over 1,000 women with breast cancer, mostly in the post-operative phase. With this extensive experience she has shown not only normal anatomical variations, but also changes associated with malignant lymph node invasion. An unfortunate defect in her work has been the lack of pathological correlation, though in

CHAPTER 1 : A BACKGROUND TO AXILLARY NODES cont.

her review she has referred to considerable pathological correlation in animal work, using radioactive colloidal gold (Sherman and Ter-Pogossian 1953, Seaman and Powers 1955, Thomas 1956).

Ege (1979) has acknowledged the difficulty of demonstrating axillary lymph nodes, noting that many workers have had to inject colloid into a number of sites, for example both the dorsum of the hand and the peri-areolar area. The topic and technique of axillary lymphoscintigraphy was reintroduced more recently by Agwunobi and Boak (1978) who used the same material as Ege (99 Tc^m ASC) and injected material into the peri-areolar tissues. This work in humans followed preliminary studies in animal tumour models (Boak and Agwunobi, 1978). In the animal work they had suggested that a decreased up-take of colloidal particles (or radioactive activity) was encountered in the tumour's primary draining lymph nodes, even in the absence of metastases. Their interest in this clinical investigation was aroused by the animal work, and they postulated that a decreased up-take by the ipsilateral axilla could be used to diagnose breast cancer, rather than assess its spread. Thirteen out of 14 patients with confirmed breast cancer had a depressed uptake of labelled colloid in the ipsilateral nodes. This compared with 29 of 32 patients with benign breast disease, who had either a normal or increased up-take compared with the opposite side. It should be pointed out that their interpretation of an abnormal or positive scan (i.e. depressed up-take in the axilla or a part of the axilla) was not the same as the many studies reviewed by Ege (1978) or by Zum Winkel and Hermann (1977).

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

Their interpretation was that such an abnormality was caused by a

reaction to the tumour in the draining nodes rather than by metastases.

This work had considerable theoretical and practical interest, not only

in the alleged ability to diagnose breast cancer, but also in

interpreting the functional activity of lymph nodes draining such a

cancer. Whether these basic hypotheses are tenable is discussed in

Chapter 7.

In Chapter 3 is described a study which involves a

re-examination of their technique and an attempt to reproduce their

findings. Their work has been extended by modifying both the

technique and interpretation of the scans in order to assess the

predictive value of such scans in diagnosing axillary node metastases.

This work is described in Chapter 4.

6.   <u>LYMPH NODE HISTOLOGY IN PATIENTS WITH BREAST CANCER</u>

As has been alluded to above, the lymph nodes in patients

with breast cancer may be affected by a number of conditions apart

from metastatic disease. The recently expanding knowledge of lympho-

cyte function, together with the sub-classification of T and B

lymphocytes into sub-groupings of these, including natural killer (K)

cells has led to further interest in the primary lymph organs,

especially the lymph nodes. A proposal for classification of node

changes has been made by Cottier and his colleagues (Cottier et al,

1972). This classification is quite comprehensive, but somewhat

tedious and complicated. It does however emphasise that alteration

in the lymph nodes can take place in one of a number of different sites,

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

including the sub-capsular and medullary sinuses, the cortex with its

primary and secondary follices, the para-cortex, and the medullary

cords. From a combination of clinical and experimental observations it

has become accepted that the lymph node cortex contains a predominance

of B lymphocytes (Gutman and Weissman 1972, Howard et al 1972, Turk

1977) especially within the germinal centres of secondary follices.

The paracortex (or 'deep' cortex) on the other hand contains

predominantly T lymphocytes. Within the sinuses are found macrophages

as well as lymphocytes and B cell derived plasma cells. Alteration to

the proportion of these various component parts and cells produce a

number of so-called 'reactions'.

The first of the reactions to receive substantial interest

was that of <u>sinus histiocytosis.</u> Black and his colleagues have

produced a series of papers over many years in which this reaction

has been studied. In a paper 20 years ago (Black and Speer, 1960)

entitled 'Lymph node reactivity in cancer patients' they described a

considerable number of different reactions which might be seen in

sections stained by a special silver technique. There were 13 in all,

including 'phagocytosis', 'recognition', 'immune reactive', and

'exhausted', but also including the group termed sinus histiocytosis

into which they sub-categorised three conditions : 'syncytial

histiocytosis', 'regular sinus histiocytotis' and 'degenerative sinus

histiocytosis'. They noted in this paper that in patients with breast

cancer surviving for five years, there were more cases of the immune and

sinus categories, (that is 'immune sinus', 'syncytial histiocytosis'

and 'sinus histiocytosis'), while these were rare patterns in those who

died early. In subsequent publications, and in preceding ones, in

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

which basic H and E sections were studied, Black reduced considerably

the number of such groups. In these the term 'sinus histiocytosis'

only, with its variations, but excluding the degenerative form, were

used. (Black et al 1953, 1956, Black and Speer 1958, Cutler et al

1966, 1969a, Black and Leis, 1971). The ultrastructural basis for the

reaction has been defined including the 'resemblance of the histiocytes

to the epithelioid cells of Tuberculosis' (Hirschl et al, 1976).

A good description of 'regular' sinus histiocytosis was

given in many of Black's papers (e.g. Black et al 1956, 1958, Cutler

et al, 1966) and this has been used by subsequent investigators. The

'reaction' consists of sinusoidal filling by large monocytic cells

with vesicular nuclei and well defined, granular, eosinophilic

cytoplasm. Unfortunately Black and his colleagues chose to grade

sinus histiocytosis from 0 to 4 (subsequently reduced to 3 grades only)

which has somewhat clouded and complicated the issue. An example of

high grade sinus histiocytosis is illustrated in Appendix Figure A.

In spite of these careful and comprehensive studies many

authorities have been reluctant to accept that sinus histiocytosis

confers any prognostic advantage in patients with breast cancer. For

example Berg (1956) carefully analysed 324 cases, and noted that sinus

histiocytosis was inversely proportional to the extent to which

metastases were found in the axillary nodes. When size of the

primary tumour and the axillary metastases were constant, the amount

of sinus histiocytosis was the same whether or not the patient died

early or late of breast cancer. In a subsequent publication (Berg,

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

1971), he appears to be less certain that sinus histiocytosis was entirely unimportant. He gives little evidence for reasons behind his change of attitude, but as this particular paper was a review of the morphological evidence for an immune response to cancer, he was obviously considering the possibility that sinus histiocytosis was just such a response.

Kister and his colleagues analysed a personal series of 318 cases of Stage A cancer operated upon by one surgeon (C.D. Haagensen - Kister et al, 1969). In spite of the fact that a pathologist experienced in Black's classification of sinus histiocytosis examined all nodes, there was no statistically significant effect of sinus histiocytosis on survival. Although other groups have studied sinus histiocytosis in patients with breast cancer, there have been considerable differences between the groups studied, and the definitions of sinus histiocytosis - as well as differences in the conclusions. Further consideration of these studies, and the reasons for their differences, are included in Chapter 7.

Cutler, Black and their colleagues have shown consistently that sinus histiocytosis is a feature of lymph nodes which can be recognised with some certainty, by pathologists in different laboratories (Cutler et al, 1966). In this and later papers they graded sinus histiocytosis from I to III and suggested that only those with higher grades had a more favourable prognosis. In one paper (Cutler et al, 1969a) they noted that the proportion of cases in which sinus histiocytosis was found was increased as more nodes were examined in

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

the mastectomy specimens. The reason for this was not explained. Nor has it been explained why a group of Japanese women undergoing mastectomy for breast cancer could show an increased proportion of sinus histiocytosis compared with British women with the same condition (Friedell et al, 1974). The possibility exists of course that a different number of nodes was excised in the two groups, though the number of nodes examined histologically was the same.

More recently different changes in the nodes have been examined. A large study was undertaken by Tsakraklides and his colleagues (Tsakraklides et al, 1974). In their classification which was based on Cottier's publication (Cottier et al, 1972), nodes were classified either <u>unstimulated</u>, <u>germinal centre predominance</u>, <u>lymphocyte predominance</u>. or <u>lymphocyte depleted</u>. No account was taken of the degree of sinus histiocytosis present, though the authors noted a tendency for this to occur with lymphocyte predominance. In this study of 277 patients with breast cancer a better survival rate was experienced in patients with lymphocyte predominance, and an unfavourable outlook was seen in those showing lymphocyte depletion. Intermediate survival rates were encountered with germinal centre predominance and unstimulated nodes. They were unable to show any significant correlation between the lymph node pattern and the age of the patient or size of the tumour etc, though there was in fact a larger proportion of small tumours in patients with lymphocyte predominance. Patients with lymphocyte depletion were also slightly older. This is consistent with a subsequent autopsy study, in which lymphocyte depletion was found more commonly in older people, and especially in those dying of malignancy. (Tsakraklides et al, 1975).

CHAPTER 1 : A BACKGROUND TO AXILLARY NODES cont.

In none of the publications referred to has there been any correlation between lymph node palpability and the various reactions discussed. Quite clearly there is an intriguing possibility that the group of patients with alleged prognostic advantage in whom lymph nodes are palpable but not suspicious (Cutler et al, 1970) has one or other of the favourable histological patterns. However, this remains unproven. Studies of these various reactions in patients with breast cancer are found in Chapters 2, 5 and 6.

With few exceptions,* all studies on the prognostic effect of node 'reactions' have been on patients undergoing radical mastectomy in the United States. A British (or Australian) study is clearly required ! Needed also is a study in which is examined the relatively small node sample obtained at simple mastectomy with node biopsy (Forrest et al, 1976).

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* The major studies of Black and Tsakraklides were from different hospitals in New York. Other major studies have come from Chicago (Hunter et al, 1975), Columbus (Majmudar et al, 1971) and Cleveland, Ohio (Moore et al, 1960), Richmond, Virginia (Silverberg et al, 1970) and Columbia University, N.Y. (di Re and Lane, 1963, Kister et al, 1969). The histology of a major Norwegian study (Cutler et al, 1969) was all examined in U.S.A. (by Black) as was the histology of the Japanese and British women reported by Friedell (Friedell et al, 1974). This last report also lacked any follow-up (prognostic) data as have the reports from Rome of a 'Host Defensive Factor' (Fegiz et al, 1977) from Buenos Aires of a 'Hyperplasia Index' (Wernicke, 1975) both of which

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

Footnote cont.

included sinus histiocytosis in the formula, and from Gdansk (Kozlowski and Hrabowska, 1978). Such data has been included in two small series from France (Masse and Chassaigne, 1962 - 78 patients) and The Middlesex Hospital, London (Wartman 1959 - 66 patients). It was not given in the only other British study, from St Mary's Hospital, London (Anastassiades and Pryce, 1966). Since the present study began there have been two reports from the People's Republic of China (Chang et al 1978, Hu 1979). See Chapter 7 for further discussion (Table 7.4).

CHAPTER 1 : A BACKGROUND TO AXILLARY NODES cont.

7.   LYMPH NODE MACRO-METASTASES AND MICRO-METASTASES

It is now quite well established that the harder one looks for metastases in axillary nodes, the more will be found (Fisher and Slack, 1970). This has not prompted widespread use of intensive searching for minute lymph nodes in axillary fat, nor for widespread serial sectioning of lymph nodes to search for small deposits. Such a search would of course be extremely time consuming and tedious. It is also of questionable value.

A number of investigators have shown that a search for small sub-capsular or other deposits within the lymph nodes does not increase the number of patients identified as of poor prognosis (Pickren 1961, Huvos et al, 1971, Fisher et al 1978). Fisher and his colleagues showed that if only a single section per node were examined, 24% of patients in whom such an examination was negative would demonstrate occult node metastases in serial sections. The size of these small tumour deposits varied from 0.02 to 1.3 mm in maximum diameter. They showed that the survival outlook of patients in whom such micro-metastases could be identified was not significantly different from those in whom even such an exhaustive study failed to demonstrate deposits. Similar findings were also encountered in the other two studies though the definition of micro-metastases differed. Such microscopic deposits are now recognised in the U.I.C.C. (1978) classification of pathological staging of breast cancer. In that classification a micrometastasis is less than 2 mm in diameter. Such a measurement pre-supposes that the maximum diameter of a deposit can be measured in more than one plane, and for purposes of convenience in the studies in this thesis a figure of 20% of cross sectional node area or less has been accepted as a micro-metastasis. In all probability the various definitions differ only in

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

a minor respect. In fact in Fisher's study his 'occult' metastases were all under 1.3 mm in diameter, whereas all macroscopic deposits had been detected in a single section of each node.

By ignoring differences between large and small deposits in axillary nodes, the results of follow-up studies could produce spurious results. This question is examined in Chapter 2, together with the effect of the node 'reactions' discussed above.

<u>SOME QUESTIONS REGARDING AXILLARY NODES IN PATIENTS WITH BREAST CANCER</u>

The above review suggests a number of important questions regarding the axillary nodes in patients with apparently operable breast cancer.

1. Is the palpation of axillary lymph nodes valueless, or can it be used as an index of prognosis ?

2. Can the pre-operative diagnosis of axillary lymph node metastases be improved by simple investigations ?

3. Can sinus histiocytosis (SH) and lymphocyte predominance (LP) (and other so-called 'reactions') be recognised by groups outside North America ? Do sinus histiocytosis and lymphocyte predominance confer a prognostic advantage if identified in the small sample of nodes excised at simple mastectomy ?

4. Can any of these 'reactions' cause lymph node enlargement ?

5.. What makes enlarged nodes palpable ?

6. Is there a group of patients with palpable 'benign' enlargement, who have a prognostic advantage ?

CHAPTER 1 : <u>A BACKGROUND TO AXILLARY NODES</u> cont.

7. In relation to the primary tumour and/or metastases, where in the
    axilla are the various node 'reactions' found ?

8. Which clinical or histological factors are useful in assessing the
    patients' prognosis after mastectomy ? Does 'superstaging' help ?
    What is the effect of micro-metastases ?

       All these questions have been investigated. The following
5 chapters describe the projects undertaken to answer them.

CHAPTER 2

PREDICTING RECURRENCE AFTER MASTECTOMY. A COMPARISON

BETWEEN CLINICAL EXAMINATION, NODAL HISTOLOGY, AND

TESTS FOR OCCULT METASTASES[*]

* Modified from a paper published in the Australian and New
Zealand Journal of Surgery. (Black et al, 1980b).

CHAPTER 2 : PREDICTING RECURRENCE

SUMMARY

In 1974 in Edinburgh a project was initiated in which patients with apparently operable breast carcinoma underwent special investigations in an attempt to identify occult metastases in bone and liver. In 1979 I reviewed the clinical and investigational data of the first 172 patients who had been followed for two years or more, and re-examined all the node histological material. Dates of first recurrence and death were determined in all patients. Conclusions from the study were as follows. Careful clinical assessment, in particular measurement of the primary tumour and palpation of the axillary nodes, was an accurate guide to the likelihood of early recurrence. Histological confirmation of node metastasis was as valuable as clinical assessment, but was not superior unless other features (including 'reactions') of node histology were considered. Micrometastases in axillary nodes did not increase the probability of early recurrence except in comparison with a group whose nodes lacked both metastases and other unfavourable features, e.g. germinal centre predominance. The majority of special investigations did not have additional predictive value, though the bone scan was useful in the small number (7%) in whom it was positive. Lowest rates of recurrence were seen in patients with small tumours and impalpable axillary nodes, which histologically were either unstimulated or showed the favourable 'reactions' of sinus histiocytosis or lymphocyte predominance.

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

INTRODUCTION

The major problem in the management of patients with breast cancer is that systemic spread has often occurred in patients with apparently localized disease. In such patients, local therapy is unlikely to influence the subsequent development of metastases. Although the initial purpose of staging patients with operable breast cancer was to allow comparisons between patients treated in different centres, it is now regarded as equally important to define those in whom early systemic or local recurrence is likely to occur. In such patients adjuvant local and systemic therapy by effective means is a necessary part of long-term control.

The histological status of the axillary nodes is of established prognostic significance, (e.g. Johnstone 1972, Atkins et al 1972). The presence or absence of metastases is accepted as the best criterion for selection of patients for trials of systemic therapy. (Fisher et al 1975a, Bonadonna et al 1976). The number of nodes involved gives additional information of the likely outcome (Majmudar et al 1971, Fisher et al 1975b, Attiyeh et al 1977) and many believe that this justifies the continuation of routine clearance of all axillary nodes in every patient. Cant and her colleagues, however, demonstrated that axillary node sampling can readily be performed to complement total mastectomy and that metastatic node status can be estimated in some 90% of patients without recourse to a complete and formal axillary dissection (Cant et al, 1975). This has been standard practice in the Edinburgh Department of Clinical Surgery during the past 10 years (Forrest et al, 1976).

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

The prognostic value of axillary node histology assumes that the state of the axillary nodes reflects the likelihood of metastatic disease in other sites. Such 'mini deposits' of tumour in bones, liver and other sites cannot be detected by routine diagnostic X-ray investigations; and in 1974 a project was started in which consecutive patients with apparently operable breast cancer were investigated by a battery of 'super-staging' tests designed to identify occult metastases (Cant et al 1977, Cant 1977). A preliminary report on the results of these special tests was most discouraging (Forrest et al, 1979).

While on study leave in Edinburgh I considered it worthwhile to examine these results in some detail and to compare the predictive value of the tests used with that of clinical examination and node histology. Both these are established staging methods, though the lack of specificity of clinical examination, especially node palpation, is acknowledged (McNair and Dudley 1960, see Chapter 1).

PATIENTS AND METHODS

Clinical material

From 1974 all patients presenting to the University Department of Clinical Surgery Breast Clinic in Edinburgh with apparently operable breast cancer were admitted to a special investigational unit for four days prior to mastectomy. During this time the diagnosis of breast cancer was confirmed by 'Tru-cut' needle biopsy and careful clinical staging repeated. Only patients with operable disease by

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

the U.I.C.C. (1974)˙T.N.M. criteria ($T_1 T_2 T_3$ (on size); $N_0 N_1$) were included.

A programme of investigations was carried out to search for occult metastases. The result of the investigations did not influence the decision to treat the patients by mastectomy. One hundred and seventy two patients, investigated and treated between October 1973 and December 1977 followed up for two years or more, formed the basis of this review.

METHODS

<u>Clinical assessment</u>

Patients were assessed after admission to hospital by at least two experienced clinicians[*], and a concensus on the local extent of disease was reached. Clinical staging was by U.I.C.C. (1974) criteria (see Table 1.1) with respect to the primary tumour size (maximum diameter measured by centimetre rule and/or callipers) and node palpability (N_0 impalpable, N_{1a} palpable but not suspicious, N_{1b} palpable and suspicious of malignancy). Other features of clinical assessment including skin tethering, and pectoral fascia or muscle fixation (T_{1b}, T_{2b}, etc.) were also noted. As there was more dis-agreement about the presence or absence of these, and as these features would not alter the patient's clinical stage (I, II etc.) they were not taken into account in subsequent analysis. Patients included in this study were those in the range (T_0) $T_{1a} N_0 M_0$ - $T_{3b} N_{1b} M_0$. No patients included in the study had clinical evidence of metastatic disease; all had negative X-ray films of chest and skeleton.

[*]Of Prof. A.P.M. Forrest and Drs H.J. Stewart (Department of Radiation Oncology), E.L.M. Cant or M.M. Roberts

CHAPTER 2 : PREDICTING RECURRENCE cont.

Special investigations

The methods used to detect occult metastases, sometimes referred to as 'superstaging' tests, have been described in detail elsewhere (Cant et al 1977, Cant 1977, Forrest et al 1979). Briefly, bone metastases were sought by a nuclear isotope scan, using a ^{99m}Tc hydroxy ethylidine disodium phosphate or disodium etidronate stannous chloride as radio-pharmaceutical and a Nuclear Enterprise mark IV gamma camera for scanning; by plasma alkaline phosphatase (bone isoenzyme by polyacrylamide gel electrophoresis); and by the 24 hour urinary output of hydroxproline, and hydroxyproline : creatinine ratio while on a gelatin free deit. Liver metastases were also sought by a nuclear isotope scan, using ^{99m}Tc sulphur-colloid as imaging agent, and by plasma estimation of alkaline phosphatase (liver isoenzyme by gel electrophoresis) and gamma glutamyl-transpeptidase levels. In 40 patients a C.T. brain scan with contrast enhancement was performed to detect possible brain metastases. All scans were reported on and interpreted by two experienced clinicians[*]. AFter a study of normal women and women with established metastatic disease (Cant, 1977) the following upper limits were accepted for normal bio-chemical estimations[+] : total alkaline phosphatase 13.5 K-A, or 100 international units per litre; hydroxyproline 33 mg per 24 hours or 31 mg/g creatinine; gamma glutamyl transpeptidase 35 international units per litre. Results for each test have been expressed only as positive (abnormal) or negative.

Node histology

The standard policy of operative treatment was total mastectomy with pectoral node biopsy (Forrest et al, 1976). This

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[*] Dr M.D. Sumerling, Senior Lecturer in Radiology and Dr M.M. Roberts, Senior Lecturer in Surgery
[+] by Dr A. Smith, Senior Lecturer, Department of Clinical Biochemistry

CHAPTER 2 : PREDICTING RECURRENCE cont.

was performed in all but four patients, who were considered, on medical grounds, to be unfit for this. Two were treated by local excision of the tumour alone; two by primary radiotherapy. The histological features of nodes removed from the 'axillary tail' region of the breast and adjoining axillary fat were determined in the laboratory of the University Department of Pathology. The distribution of the nodes sampled from the first 50 patients has been published (Cant et al, 1975). For the purposes of this study all available histological sections were reviewed personally to confirm the findings and to grade metastatic involvement as gross or microscopic, depending on whether more or less than 20% of the node sectional area was occupied by metastasis. Nodes free of gross metastases were also assessed with respect to sinus histiocytosis (S.H., Black and Speer 1958, Cutler et al, 1969a), lymphocyte predominance, germinal centre predominance or lymphocyte depletion (L.P., G.C.P., L.D.) (Tsakraklides et al, 1974). Nodes showing none of these features were classed unstimulated (U.S.). A full description of the criteria for classification of these 'reactions' is given in the Appendix, Figures A1 to A6.

Follow-up

Ninety-five percent of the patients were reviewed every 3 months for 2 years and thereafter at longer intervals in a special clinic. The remaining 5% were seen regularly by a surgeon or general practitioner in communication with members of the follow-up clinic. The median time of follow-up was 3.0 years (range 2.0 - 5.1 yrs). During 1979 all patients alive were reviewed by Dr H.J. Stewart and myself. The case notes of all who had died were individually scrutinised.

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

When recurrence was suspected this was confirmed histolog-
ically in all patients except those with typical X-ray features of
bony metastases or gross clinical evidence of liver involvement. Of
the patients who died only 5, in whom there had been no clinical
suspicion of recurrence, were accepted as dying of other causes; two
of myocardial infarction; two of psychiatric illness (depression,
suicide); and one following a motor accident. Recurrence has been
recorded as local (i.e. local-regional recurrence without evidence
of dissemination), and as disseminated, this including those who had
local-regional as well as systemic disease. The follow-up data,
clinical assessment and the results of special tests are shown for
all patients in Appendix Table A.

Statistical comparisons of the recurrence and fatality rates
between groups were by Chi^2 analysis and log rank test. For the latter,
recurrence free and survival intervals were calculated, using the
criteria of Hayward et al (1977) to define the date of first recurrence.
All clinical, investigational and histological data, times of
recurrence etc., together with additional factors not discussed in
this chapter were entered into punch cards for computer analysis.
These are shown in Appendix Table CI.

<u>RESULTS</u>

Statistical analyses and survival curves are shown in the
Appendix, Tables CII and Figures C1 to C8.

CHAPTER 2 : PREDICTING RECURRENCE cont.

Special investigations

In 53 patients one or more tests were positive, and in 119 all tests were negative. The recorded recurrence and death rates show no difference between patients in these two groups (Table 2.1). In Tables 2.2 and 2.3 the site of recurrence and total rates of recurrence are related to the results of individual tests. No individual test predicted a statistically significant increase in total recurrences. In those patients with evidence of suspected bone metastases (Table 2.2) a positive bone scan was of realistic value in predicting bone recurrence; 6 of 12 patients (50%) developing overt skeletal metastases compared with 22 of 160 (14%) in those whose scan was negative. This difference was statistically significant (P = 0.04). A positive alkaline phosphatase (bone isoenzyme) also had some predictive value, but this was not statistically significant. A negative bone scan, normal alkaline phosphatase, or normal urinary hydroxyproline, were of no value in predicting freedom from recurrence.

TABLE 2.1

Recurrence within 2 years after treatment of 172 patients with operable breast cancer, showing the rates in those with positive or negative tests for occult metastases.

Tests for occult metastases	No.	RECURRENT DISEASE			Died of recurrence
		Local	Disseminated	Total	
POSITIVE	53	6	13	19 (36%)	12
NEGATIVE	119	6	35	41 (34%)	26
TOTAL	172	12	48	60 (35%)	38

CHAPTER 2 : PREDICTING RECURRENCE cont.

TABLE 2.2

Recurrence within 2 years in 172 patients with operable breast cancer, showing the rates in those with positive or negative tests for bone metastases.

TEST	NO.	RECURRENCE	
		BONE	TOTAL (%)
NUCLEAR SCAN			
+ve	12	6^+	* 7 (58)
-ve	160	22	53 (33)
ALKALINE PHOSPHATASE			
+ve	10	3	∅ 5 (50)
-ve	162	25	55 (34)
URINARY HYDROXYPROLINE			
+ve	26	5	8 (31)
-ve	144	23	52 (36)
TOTAL	172	28	60 (35)

+ Computer analysis $Chi^2 = 6.45$, 2 degrees of freedom; P = 0.04

* See appendix Table CIIb; P = 0.08

∅ See appendix Table CIIb; P = 0.06

No other test results approached statistical significance.

CHAPTER 2 : PREDICTING RECURRENCE cont.

TABLE 2.3

Recurrence within 2 years in 172 patients with operable breast cancer showing the rates in those with positive or negative tests for liver metastases.

TEST	NO.	RECURRENCE	
		LIVER	TOTAL (%)
NUCLEAR SCAN			
+ve	11	1	4 (36)
-ve	161	19	56 (35)
ALKALINE PHOSPHATASE			
+ve	5	1	2 (40)
-ve	167	19	58 (35)
γ GLUTAMYL TRANSPEPTIDASE			
+ve	13	1	4 (31)
-ve	158[*]	19	56 (35)
TOTAL	172	20	60 (35)

* Omitted in 1 patient

No test result was statistically significant

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

In the whole group of 172 patients, 28 patients (16%) developed bone metastases. A positive bone scan alone predicted only 6 and a raised alkaline phosphatase 3. However, bony metastases have developed in all 4 patients in whom a positive bone scan was associated with either an elevated serum alkaline phosphatase or elevated urinary hydroxyproline level.

Overall 20 patients (12%) developed liver metastases (Table 2.3). Only 1 was predicted by each of the liver tests (scan, alkaline phosphatase, gamma glutamyl-transpeptidase), and none of these 20 patients had more than one test positive. Investigations for liver metastases were especially poor in predictive power. Neither liver scan, nor plasma estimations of alkaline phosphatase and gamma glutamyltranspeptidase, discriminated between those who were destined or not to develop liver metastases in the period of follow-up (Table 2.3).

All 40 patients undergoing CT brain scan had negative results.

Clinical assessment

Tables 2.4 and 2.5 show the recurrence rate in patients according to tumour size and node status. There was progressive and statistically significant increase in the rate of recurrence as the size of the tumour increased ($P < 0.0001$). Total recurrence rates in those with primary tumours of a size greater than 5 cm reached 60%. Clinical node status also was useful : 54% of those classified N_{1b} developed recurrence, compared with only 18% classified N_0 ($P < 0.0005$). Those assessed N_{1a} had

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

Intermediate rates of recurrence, and did not fare significantly better than N_{1b} cases. Survival curves relating to clinical node assessment are in Appendix Figure C1.

TABLE 2.4

Recurrence rates after treatment of 167[*] patients with operable breast cancer, classified according to tumour size (clinical measurement).

TUMOUR SIZE (CM)	RECURRENT DISEASE			DIED OF RECURRENCE [ø]
	LOCAL	DISSEMINATED	TOTAL[+]	
⩽ 1 cm (11)	1	0	1 (9%)	0
> 1-2 cm (28)	0	5	5(18%)	5 (18%)
> 2-3 cm (45)	4	9	13(29%)	8 (18%)
> 3-5 cm (63)	5	22	27(40%)	16 (26%)
> 5 cm (20)	1	11	12(60%)	8 (40%)
TOTAL (167)[*]	11	47	58(35%)	37

[*] In 5 patients the tumour size was uncertain.

[+] Computer analysis (Appendix Table CIIb) $Chi^2 = 37$, 7 degrees of freedom; $P < 0.0001$

[ø] (Appendix Table CIIc) $Chi^2 = 20.9$, 7 degrees of freedom, $P = 0.004$

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

<u>TABLE 2.5</u>

Recurrence rates after treatment of 171[*] patients with operable breast cancer, classified according to clinical node status.

CLINICAL NODE STATUS	RECURRENT DISEASE			DIED OF ∅ RECURRENCE
	LOCAL	DISSEMINATED	TOTAL[+]	
N_0 (85)	2	13	15 (18%)	10
N_{1a} (12)	1	4	5 (42%)	3
N_{1b} (74)	9	31	40 (54%)	25
TOTAL (171)	12	48	60 (35%)	38

* Node status not recorded clearly in one patient.

+ Computer analysis (Appendix Table CIIb) Chi^2 = 17.6, 2 degrees of freedom; P = 0.0002.

∅ (Appendix Table CIIc) Chi^2 = 7.8, 2 degrees of freedom; P = 0.021.

Node histology

The histological features of available nodes from each patient are shown in Appendix Table B.

In 140 of the 172 patients, nodes were identified at mastectomy for histological examination. Thus in 30 of 172 patients (19%), surgeons failed to identify nodes. When identified the number of nodes examined ranged from 1 to 8 with a median of 1. Recurrence rates are related to the histological features of identified nodes in Table 2.6. Patients with microscopic involvement had a lower rate of recurrence than those

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

with gross metastases (P<0.05), and the same recurrence rate as those
with negative nodes.

In all, 37 of 73 patients with metastatic nodes (51%) developed
recurrent disease compared with 11 of 67 (16%) with negative nodes. These
values are similar to those of clinical node status (Table 2.5 above).
The 32 patients in whom node histological assessment was not done had a
recurrence rate between that of those with proven negative and proven
positive nodes. In Table 2.7 those patients with nodes proven histolog-
ically to be uninvolved have been subdivided according to the features
of node 'reaction' evaluated. Although the numbers are small germinal
centre predominance and lymphocyte depletion appear to be unfavourable
signs.

Taking all node features into account there were 3 groups of
patients of low, intermediate, and high probability of recurrence : those
with lymphocyte predominance, sinus histiocytosis or unstimulated nodes
had a recurrence rate of 9%; those with 'micrometastases', lymphocyte
depletion or germinal centre predominance had an intermediate risk of
recurrence (23%), while those with gross metastases had a recurrence
rate of 58%. The relevant disease free survival curves are in the
Appendix Figures C2 and C4.

Because group sizes were larger, the predictive values of nodal
histology and clinical status were stronger even than the best of the
special investigations, i.e. bone scan. Furthermore, 6 of 7 patients with
positive bone scans who developed recurrence had palpable and suspicious
(N_{1b}) nodes; the seventh patient had gross node metastases in histological
assessment.

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

<u>TABLE 2.6</u>

Recurrence rates after treatment of 172 patients with operable breast cancer classified according to node metastatic status.

NODE METASTASES	RECURRENT DISEASE			DIED OF RECURRENCE
	LOCAL	DISSEMINATED	TOTAL	
ABSENT (67)	4	7	11 (16%)	5
MICROMETASTASES (13)	0	2	2 (15%)	1
GROSS METASTASES (60)	4	31	35 (58%)	27
UNKNOWN (NO HISTOLOGY) (32)	4	8	12 (38%)	5
TOTAL 172	12	48	60 (35%)	38

<u>TABLE 2.7</u>

Recurrence rates within 2 years after treatment of 140 patients with operable breast cancer stratified according to node histology. Patients in the first 5 groups had no evidence of metastases; in the first 3 there were no 'disadvantageous' histological features.

NODE HISTOLOGY	RECURRENT DISEASE			DIED OF RECURRENCE[+]
	LOCAL ONLY	DISSEMINATED + LOCAL	TOTAL RECURRENCE	
LYMPHOCYTE PREDOMIN-ANCE (8)	0	1	1)	1
SINUS HISTIOCYTOSIS (7)	0	0	0) 3 9%*	0
UNSTIMULATED (21)	1	1	2)	1
GERMINAL CENTRE PREDOMINANCE (27)	2	3	5)	2
LYMPHOCYTE DEPLETION (4)	1	2	3) 10 23%	1
MICROMETASTASES (13)	0	2	2)	1
GROSS METASTASES (60)	4	31	35 58%	27
TOTAL 140	12	48	60 35%	38

* Computer analysis (Appendix Table CIIb) $Chi^2 = 28.8$, 3 degrees of freedom; $P < 0.0001$.

+ (Appendix Table CIIc) $Chi^2 = 34.1$, 8 degrees of freedom, $P < 0.0001$

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

<u>DISCUSSION</u>

A number of individual prognostic factors have been described in breast cancer. These include the oestrogen receptor content of the tumour (Cooke et al, 1979); low peripheral blood lymphocyte count (Papetsas et al 1976, Meyer (1978) or high 'monocyte maturation' (Taylor and Currie, 1979); lysozyme production (Oladimeji et al, 1979); a rising 'pregnancy associated alpha macroglobulin' (Anderson, 1979) and skin oedema over the tumour measured in mammograms (Shukla et al, 1979). However, many of these tests depend upon considerable local expertise or special laboratory facilities and are not universally available. On the other hand clinical staging, plain radiology, histopathology and most of the special investigations performed in this study are available in most centres. Histological node status and clinical staging remain of fundamental importance, and it is only in comparison with these that the results of additional investigations for metastatic disease can be assessed. Originally the special tests used were called 'superstaging' tests (Cant et al, 1977), an unfortunate term in view of their low sensitivity and poor predictive value.

Of the tests chosen, those for bone metastases proved more reliable than did tests for liver metastases. This is in agreement with Kitchen et al (1979), who reported 85 patients, 9 with positive bone scans, 8 of whom subsequently developed bone metastases. This is a higher proportion than in the present series. However, in their study a number of false positive scans were eliminated from analysis. Bishop et al (1979) had a much lower rate of positive bone scans (less than 3%), and as a consequence found this investigation of very little value in

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

predicting recurrence. In the experience from this study the bone scan

has been the best of the special investigations. However, even with

a positive scan those who subsequently developed metastases had

clinical or histological features which independently predicted a poor

prognosis, i.e. axillary node metastases. Nevertheless the findings

are in agreement with those of Kitchen that an abnormal bone scan

appears to have some predictive value, especially when associated with

features such as metastatic nodes. (Kitchen et al, 1979).

Investigations to detect liver metastases were especially

unrewarding. The disappointing results from liver nuclear scans are

entirely comparable with the poor predictive value experience by Wiener

and Sadis (1978). As a result the Edinburgh group no longer uses

isotopic liver scans, and are currently assessing the value of ultra-

sound. In spite of these poor results one cannot accept the suggestion

by Thomas that some patients at risk should undergo laparotomy to search

for abdominal metastases (Thomas et al, 1978). The Edinburgh group no

longer measure urinary hydroxyproline; nor have they continued with CT

brain scans. They now recommend that positive bone scans should be more

energetically investigated, proceeding in some cases to bone biopsy. A

less comprehensive preoperative use of bone scans has been suggested

(Baker, 1977). This is discussed in Chapter 7.

An important aspect of the pre-operative in-patient evaluation

of patients is that time is allowed for them to be carefully assessed

clinically, and to gain reassurance from nursing and other staff. It was

my impression that these patients were well prepared for mastectomy by

their period of hospitalisation.

CHAPTER 2 : <u>PREDICTING RECURRENCE</u> cont.

A notable feature emerging from this study has been the predictive value of palpable and suspicious (N_{1b}) axillary lymph nodes. If only the presence or absence of metastases was noted in the histological report, clinical assessment was as useful as histological examination of the lower axillary nodes. The success of clinical examination has been dependent upon very strict criteria of assessment, including a consensus agreement by a number of experienced observers. As a result there has been a good correlation between clinical and pathological node status, 79% of patients classified N_{1b} having metastases, compared with 32% of those classified N_0. The details of this correlation are in Chapter 5.

The other features of node histology, especially the so-called 'reactions' of sinus histiocytosis and lymphocyte predominance have enabled three groups to be defined with low (lymphocyte predominance, unstimulated and sinus histiocytosis) medium (lymphocyte depletion, germinal centre predominance, micrometastases) and high risk of early recurrence (gross metastases). These findings are in broad agreement with those in other reports. A number of groups has observed improved outlook in patients with nodes showing sinus histiocytosis, (Black et al 1953, Cutler et al 1969a, Hunter et al 1975, for example), while Tsakraklides indicated an improved prognosis with lymphocyte predominance, as opposed to germinal centre predominance or lymphocyte depletion. (Tsakraklides et al, 1974). A poor outlook for patients with germinal centre predominance compared with sinus histiocytosis was also noted by Hunter et al (1975). These and other studies, some at conflict, are discussed at length in Chapter 7.

CHAPTER 2 : PREDICTING RECURRENCE cont.

Many of these 'reactions' are not easily assessed and in this series they were assessed on a relatively small number of nodes from each patient (0 to 8, median 1). With a larger sample of nodes it is likely that more patients could have had nodes classified with one or other of the more favourable 'reactions', and less classified as unstimulated (Cutler et al, 1969a, and see Chapter 5). There is certainly no widespread enthusiasm among pathologists to comment upon such 'reactions' in the axillary nodes of patients undergoing mastectomy. However, even if these are ignored, the very obvious difference in outlook between those patients with gross and those with micrometastases should be noted, an observation which is becoming increasingly well recognized (Fisher et al, 1978, see Appendix Figure C4).

This study has shown the useful prognostic significance of node histology and careful clinical assessment, together with the poor results of the 'superstaging' tests for occult metastases. Further analysis and observation are required to show which features are of greatest independent value, an important task in view of the current trend towards less comprehensive sampling of axillary nodes for histological assessment.

CHAPTER 3

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AXILLARY LYMPHOSCINTIGRAPHY IN THE DIAGNOSIS OF BREAST

CANCER *

*   This chapter is a modification of a paper published in the

    British Journal of Surgery (Black et al, 1981).

CHAPTER 3 : <u>DIAGNOSTIC LYMPHOSCINTIGRAPHY</u>

<u>SUMMARY</u>

The technique of axillary lymphoscintigraphy described by Agwunobi and Boak (1978) was investigated and modified in 79 patients, 11 with benign breast disease and 68 with carcinoma. Subareolar injection of $100\mu C_1$ ^{99}Technetium Antimony Sulphide colloid in 0.1 ml allowed satisfactory scans in only 13 of 46 patients (28%), but intradermal injection improved this to 30 of 33 (90%). Using the diagnostic criterion of a depressed uptake by the ipsilateral axilla, the 43 interpretable scans showed the following : 2 of 7 patients with benign breast disease had positive (abnormal) scans, while in 36 patients with cancer the scan was positive in only 13. Even after modification which reduced the proportion of uninterpretable scans, it was not possible to confirm that there is a scintiscan pattern which is due to local malignancy.

<u>INTRODUCTION</u>

Agwunobi and Boak (1978) reported a technique of axillary lymphoscintigraphy in which ^{99}Technetium labelled Antimony Sulphide Colloid ($^{99}Tc^m$ ASC) was injected beneath the areola. In their study a depressed uptake was seen in the ipsilateral axilla in 13 of 14 patients with operable breast cancer. On the other hand 29 of 32 patients with benign breast disease had a normal or increased uptake by the ipsilateral axilla. They suggested that such a test would be useful to diagnose breast cancer, and that the depressed uptake by the axilla might represent a cellular response to cancer by the primary lymph nodes. Their technique has been investigated and modified to provide more interpretable scans in 68 patients with breast cancer and 11 with benign breast disease.

CHAPTER 3 : DIAGNOSTIC LYMPHOSCINTIGRAPHY cont.

MATERIALS AND METHODS

Patients

Sixty eight patients with apparently operable breast cancer
(T_1, N_0, M_0 - T_3, N_{1b}, M_0) were studied during a pre-operative course
of investigations designed to confirm the diagnosis of carcinoma and
to exclude distant metastases ('superstaging', see Chapter 2, Cant
1977, Cant et al, 1977). The diagnosis of carcinoma was made by a
combination of clinical examination and mammography, together with
aspiration cytology and 'Tru-cut' needle biopsy. The majority of
patients with proven cancer were treated by mastectomy with excision
of lower axillary nodes, a minor extension of the operation of simple
mastectomy and pectoral node biopsy (Forrest et al, 1976). In two
patients treatment of the primary tumour was by radiotherapy because of
skin invasion by the primary tumour, and in two cases systemic therapy
was used; in one because a small supraclavicular node was shown to
contain metastases; and, in the other because of anaemia due to bone
marrow invasion.

Eleven patients with benign breast disease were also studied,
8 were assessed as out-patients in the earlier part of the investigation,
while the other three were patients suspected initially of malignancy.
They underwent the above investigations until carcinoma was excluded by
biopsy, or by aspiration of a cyst.

Brief clinical details of these patients are in Appendix Tables
DI and DII.

CHAPTER 3 : <u>DIAGNOSTIC LYMPHOSCINTIGRAPHY</u> cont.

<u>Technique of lymphoscintigraphy</u>

The technique employed for the first 47 studies was similar to that used by Agwunobi and Boak (1978). (Method 1 in Appendix Table D). Briefly, approximately $100\,\mu\,C_1$ $^{99}Tc^m$ was injected beneath the areola, and the patients asked to massage the injection site gently for the next hour. At 3 hours the region of the breasts, axillae and shoulders was scanned to detect radioactivity at the injection site and the axillae. At first the technique differed from the above in only three minor respects : (1) a commercially available ASC product 'Labellaid' (Philips Duphar) was used; (2) it was in a smaller volume (0.1 ml) as recommended for internal mammary lymphoscintigraphy by Ege (1976, 1977, 1978); and, (3) scanning was performed on a 'Cleon 760' multi detector scanner rather than a gamma camera. Subsequently further modifications were made to improve the reliability of the scan. For the last 32 studies the ASC was injected intradermally, at the lateral edge of the areola (Method 2 in Appendix Table D). In most studies the ASC was mixed with hyalase. As almost all patients experienced moderate pain with the intradermal injection it was preceded by 0.5 ml 1% Xylocaine subcutaneously. Contrary to recommendations of the above authors, in 4 patients the scan followed a recent open biopsy. In all other patients with suspected cancer, scintigraphy was preceded by needle aspiration cytology, which (occasionally) caused considerable bruising.

<u>Interpretation of scan</u>

For the purpose of this analysis scans were interpreted strictly according to the criteria of Agwunobi and Boak (1978).

CHAPTER 3 : <u>DIAGNOSTIC LYMPHOSCINTIGRAPHY</u> cont.

(Criteria A in Appendix Table D). An abnormal (positive) scan,
suggesting the possibility of malignancy, was accepted if there was
depressed uptake by the ipsilateral axilla. A normal (benign) scan
was accepted if the uptake in the ipsilateral axilla was equal or
increased compared with the contralateral axilla. In a large number of
cases there was negligible uptake by either axilla. Such scans were
regarded as uninterpretable. Interpretation was independently done by
Dr Merrick and myself and was entirely visual. Examples are shown in
Appendix Figures D1 to D4. No attempt was made to identify individual
nodes, nor were comparative counts performed. Where there was disagree-
ment between observers, the result was also classified as uninterpretable.

<u>RESULTS</u>

Only 13 of the first 46 scans were interpretable (28%) : 5
of 9 patients with benign breast, and 8 of 37 with breast cancer. After
modification in the technique as above, 30 of the last 33 scans were
satisfactory (90%). Thus a total of 43 scans only were satisfactory,
and the results are shown as Criteria A in Table D of the Appendix and
summarised in Table 3.1. It can be seen that in both benign and malignant
breast disease a proportion of abnormal scans was seen, using the criteria
stated. However, even in the patients with carcinoma the majority of
interpretable scans (23 of 36) were normal. Clearly there was no pattern
of uptake by the axillary lymph nodes which was typical of carcinoma in
the corresponding breast.

CHAPTER 3 : <u>DIAGNOSTIC LYMPHOSCINTIGRAPHY</u> cont.

<u>TABLE 3.1</u>

The results of 79 scans, of which 43 were interpretable. Criteria of 'benign' and 'malignant' as in text, (Criteria A in Appendix Table D).

FINAL DIAGNOSIS	SCAN 'BENIGN'	SCAN 'MALIGNANT'	UNINTERPRETABLE I.E. NEGLIGIBLE UPTAKE
BENIGN (11)	5	2	4
MALIGNANT (68)	23	13	32
TOTAL (79)	28	15	36

CHAPTER 3 : <u>DIAGNOSTIC LYMPHOSCINTIGRAPHY</u> cont.

<u>DISCUSSION</u>

Demonstration of lymph nodes by lymphoscintigraphy has been used in a number of different regions of the body, and some of the earlier results have been reviewed recently by Zum Winkel and Hermann (1979).

The first agent used was radioactive gold colloid (Au^{198} Kazem et al 1969), but this produced an unacceptable local radiation dose. Other agents used include Indium Hydroxide (Goodwin et al, 1970), Antimony Sulphide Colloid (Goranson and Jonsson 1974, Agwunobi and Boak 1978, Ege 1976, 1977, 1978) and Stannous Phytate (Osborne et al, 1979). The largest series of lymphoscintigraphy studies is that of Ege (1978), who used ASC as in this present study. She has now examined the internal mammary nodes of over 2,000 patients, including over 1,000 with breast carcinoma. The same agent was also used by Jonsson to examine the inguinal nodes in patients with melanoma (Jonsson et al, 1979). In most of these studies abnormal scans have been interpreted as representing nodal metastases when a defect has been shown on one side compared with a group of nodes on the opposite (normal) side.

However, Agwunobi and Boak (1978) suggested that a depressed uptake of labelled colloid might be due to a reaction to cancer within the lymph node, rather than to metastatic replacement. Although the technique used initially in this study was that described by these authors, it was necessary to modify it considerably to obtain consistent scans of axillary nodes. In spite of this it has not been possible to

CHAPTER 3 : <u>DIAGNOSTIC LYMPHOSCINTIGRAPHY</u> cont.

reproduce their findihgs. It appeared that not only has the method
required modification, but that the interpretation of results needed
alteration to conform more with the majority of the above reports.
Such an interpretation, together with a pathological node correlation
is described in Chapter 4.

        The difference between the results in this chapter and those
of Agwunobi and Boak (1978) is difficult to explain, but may be associated
with factors such as colloidal particle size (Ege, 1976), the way in
which the massage is performed, and depth of injection. These and other
factors are discussed further in Chapter 7. The intradermal injection
proved to be painful in many patients. Indeed it was because it was
noted that many of the more meaningful scans in the earlier series were
painful, that a change to the intradermal route of injection was tried.
As a result it became necessary to precede the injection with subcutaneous
local anaesthetic. The cause of the discomfort is uncertain, as the
colloid suspension is isotonic.

        From this experience it has not been possible to demonstrate
a pattern of lymphoscintiscan which is typical or diagnostic of local
malignancy. Chapter 4 concerns the investigation to determine whether
lymphoscintigraphy can be reliably used to detect axillary node
metastases from breast cancer.

CHAPTER 4

LYMPHOSCINTIGRAPHY AS A PREDICTOR OF AXILLARY NODE METASTASES

IN BREAST CANCER*

* A modified version of a paper published in 'Lancet' (Black

et al, 1980a)

CHAPTER 4 : <u>LYMPHOSCINTIGRAPHY FOR METASTASES</u>

<u>SUMMARY</u>

A technique of axillary lymphoscintigraphy was used to investigate 31 patients with breast carcinoma. Intradermal injection of 100 μC_1 ^{99}Technetium Antimony Sulphide Colloid in 0.1 ml produced technically satisfactory scans of axillary lymph nodes in 28 patients (90%). A defect in the lower axillary uptake on the side of the lesion was seen in 10 patients with node metastases from breast cancer (9 confirmed histologically). Normal scans were seen in the remaining 18 patients with breast cancer. In three of the latter nodal metastases were found, but in two these were micrometastases only. Axillary lymphoscintigraphy improved considerably the clinical assessment of node status, correcting 5 of 6 patients misclassified by clinical examination.

<u>INTRODUCTION</u>

The optimal management of patients with apparently localised breast carcinoma is dependent upon accurate clinical staging. If distant metastases can be excluded with some assurance, most patients with breast cancer will be treated by mastectomy, adjuvant radiotherapy and/or chemotherapy being reserved for those in whom axillary node metastases are demonstrated histologically. However, in up to 30% of patients, nodes will not be sampled by total mastectomy including the parenchymatous axillary tail of the breast unless additional nodes are sought in the axillary fat (Cant et al, 1975). A test which would predict the axillary node status pre-operatively is obviously desirable. Agwunobi and Boak (1978) reported a technique of axillary lymphoscintigraphy in which ^{99}Technetium Antimony Sulphide Colloid (^{99}Tc^{m} ASC) was injected beneath the areola. This technique was modified to demonstrate changes which are associated with axillary node metastases.

CHAPTER 4 : <u>LYMPHOSCINTIGRAPHY FOR METASTASES</u>

<u>MATERIALS AND METHODS</u>

<u>Patients</u>

Thirty one patients with apparently operable cancer (T_1, N_0, M_0 - T_3, N_{1b}, M_0) were studied during a preoperative course of invest-igations designed to confirm the diagnosis of carcinoma and to exclude distant metastases ('superstaging', Chapter 2, Cant 1977, Cant et al, 1977). Each patient was examined by at least three experienced observers[*] and her clinical node status agreed by consensus (U.I.C.C. 1974, 1978 criteria; N_0 impalpable, N_{1b} palpable and clinically suspicious, N_{1a} palpable, not suspicious nodes). Twenty eight patients were treated by mastectomy with excision of lower axillary nodes, a minor extension of the operation of simple mastectomy and pectoral node biopsy. (Forrest et al, 1976). Three patients were treated by other means : one received systemic therapy when a small supra-clavicular node was shown to contain metastases; and, 2 others received primary radiotherapy because of skin invasion. After mastectomy all nodes in the resectate were dissected out, and individually mapped, weighed and examined as described in chapters 5 and 6. In addition to the 31 patients with cancer, 2 patients with benign disease were studied. They were suspected initially of malignancy and underwent the above investigations until carcinoma was excluded by biopsy. Brief clinical details of patients are in Appendix Table D.

<u>Technique of lymphoscintigraphy</u>

The technique employed was modified considerably from that used by Agwunobi and Boak (1978). (Method 2 in Appendix Table D). Briefly, approximately 100 μC_1 $^{99}Tc^m$ ASC in 0.1 ml was injected intra-

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[*] R.B. Black, Dr H.J. Stewart, Prof. A.P.M. Forrest

CHAPTER 4 : <u>LYMPHOSCINTIGRAPHY FOR METASTASES</u> cont.

dermally after 0.5 ml subcutaneous 1% Xylocaine, and the patient asked
to massage the injection site gently for the next hour. The ASC
('Labellaid', Philips Duphar) was mixed with hyalase in most studies,
and the injection placed at the lateral border of the areola. At three
hours the region of the breasts, axillae and shoulders was scanned to
detect radioactivity at the injection site and the axillae, using a
'Cleon 760' multi detector scanner. In 4 patients the scan followed a
recent open biopsy. In the remainder the only prior interference was
needle aspiration for cytology. Even this, however, on occasions caused
considerable bruising.

<u>Interpretation of scan</u>

As individual nodes cannot be identified by this technique,
only three broad interpretations were used. The scans were accepted
as normal - or more strictly 'no abnormality detected' (NAD) - if groups
of lower axillary nodes were clearly demonstrated in each axilla. The
scan was regarded as abnormal and suggestive of metastatic involvement
if groups of nodes were identified on each side, but that some lower
axillary nodes could be identified only on the contralateral side, there
being a defect, as it were, in the lower ipsilateral axilla. If node
uptake on both sides was insufficient for independent observers to
classify the scan consistently into one of the above two categories,
it was regarded as uninterpretable. These are Criteria B in Appendix
Table D. They conform with those of Ege (1978) and others. As in
Chapter 3 scans were read independently by Dr Merrick and myself, Dr
Merrick being unaware of the clinical features of the patient. Examples
of scans are shown in Appendix Figures D1 to D4.

CHAPTER 4 : <u>LYMPHOSCINTIGRAPHY FOR METASTASES</u> cont.

<u>RESULTS</u>

Of the 33 scans using this technique 30 were satisfactory including the 2 patients with benign breast disease, both of whom had normal scans. Of the 28 satisfactory scans in patients with cancer 18 were normal, and 10 abnormal. As explained above, 2 patients were treated by radiotherapy (1 in each group) and node histology was not obtained, leaving 9 with abnormal, and 17 with normal scans for evaluation. All 9 with abnormal scans had gross metastases in axillary nodes, whereas only 1 of the 17 with a normal scan had gross deposits. Two others with micrometastases only had normal scans.

These results are shown in Appendix Table D (Method 2). They are summarised in comparison with clinical assessment in Table 4.1. Although 5 of the 6 patients classified N_{1b} had gross nodal deposits there were also 5 patients with such deposits who had been classified N_0. The 2 patients with micrometastases were also clinically N_0.

<u>TABLE 4.1</u>

Correlation between clinical, scintigraphic and histological node status in 26 patients undergoing mastectomy. Histologically confirmed gross nodal metastases shown in brackets. [*]There are two other patients, not shown, who had micrometastases only.

SCINTISCAN RESULT	CLINICAL NODE STATUS N_{1b}	N_0	TOTAL
ABNORMAL SCAN	5 (5)	4 (4)	9 (9)
NORMAL SCAN	1 (0)	16 (1)[*]	17 (1)
TOTAL	6 (5)	20 (5)	26 (10)

CHAPTER 4 : <u>LYMPHOSCINTIGRAPHY FOR METASTASES</u> cont.

Thus, if the micrometastases are excluded, (they were detectable neither clinically nor by the scintiscan) it can be seen that the scan predicted the histological node status in 25 of 26 patients, and corrected 5 of the 6 patients misclassified clinically. The scan results of the two patients treated by radiotherapy were in agreement with the clinical classification, viz. 1 patient with a normal scan was classified N_0, and 1 with an abnormal scan, classified N_{1b}.

In 4 patients normal scans followed recent open biopsy.

DISCUSSION

Zum Winkel and Hermann (1979) have recently reviewed the demonstration of lymph nodes by lymphoscintigraphy in a number of regions of the body. The largest lymphoscintigraphy study is that of Ege (1978), who examined the internal mammary nodes of over 2,000 patients, including over 1,000 with breast carcinoma, using Antimony Sulphide Colloid. The same agent was also used by Jonsson to examine the inguinal nodes in patients with melanoma. (Jonsson et al, 1979). In both of these studies, the criteria used for abnormal scans were similar to those in this chapter (Criteria B), and quite different from Agwunobi and Boak, (1978) who felt that depressed uptake (Criteria A) in the ipsilateral axilla was caused by a reaction to local malignancy and not by metastatic disease. The study in Chapter 3 is unable to confirm their observations, i.e. it is felt that the lymphoscintigraphy pattern cannot be relied upon to diagnose local malignancy. The study in this chapter suggests that, in keeping with the majority of other reports, a defect in the scintigraphic pattern is most likely due to metastatic disease in the nodes.

CHAPTER 4 : <u>LYMPHOSCINTIGRAPHY FOR METASTASES</u> cont.

In most studies, pathological correlation has not been obtained, though a good correlation was reported in inguinal nodes with melanoma using Antimony Sulphide Colloid (Jonsson et al, 1979) and in the internal mammary nodes of patients with breast cancer using Stannous Phytate (Osborne et al, 1979). The present study is the first using Antimony Sulphide Colloid in which histological correlation has been demonstrated in the axilla. An almost complete separation between metastatic and normal nodes was obtained. Patients with micrometastases were not detected by scintigraphy, but such deposits do not profoundly affect the prognosis of patients compared with negative nodes. (Huvos et al 1971, Fisher et al 1978, and see Chapter 2). Furthermore, the small deposit in one patient was overlooked by the reporting pathologist.

This small series has demonstrated that lymph nodes may be assessed with some assurance pre-operatively, 5 of 6 patients misclassified by clinical examination being correctly assessed. The ability to stage patients accurately before operation is of particular value if node histology is not regularly obtained at mastectomy. It would also be of great value should adjuvant chemotherapy or radio-therapy be used pre-operatively. It might also be useful to diagnose patients with minimal cancer, who are unlikely to need post-operative radiotherapy, and who might benefit from insertion of a mammary prosthesis at the time of mastectomy. This is discussed further in Chapter 7.

CHAPTER 4 : <u>LYMPHOSCINTIGRAPHY FOR METASTASES</u> cont.

Further study will be required to reduce the number of unsatisfactory scans (10%), and to define whether massage and hyalase are necessary. The scan interpretation was not hampered by recent needle trauma and bruising. Indeed the scan was normal even after recent open biopsy. It appears therefore that only major lymph node replacement, such as occurs with metastatic cancer, regularly produces an abnormal scan.

CHAPTER 5

CLINICO-PATHOLOGICAL CORRELATION OF NODE ASSESSMENT IN

PATIENTS WITH EITHER SMALL OR MEDIUM SIZED NODE SAMPLES

AT MASTECTOMY

CHAPTER 5 : <u>CLINICO PATHOLOGICAL NODE ASSESSMENT</u>

<u>SUMMARY</u>

The clinical and histological node status was determined in each of 190 patients undergoing mastectomy for cancer. Fifty patients formed a prospective group. Histological assessment included gross and microscopic metastatic deposits, and a number of benign 'reactions' including sinus histiocytosis and lymphocyte and germinal centre predominance. The correlation for all 190 patients was as follows : N_0 (impalpable nodes) 32% nodal deposits, 28% sinus histiocytosis and/or lymphocyte predominance, 26% germinal centre predominance; N_{1a} (palpable, not suspicious, nodes) 10% metastatic deposits, 20% sinus histiocytosis/ lymphocyte predominance, 50% germinal centre predominance; N_{1b} (palpable nodes, suspicious of metastases) 79% deposits, 6% sinus histiocytosis/ lymphocyte predominance, 9% germinal centre predominance. The correlation was improved if gross metastases alone were considered, viz. N_0 19%, N_{1b} 74%.

Though more nodes were excised, and assessed, in the prospective group (median 6 nodes cf median 1) the proportion with metastatic deposits or germinal centre predominance was the same. However, the proportion in which sinus histiocytosis and lymphocyte predominance were identified was significantly increased in the larger node sample.

<u>INTRODUCTION</u>

Assessment of axillary nodes is imprecise. Indeed, some have gone so far to say that palpation of axillary nodes plays no part in the clinical staging of patients with breast cancer (McNair and Dudley, 1960). The experience of some groups would appear to bear out this discouraging attitude. In one report (Wallace and Champion, 1972) only 45% of patients who were clinical Stage II (i.e. those with palpable

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

axillary nodes) had node metastases confirmed, compared with 26% of those who were clinical Stage I (impalpable nodes). On the other hand Cutler et al (1970) demonstrated nodal metastases in 85% of patients in whom axillary nodes were palpable and suspicious, and further identified a group with palpable non-suspicious nodes in whom only 36% had nodal metastases. It was suggested, furthermore, that this latter group had a prognosis which was better even than those with impalpable nodes (Cutler et al 1969b, 1970). The cause of such non-malignant enlargement of nodes with apparent prognostic advantage was not defined. However, two histological 'reactions' have been associated with such an advantage, sinus histiocytosis (Black et al 1953, Cutler et al 1969a), and lymphocyte predominance (Tsakraklides et al, 1974).

The present study was undertaken to correlate the clinical and histological node status in a group of patients undergoing mastectomy for breast cancer after careful clinical assessment. A retrospective and a prospective group were studied for comparison. In the latter a greater sample of nodes was excised for histological assessment. It was considered important to see whether the proportion of patients with metastatic or 'reactive' nodes would be increased by this means.

<u>PATIENTS AND METHODS</u>

Two hundred and twenty two patients were initially included in the study, a retrospective series of 172 consecutive patients undergoing a number of pre-operative 'superstaging' investigations (Cant et al, 1977) described in Chapter 2 and a prospective group of 50

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

consecutive patients whose pre-operative investigations included

lymphoscintigraphy (Chapters 3 and 4). In the latter group a larger

number of lymph nodes was excised for histological examination at the

time of simple (total) mastectomy and node biopsy (Forrest et al, 1976,

Forrest, 1977). Nodes were carefully mapped, weighed and measured, as

described in Chapter 6. In the retrospective series of 172 patients,

32 had no nodes sampled at mastectomy and were excluded from analysis;

2 (of the 140 in this group) underwent bilateral mastectomy. There

were thus 192 axillae (50 plus 142) for clinical and histological

correlation. <u>Clinical node status</u> was assessed by palpation on each

patient during the course of her pre-operative in-patient investigations.

Axillary node status was as agreed by consensus of at least 3 experienced

observers[*], using U.I.C.C. (1974, 1978) criteria, viz. N_0, impalpable

ipsilateral axillary nodes; N_{1a} palpable ipsilateral nodes, not suspic-

ious of metastases; N_{1b} palpable mobile nodes, metastases suspected.

<u>Histological examination</u> of all nodes was performed initially in the

laboratory of the University Department of Pathology. As required in

the Scottish breast cancer trials, 10 sections were examined from one

node, usually the closest to the tumour and/or most obvious node, in

each patient; remaining nodes were sectioned at 0.5 cm intervals, the

slices being arranged in such a way as to maximise the probability of

detecting micrometastases as described in Chapter 6 (Wilkinson and

Hause, 1974). Histological sections of all available material from

the retrospective series was reviewed personally. In the prospective

series an additional and independent assessment was made by either Dr

R.J.C. Steele or Dr W.J. Collins who also undertook the sectioning of

nodes. Nodes containing metastases were classified according to

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[*] Prof. A.P.M. Forrest, Dr H.J. Stewart, Dr M.M. Roberts inter alia;
A.P.M. Forrest, H.J. Stewart and R.B. Black in the prospective series.

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

whether they were involved by gross metastases or micrometastases,
the latter definition being used when tumour deposits occupied 20% or
less of the sectional area of a node. Nodes which were free of metastases
were classified according to whether they showed the features of sinus
histiocytosis (Black et al, 1956 Cutler et al, 1969a), lymphocyte
predominance, germinal centre predominance or lymphocyte depletion
(Tsakraklides et al, 1974). Definitions and illustrations of these
'reactions' are in Appendix Figures A1 to A6. Nodes showing none of
the above 'reactions' were classified as either unstimulated or fatty
if more than 80% of the sectional area of the node was replaced by
adipose tissue.

Patients (or more specifically axillae) were categorised
according to the predominant histological feature in the following
manner. In those where only a single node was obtained (as in many from
the retrospective series) the feature of this node was used. Where more
nodes were obtained axillae were classed as containing metastases (gross
or microscopic) if any node contained such a deposit; otherwise they
were assigned either to whichever 'reaction' (germinal centre predominance
or sinus histiocytosis/lymphocyte predominance) predominated or to
unstimulated, if neither metastases nor these reactions were present.

Statistical comparisons were made by Chi^2 analysis, and the
Wilcoxon rank sum test.

RESULTS

Histological and clinical features of all patients are shown
in the Appendix (Tables A, B, D and E). A larger number of nodes was

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

obtained in the prospective series. As a consequence the major histolog-
ical feature of deposit free nodes did not always consist of a single
'reaction'. Where more than one reaction was seen the axilla was classed
as showing sinus histiocytosis and/or lymphocyte predominance (for
example) if it predominated even if germinal centre predominance, say,
was present in some nodes.

In the prospective series of 50 patients 31 were classed N_0,
1 N_{1a} and 18 N_{1b}. In the retrospective series the numbers were : N_0 64,
N_{1a} 9, and N_{1b} 69. This slightly increased proportion of N_0 axillae
in the prospective series compared with N_{1b} reached marginal statistical
significance viz. $Chi^2 = 2.71$ $P = 0.05$. Such an apparent difference is
thought to have occurred by chance, as both series were consecutive and
unselected in all respects except one, viz, in the retrospective group
32 patients were excluded because nodes were not excised. However, as
was shown in Chapter 2 this sub-group had a prognosis indistinguishable
from the whole group, and it therefore seems unlikely that the exclusion
of these 32 patients would have accounted for any apparent difference
between the series.

The correlation between clinical node status and the predominant
histological feature is shown in Table 5.1. It includes both the
prospective and retrospective series. Unstimulated lymphocyte depleted
and fatty nodes are all shown as unstimulated. In the combined series nodes
from 79% of patients classified N_{1b} contained either gross or microscopic
metastatic deposits, compared with 32% of those with impalpable nodes
(N_0). This difference is even greater, in that 12 of the 30 N_0 patients

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

with metastases had micrometastases only, compared with only 5 of the 69 patients classified N_{1b}.

The non-metastatic 'reactions' were commoner in patients classified N_0 and N_{1a}. Germinal centre predominance was especially common in those classified N_{1a}, though the differences were not statistically significant.

The Table shows that a similar proportion from the two series had metastases, but that more in the prospective group showed sinus histiocytosis and/or lymphocyte predominance. These differences are seen more clearly in Table 5.2 which shows the proportion of axillae with <u>any</u> feature rather than the predominant 'reaction' only. Although more nodes were excised for examintion in the prospective series, (median 6 cf median 1) the proportion of axillae with gross or micro-metastases was the same in both groups. Similarly, the germinal centre predominance 'reaction' was seen with equal frequency in the two series. However, the proportion of axillae with fatty, unstimulated and lymphocyte depleted nodes, and with nodes showing the 'reactions' sinus histiocytosis and lymphocyte predominance was considerably increased in the prospective series.

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

<u>TABLE 5.1</u>

Correlation between clinical node status and the predominant histological feature of nodes from 192 axillae. SH = sinus histiocytosis; LP = lymphocyte predominance; GCP = germinal centre predominance; US = unstimulated (including fatty and lymphocyte depleted).

CLINICAL NODE STATUS	NO.	HISTOLOGICAL FEATURES				
		GROSS METAS-TASES	MICRO-METAS-TASES	SH AND/OR LP	GCP	US
A Prospective series						
N_0	31	6	4	13	5	3
N_{1a}	1	0	0	0	0	1
N_{1b}	18	14	1	3	0	0
B Retrospective series						
N_0	64	12	8	14	20	10
N_{1a}	9	1	0	2	5	1
N_{1b}	69	49	4	2	8	5
C Combined series						
N_0	95	18 (19%)	12 (13%)	27 (28%)	25 (26%)	13
N_{1a}	10	1	0	2 (20%)	5 (50%)	2
N_{1b}	87	64 (74%)	5 (6%)	5 (6%)	8 (9%)	5
TOTAL	192	83	17	34	38	20

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

TABLE 5.2

The proportion of axillae in which nodes were found containing metastases, 'reactive' or other features. Comparison between the prospective and retrospective series using Chi^2 analysis, or Wilcoxon[*] rank sum test. N.S. not significant.

	PROSPECTIVE		RETROSPECTIVE		DIFFERENCE
	(50)		(142)		
GROSS METASTASES	20	40%	60	42%	NS
MICROMETASTASES	5	10%	12	8%	NS
SINUS HISTIOCYTOSIS	16	32%	11	8%	p < 0.001
LYMPHOCYTE PREDOMINANCE	17	34%	9	6%	p < 0.001
GERMINAL CENTRE PREDOMINANCE	15	30%	38	27%	NS
LYMPHOCYTE DEPLETION	12	24%	9	6%	p < 0.01
FATTY	30	60%	15	11%	p 0.001
UNSTIMULATED	38	76%	41	29%	p < 0.001
NO. NODES TOTAL	350		271		
RANGE	1 - 19		1 - 8		)
MEDIAN	6		1		)p < 0.01[*]
MEAN	7		1.9		)

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

<u>DISCUSSION</u>

This study has shown that patients with breast cancer in whom clinical node metastases are strongly suspected (N_{1b}) by a trained clinician have a very high chance (79%) of having node metastases confirmed histologically. This figure is comparable with that obtained by Cutler et al (1970), but much greater than that from an earlier Edinburgh series (Wallace and Champion, 1972) in which only 45% had metastases confirmed. The explanation for this improvement is not immediately apparent, as it is likely that patients in the two groups were similar. Perhaps in part it is due to the strict criteria used for the patients' clinical node status. It was not sufficient to classify a patient N_{1b} unless an experienced observer could 'persuade' his or her colleagues that nodes were indeed palpable. It was insufficient for a single observer to be able to palpate nodes.

On the other hand, and perhaps for this reason, a slightly larger percentage of patients with impalpable nodes subsequently had node metastases confirmed, i.e. 32% in this series compared with 26% from Wallace and Champion (1972). However, amongst those with impalpable nodes, deposits were commonly only micrometastases (12 of the 30 patients) which do not carry a significantly worse prognosis than nodes free of metastases (Huvos et al 1971, Fisher et al 1978, and see also Chapter 2). If only gross metastases are considered, the percentage of patients with such deposits were : N_{1b} 74%, N_0 19%. This marked difference is reflected in a significantly worse prognosis in those classified N_{1b} as shown in Chapter 2.

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

The figure of 19% gross metastases in N_0 patients is strikingly similar to the 17% of Stage I patients in Baum's series who developed 'progressively enlarging nodes' during follow up after simple mastectomy without lymph node biopsy (Baum, 1979).

The study has shown some apparent differences in node correlation between the prospective and retrospective series. However, the proportion of the two series in whom nodal metastases were demonstrated (either gross or microscopic) was remarkably similar. This suggests that the two series of patients were comparable, in spite of the apparent increased proportion of those with the N_0 node status in the prospective group. It seems less likely that the larger node sample from these patients compensated to raise the rate of demonstrated nodal deposits. In the controlled Cardiff-St Mary's trial the rate of detection of such deposits was as high in the small node sample, from simple mastectomy, as in the larger sample from radical mastectomy (Roberts et al, 1973).

On the other hand there was a significantly increased proportion in the prospective series who had nodes showing sinus histiocytosis, lymphocyte predominance, lymphocyte depletion, fatty infiltration, or no reaction at all (unstimulated nodes). It seems most probable that the explanation for this difference is to be found in the significantly larger sample of nodes obtained for examination. There are only three other possible explanations, all of which seem less plausible : (1) there could have been a real difference between the groups in the patients studied; (2) certain 'reactions' may have been overlooked by the single observer in the retrospective series (this is discussed

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

further in Chapter 7); and, (3) lymphoscintigraphy may have caused
a 'reaction' in the nodes. This last suggestion can almost certainly
be discounted. It is hardly likely to cause all the above 'reactions' -
or non reactions.

If the small injection of 0.1 ml colloid suspension caused
any reaction at all, the most likely one would be germinal centre
predominance. Yet in spite of the larger node sample, this particular
reaction was seen with no higher frequency in the prospective series
than in the retrospective one.

It seems most likely, therefore, that increasing the size
of the node sample excised at mastectomy is the explanation for the
increased proportion of certain node 'reactions'. The reason why some
node features are increased by this means, but not others (notably
metastases or germinal centre predominance) is examined separately
in Chapter 6. It is concerned with the 'geographical' position in which
the various types of nodes are to be found.

It has not been possible to demonstrate that palpable non-
suspicious lymph nodes (N_{1a}) display histological appearances (i.e.
sinus histiocytosis or lymphocyte predominance) which have an alleged
prognostic advantage (Cutler et al 1969a, Tsakraklides et al, 1974).
In this series only a small number of patients (10) were classified N_{1a}
and although half of these had germinal centre predominance this is not
a feature associated with improved prognosis (Tsakraklides et al 1974,
Hunter et al 1975, and see also Chapter 2). In only 2 of the 10 were

CHAPTER 5 : <u>CLINICO-PATHOLOGICAL NODE ASSESSMENT</u> cont.

the more favourable 'reactions' sinus histiocytosis and/or lymphocyte predominance found. This may be an underestimate as 9 of the 10 patients classified N_{1a} were in the retrospective series in whom a smaller number of nodes was examined. On the other hand those in the N_{1a} node status did not fare better than those with impalpable nodes (N_0 - see Chapter 2) in spite of the fact that few of them had metastases. The precise definition of the node 'reaction' of such a group remains elusive. This is further considered in Chapter 7.

CHAPTER 6

SITE SIZE AND SIGNIFICANCE OF PALPABLE, METASTATIC AND/OR

'REACTIVE' NODES IN OPERABLE BREAST CANCER

CHAPTER 6 : PALPABLE AND 'REACTIVE' NODES

SUMMARY

A study was undertaken to determine the size and nature of palpable axillary lymph nodes in 50 patients undergoing mastectomy for breast cancer. 350 individual nodes (1-18 per patient, median 6) were weighed, measured, and their position mapped with respect to the primary tumour. Each node was examined histologically, and classified : (a) unstimulated; (b) 'metastatic' (gross or microscopic); (c) 'reactive' viz. sinus histiocytosis; lymphocyte predominance; germinal centre predominance; lymphocyte depletion; or, (d) fatty replacement. All node categores (b) (c) and (d) were larger than unstimulated nodes (maximum diameter 0.2 - 2.0 cm, median 0.8 cm, weight 0.02-0.88 g, median 0.11 g). Patients with palpable nodes had at least one in the axillary node sample which exceeded 1.5 cm diameter and/or 1.0 g in weight. Above these limits metastatic nodes were palpable in 15 of 18 patients, but 'reactive' nodes were palpable in only 3 of 14 patients. Nodes with metastatic deposits or germinal centre predominance were found lower in the axilla than nodes showing sinus histiocytosis, lymphocyte predominance, lymphocyte depletion, or fatty replacement. From their relative positions it seems more likely that the less favourable[*] germinal centre predominance, rather than sinus histiocytosis or lymphocyte predominance, is a 'reaction' to the malignant process within the breast.

INTRODUCTION

Preoperative clinical staging of patients with breast cancer may be unreliable because of observer error and inconsistency in assessing significantly enlarged nodes (McNair and Dudley, 1960).

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* See Chapter 2.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

In previous studies confirmation of malignancy in patients with significant palpable nodes has varied from 45% (Wallace and Champion, 1972) to 85% (Cutler et al, 1970). Non-malignant node enlargement, and therefore palpability, is even less well understood. Cutler and his colleagues suggested that a non-malignant cause of palpable node enlargement was associated with an improved prognosis (Cutler et al, 1970), but the precise nature of the reaction was not defined. Primarily the present study was undertaken to determine the size of axillary nodes, to examine the position of metastatic and 'reactive' nodes, and to correlate these with the patients' clinical node status as assessed before mastectomy. A secondary aim of the study was to explore the reasons why the proportion of patients with nodes showing some 'reactions' but not others, could be increased, by expanding the node sample that was excised at the time of mastectomy, as shown in Chapter 5.

MATERIAL AND METHODS

Patients

Fifty patients were studied. All had apparently operable breast cancer, and had been admitted to hospital for a series of 'superstaging' investigations as described in Chapter 2 (Cant et al, 1977) and, in addition, for lymphoscintigraphy of the axillary nodes as described in Chapters 3 and 4. In order to correlate scintigraphic changes with node histology, it was decided to excise more nodes than is usual in simple mastectomy with pectoral node biopsy (Forrest et al, 1976). Patients were carefully examined by at least three experienced observers, (A.P.M. Forrest, H.J. Stewart, R.B. Black) and in each case a consensus was reached as to whether axillary nodes were palpable or not.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

Preparation of lymph nodes

      At operation, in addition to nodes in the 'axillary tail' of the breast, a block of tissue was excised below the axillary vein up to the lateral border of pectoralis minor. Sutures were placed at the apex of dissection and on the anteromedial aspect of this block of tissue in order to identify the location of nodes within it. Before processing in the University Department of Pathology, the axillary tail and the block of axillary tissue were dissected carefully and each node excised, labelled and plotted on a sketch 'map' for subsequent identif- ication of its position. Diagrams of the sketch 'maps' are shown in Appendix Figures E. Each node was then cleaned of fat, weighed and measured before sectioning for histological examination.

Node histology

      In each block of axillary contents the node nearest to the tumour was sectioned 10 times; the remainder were cut at 0.5 cm inter- vals, the slices being arranged so that sections were taken from non- opposing surfaces, i.e. in such a way as to maximise the probability of detecting micrometastases (Wilkinson and Hause, 1974). Histological sections were examined and reported by members of the University Department of Pathology and independently reviewed blind by either Dr R. J.C. Steele or Dr W.J. Collins, in addition to myself. Nodes were classified as containing gross metastases (over 20% of sectional area involved by tumour) or micrometastases, or displaying any of the following 'reactions' : sinus histiocytosis (Black et al 1956, Cutler et al 1969a), lymphocyte predominance, germinal centre predominance, or lymphocyte depletion (Tsakraklides et al, 1974). Remaining nodes were classified as either unstimulated, or fatty when the sectional area

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

consisted of over 80% adipose tissue. For the purpose of analysis
only those nodes showing marked sinus histiocytosis or lymphocyte
predominance were graded as such. Nodes were graded germinal centre
predominance if there were 6 or more enlarged secondary follicles in
one cross section of a lymph node. Definitions and examples of node
'reactions' are illustrated in Appendix Figures A1 to A6. Where there
was disagreement amongst observers as to the classification of
individual nodes (less than 10% of the time) sections were reviewed by
both until agreement was reached.

Distribution of nodes

The sketches of the excised axillary contents, showing the
location of each node, were used to assess any differences between
the distribution of metastases and 'reactions'. The following
descriptive terms were applied in order to avoid the ambiguity of
'proximal' and 'distal' : the position in the axillary block closest
to the tumour was termed 'focal', this being in the lower-most
anterior aspect of the axilla; positions further away from the tumour
were termed 'centrifugal'. In axillae containing nodes of more than
one classification each category was assigned to either the 'focal' or
the 'centrifugal' position, with respect to each other category. The
significance of differences between the positions occupied by each
category with respect to each other category was examined by the sign
test. Such comparisons were only possible in those axillae where
nodes of more than one type were identified. Sketches of such axillae
are illustrated in Appendix Figure E.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

Comparison was made between the sizes of each node category and unstimulated (normal) nodes, using the Wilcoxon rank sum test, and sign test, checked where significance was borderline by the Wilcoxon signed rank sum test comparing paired median values within the same patient. Differences between the palpability of enlarged nodes were calculated by Chi^2 analysis.

<u>TABLE 6.1</u>

The median and range of sizes (max. diameter) of 350 nodes from 50 patients, classified according to the predominant histological feature.

HISTOLOGICAL CATEGORY	NO.	MEDIAN	RANGE	cf. UNSTIMULATED NODES*
UNSTIMULATED	120	0.8 cm	0.2-2.0 cm	
METASTATIC	46	1.5 cm	0.6-5.0 cm	$p < 0.01$
LYMPHOCYTE PREDOMINANCE	36	1.5 cm	0.5-3.1 cm	$p < 0.01$
GERMINAL CENTRE PREDOMINANCE	29	1.5 cm	0.5-3.1 cm	$p < 0.01, < 0.05$
SINUS HISTIOCYTOSIS	30	1.0 cm	0.2-2.0 cm	NS
FATTY	89	1.5 cm	0.5-3.5 cm	$p < 0.01$

* Wilcoxon rank sum, and sign tests.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

TABLE 6.2

The median and range of sizes (weight) of 350 nodes from 50 patients,

classified according to the predominant histological feature.

HISTOLOGICAL CATEGORY	NO.	MEDIAN	RANGE	cf. UNSTIMULATED NODES
UNSTIMULATED	120	0.11 g	0.02-0.88	-
METASTATIC	46	0.45 g	0.06-15.5	$p < 0.01$
LYMPHOCYTE PREDOMINANCE	36	0.40 g	0.06-2.38	$p < 0.01, < 0.05$
GERMINAL CENTRE PREDOMINANCE	29	0.55 g	0.13-2.09	$p < 0.01$
SINUS HISTIOCYTOSIS	30	0.25	0.02-1.32	$p < 0.05$
FATTY	89	0.64	0.05-3.45	$p < 0.01$

* Wilcoxon rank sum, and sign tests.

RESULTS

The clinical node status, and individual node sizes from all

patients are shown in Appendix Table E. A total of 350 nodes was

examined from the 50 axillae (1-18 per patient, median 6). Tables

6.1 and 6.2 show the median and range of sizes (maximum diameter and

weight repsectively) of nodes in the 'metastatic', 'reactive', and other

categories. The few lymphocyte depleted nodes were similar to the

fatty nodes, and are included amongst them. The median size of nodes

in each category was greater than unstimulated (normal) nodes. This

difference was statistically significant except in the case of sinus

histiocytosis where the weight, but not the diameter, was significantly

greater. There was, however, considerable overlap, and this is shown

in Figures 6.1 and 6.2. In these, closed circles represent the largest

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

<u>FIGURE 6.1</u>

Maximum diameter (cm) of 350 nodes from 50 axillae classified according to the predominant histological feature.   Occasional nodes showing more than one feature are shown in more than one column.

SH^{++} = marked sinus histiocytosis

LP   = lymphocyte predominance

GCP = germinal centre predominance

U/S = unstimulated (normal)

Closed circles represent the largest node from patients with palpable nodes.

* 3 enlarged impalpable nodes containing micrometastases only.

+ 2 patients with palpable and metastatic nodes, in whom a non-metastatic node may have been the palpable one.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

<u>FIGURE 6.2</u>

Weight (g) of 350 nodes from 50 axillae classified according to the
predominant histological feature.   Occasional nodes showing more than
one feature are shown in more than one column.

SH^{++} = marked sinus histiocytosis

LP   = lymphocyte predominance

GCP = germinal centre predominance

U/S = unstimulated (normal)

Closed circles represent the largest node from patients with palpable
nodes.

* 3 enlarged impalpable nodes containing micrometastases only.

+ 2 patients with palpable and metastatic nodes, in whom a non-metastatic
   node may have been the palpable one.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

node in each patient whose nodes were palpable before operation.
Occasional nodes are shown in more than one column if more than one
dominant feature was present, eg. sinus histiocytosis and lymphocyte
predominance.

In two patients with palpable nodes, and with metastases, it
was not possible to define whether the largest (non-malignant) node
or the smaller node with a metastatic deposit was the palpable one. The
two figures demonstrate that in all patients with palpable nodes, at
least one node was $\geqslant$ 1.5 cm diameter and/or $\geqslant$ 1.0 g in weight. Though
it is not possible to be certain that the largest node was in each case
the palpable one, it does appear that the limit of palpability in the
lower axilla is of this order of magnitude. However, it was only in
the 'metastatic' group of nodes that the majority of nodes enlarged by
these criteria were palpable.

Table 6.3 shows the predominant cause of enlargement of lymph
nodes in the 44 patients in whom at least one node was $\geqslant$ 1.5 cm in
maximum diameter. Such enlarged nodes were palpable in 15 of the 18
patients who had node metastases, but in only 3 of the 26 patients whose
node enlargement was non-malignant, a significant difference (Chi^2 = 19.8,
P $<$ 0.001). There was in addition one patient with fatty node
enlargement which was possibly palpable (see Fig. 6.1), but this
patient also had a small node with a metastatic deposit. In 12 of the
44 patients fat was the cause of node enlargement, while in 32 patients
other causes were implicated. Even if one accepts the possibility that
one enlarged node in the fatty group was palpable, there were 18
patients with palpable nodes amongst the 32 others.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

This difference is also statistically significant (Chi^2 = 6.12 p < 0.01).

Thus for all practical purposes enlarged fatty nodes were impalpable,

and only a small portion of enlarged, 'reactive' nodes were palpable.

TABLE 6.3

The causes of lymph node enlargement ($\geqslant$1.5 cm diameter) in 44 patients

in only 18[*] of whom were nodes palpable. [*]In an additional one patient

an enlarged fatty node may have been palpable. (See Fig. 6.1).

CAUSE OF ENLARGEMENT	NO.	NO. PALPABLE
GROSS METASTASES	18	15
SINUS HISTIOCYTOSIS AND/OR LYMPHOCYTE PREDOMINANCE	11	3
GERMINAL CENTRE PREDOMINANCE	3	0
FATTY + LYMPHOCYTE DEPLETION	12	0[*]
TOTAL	44	18[*]

A schematic diagram of the distribution of lymph node categ-

ories within the axillae of patients with breast cancer is shown in

Figure 6.3. The rational basis for this diagram can be understood by

studying Table 6.4 which shows the comparisons between the various types

of node as to whether they were 'focal' or 'centrifugal' with respect

to other node categories. Nodes containing metastases and nodes showing

germinal centre predominance tended to occupy the 'focal' position

whereas nodes showing sinus histiocytosis or lymphocyte predominance

occurred more or less randomly in the axilla. Fatty nodes and lymphocyte

depleted nodes, on the other hand, tended to occur in the 'centrifugal'

position, i.e., they were higher and more proximal in the axilla.

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

<u>FIGURE 6.3</u>

Diagrammatic sketch of an axillary block (excised at mastectomy) in which nodes of all categories are present.
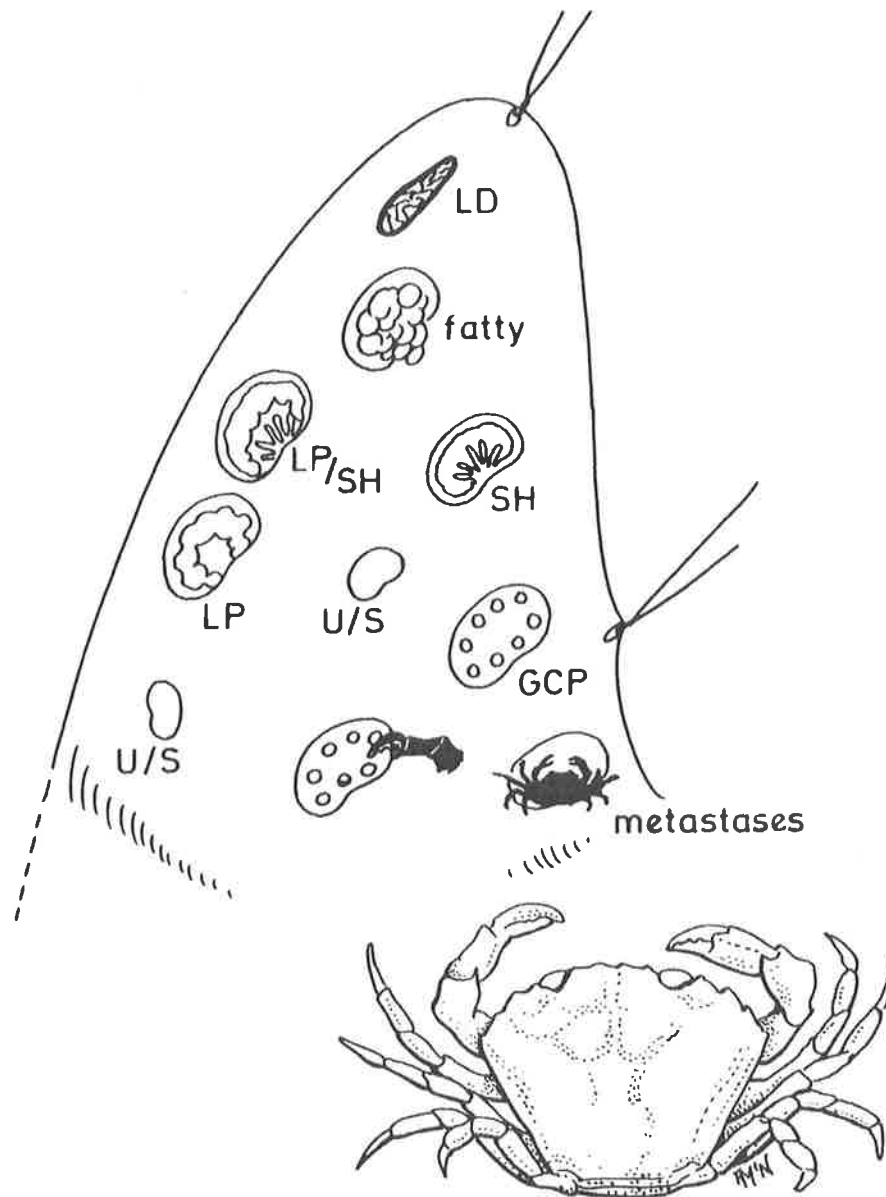
LP   = lymphocyte predominance

SH   = sinus histiocytosis

GCP = germinal centre predominance

LD   = lymphocyte depletion

U/S = unstimulated

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

TABLE 6.4

Comparison between the positions within the axilla occupied by nodes showing different histological features.

COMPARISON	'FOCAL'	'CENTRIFUGAL'	DIFFERENCE[*]
METASTASES v. OTHERS	15	1	p 0.01
GCP v. OTHERS	18	3	p 0.01
GCP v. SH	14	0	p 0.01
GCP v. LP	8	1	p 0.05
FATTY v. OTHERS	1	11	p 0.01
LD v. OTHERS	1	8	p 0.05
LP v. SH; SH, LP v. OTHERS	$\doteqdot$	$\doteqdot$	NS
MET. v. GCP	6	1	NS

* Sign test

GCP = germinal centre predominance

SH = sinus histiocytosis

LP = lymphocyte predominance

LD = lymphocyte depleted

MET = metastatic

NS = not significant

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

<u>DISCUSSION</u>

The study was undertaken in order to determine, if possible, the sensitivity of node palpation, and to explain why the proportion of patients with some but not all types of 'reactive' nodes may be increased by expanding the size of the node sample excised at mastectomy (Chapter 5). The study has demonstrated that many of the so-called 'reactive', as well as fatty nodes are enlarged compared with normal (unstimulated) nodes, though this difference is only slight in nodes showing sinus histiocytosis.

Although one cannot be dogmatic it appears that nodes are rarely palpable unless they exceed 1.5 cm in maximum diameter or 1g in weight. But even with these criteria of enlargement, 'reactive' nodes are infrequently palpable. There are perhaps two reasons for this : firstly, they are almost always softer than nodes enlarged by gross metastatic deposits, which were palpable in 15 out of 18 patients in this study. Secondly, many of the 'reactive' lymph nodes appear to occur higher in the axilla. In Table 6.4 it is shown that nodes with sinus histiocytosis and/or lymphocyte predominance occurred anywhere in the axilla, but that they were 'centrifugal' with respect to nodes with metastases or germinal centre predominance. On the other hand fatty and lymphocyte depleted nodes had a distinct predilection for the 'centrifugal' position, and would appear to be rarely, if ever, palpable.

This study has also demonstrated that nodes containing metastases and nodes showing germinal centre predominance occur 'focally' i.e. lower in the axilla, and are thus likely to be sampled even when only a small number of nodes is excised. This is the probable

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

explanation for the finding in Chapter 5 that increasing the size of
the node sample did not increase the proportion of nodes with metast-
ases or germinal centre predominance but did enhance the likelihood of
discovering fatty nodes or those showing sinus histiocytosis, lymphocyte
predominance or lymphocyte depletion.

Cutler and his colleagues (Cutler et al, 1970) also noted that
the percentage of patients with nodes showing sinus histiocytosis
increased as a larger number of nodes was examined. It is of interest
that sinus histiocytosis was said to be more prevalent in nodes
excised from Japanese women than from a group of British women undergoing
mastectomy (Freidell et al, 1974). However, the number of nodes excised
and examined was not stated, and the apparent racial differences might
have been a result of the sampling technique.

The findings on the distribution of 'metastatic' and 'reactive'
lymph nodes should give encouragement to those who sample only one or
two nodes at mastectomy, in that the lower most anterior ones are most
likely to contain metastases if they are present. Furthermore, although
not claimed from this study that nodes were exhaustively examined for
micro-metastases[*], the findings suggest that should multiple sections
be taken of lymph nodes, it will be more rewarding if nodes in the
'focal' position are examined in this way. This is the likely site of
the node or nodes referred to as 'pectoral' in Chapter 5 (Forrest et al,
1976).

The 'focal' position of nodes showing germinal centre predomin-
ance as compared with those showing sinus histiocytosis and lymphocyte

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[*] The 0.5 cm cuts used would have a 80% probability of detecting a 4 mm
     metastasis and a 40% probability of detecting a 2 mm deposit (Wilkinson
     and Hause, 1974).

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE' NODES</u> cont.

predominance is of interest as, in many of the nodes showing micro-
metastases, germinal centre predominance was also present. An example
of this is illustrated in the Appendix Figure A6. It seems probable
that the germinal centre predominance 'reaction' is associated with
occult metastatic spread of tumour and it may be significant that
this reaction appears to carry a worse prognosis than the more favourable
'reactions' of sinus histiocytosis and lymphocyte predominance (Cutler
et al, 1969a, Tsakraklides et al, 1974, Hunter et al 1975, and see
Chapter 2).

Why germinal centre predominance, with a prominent B
lymphocyte response, should be disadvantageous is not easy to explain,
and any attempt to do so is merely speculative. On the other hand it
has not been shown that sinus histiocytosis and lymphocyte predominance
are 'focal' effects. Under this circumstance it is not possible to
conclude that they are in any way 'reactive' to the nearby tumour.
They may merely be features of normal axillary nodes, which are replaced
(by germinal centre predominance and/or metastases) as the tumour
progresses. This possibility is discussed at length in Chapter 7.

Only one of the patients in this study had the palpable non-
suspicious nodes (N_{1a}) which have been associated with a good prognosis
(Cutler et al, 1970). It was impossible therefore to define the cause
of such enlargement. What was shown was that, though lymph nodes may be
enlarged by a variety of processes, metastatic involvement is by far
the most likely one to render them palpable. It is also confirmed that
the nodes nearest to the primary tumour are more prone to metastatic

CHAPTER 6 : <u>PALPABLE AND 'REACTIVE'NODES</u> cont.

involvement than are those situated higher in the axilla. Both of these findings are reassuring in the present climate of conservative surgery for breast cancer. It seems prudent to continue the practice of node excision at the time of mastectomy (Forrest et al, 1976, Forrest, 1977). The question of how many nodes should be removed is further considered in Chapter 7.

CHAPTER 7

THE AXILLARY NODES IN PERSPECTIVE.

SOME FURTHER COMMENTS ON THE STUDY FINDINGS

CHAPTER 7 : <u>THE AXILLARY NODES IN PERSPECTIVE</u>

Although the studies described in this thesis have been directed at different aspects of the assessment and management of patients with breast cancer, they have all been concerned, to a greater or lesser extent, with axillary lymph nodes.

<u>PROGNOSTIC FACTORS IN BREAST CANCER</u>

The first study, (Chapter 2) was concerned with the clinical and histological assessment of axillary nodes as a guide to prognosis. More especially, it was concerned with the predictive value of various node categories in determining whether early recurrence was likely or not. In common with previous studies the following features were confirmed as powerful prognostic determinants : the <u>size</u> of the primary tumour (Fisher et al 1969, 1975b, Haagensen 1974, Hamilton et al 1974, Co-operative Breast Cancer Group 1978, Blamey et al 1979, Nemoto et al 1980); the <u>clinical node status</u>, (Cutler et al 1970, Fisher et al 1975b, Murray et al 1976, Langlands et al 1979); and the <u>histological node status</u> with respect to metastatic deposits (Johnstone 1972, Haagensen 1974, Hamilton et al 1974, McLaughlin et al 1978, Co-operative Breast Cancer Group 1978, Blamey et al 1979, Nemoto et al 1980).

However, in contrast with the importance of defining whether gross nodal metastases are present or not, the earlier reports that microscopic lymph node deposits are of little prognostic consequence (Pickren 1961, Huvos et al 1971, Attiyeh et al 1977, Fisher et al 1978) have been confirmed. In addition, there was some suggestion from this study that the allegedly favourable 'reactions' (Black et al 1953, Cutler et al, 1969 etc.) of <u>sinus histiocytosis</u> and <u>lymphocyte predominance</u> (Tsakraklides et al, 1974) confer disease free-survival advantage. However, in this series these

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - NODE HISTOLOGY</u>

two categories were linked with patients who had unstimulated nodes in contradistinction with Cutler's studies (Cutler et al, 1969a). Patients in these three groups had a particularly good prognosis. By way of contrast patients lacking node metastases but showing other features of node histology (<u>germinal centre predominance</u> and <u>lymphocyte depletion</u>) had a less favourable outlook. As explained below, the linking of three node categories (sinus histiocytosis, lymphocyte predominance and unstimulated) is probably justifiable, as it is very likely that many of the patients with unstimulated nodes would have had nodes with the more favourable features (sinus histiocytosis and/or lymphocyte predominance) had more nodes been available for assessment. Such findings do not prove that sinus histiocytosis or lymphocyte predominance confer any specific protective effect on the patient. It seems equally probable that they merely represent an absence of metastatic disease. This point of conflict is discussed below (see 'reactive nodes').

In this retrospective series, only a small number of nodes was sampled (0-7, median 1). Yet the <u>histological node status</u> (where available), was extremely useful in predicting recurrence. This statement must be qualified by two riders. First, it was insufficient merely to define whether nodes were positive or negative with respect to <u>metastases</u>. Not only was it important to show whether metastases were present, and whether they were <u>microscopic or gross</u>, but it was important also to define what 'reaction' was present in nodes free of metastases. Second, it was important also to define (Appendix Table CII(b) and Figures C2, 3 and 4) <u>the number of nodes involved</u> with metastatic deposits. Although this has been demonstrated previously with respect to radical mastectomy specimens, it was impossible in this study to examine a large number of nodes.

CHAPTER 7 : DISCUSSION - PROGNOSIS - NODE HISTOLOGY

A number of authors (Majmudar et al 1971, Fisher et al 1975b, Attiyeh et al 1977), have suggested that there is a 'cut off' point, when four or more nodes are involved, beyond which prognosis markedly alters. Such a 'cut off' could not be examined, as the majority of patients had only one or two nodes (even none) available for examination. However, Table CII(b) and Figure C4 in the Appendix clearly show the profound difference in outlook between those with micro-metastases, those in whom only one node had gross metastases, and those in whom either the only node removed contained metastases or there were metastases in more than one node. In other words even with such a small node sample it was possible to suggest two 'cut-off' points in patients with metastatic nodes, producing three groups with profoundly different potential for early recurrence. (Figure C4).

It is perhaps self-evident that nodes must be removed at mastectomy in order to gain this prognostic information. Patients in this study in whom no nodes were available for assessment, had a prognosis in terms of early recurrence indistinguishable from the total group. On the other hand, patients without nodes available for histology could be assigned to a prognostic group on the basis of the carefully measured tumour size (see Table 2.4). This fact is recognised in the U.I.C.C. (1974, 1978) staging system, in which patients are placed in Stages I, II and III purely on tumour size (Table 1.1). However, tumour size alone does not seem to be used as a basis for deciding whether adjuvant chemotherapy or radiotherapy should be used. Perhaps it could be, especially in patients (or places) where nodes are not examined histologically.

How diligently should one search for axillary nodes at mastectomy ? The earlier reports from Edinburgh suggested that if only the axillary tail

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - OESTROGEN RECEPTOR</u>

of the breast was examined nodes would be found in a substantial proportion

(90%) of cases (Cant et al 1975, Cant 1977).   This recommendation, however,

may be a little misleading in that in those studies nodes were sought by

the surgeon at operation in addition to the careful dissection of the

axillary tail (Forrest et al, 1976).   In spite of such a policy a proport-

ion of patients in the present series (32 of 172, i.e. 19%) had no nodes

available.   This problem is discussed further below (see 'node sampling').

Although not a primary concern in this series, there has been much

recent interest in the question of 'biological behaviour' of the tumour.

One estimate of biological behaviour being examined is the <u>oestrogen</u>

<u>receptor protein content</u> (ER) of the tumour (Hahnell and Twaddle 1973,

Hawkins et al 1975, McGuire 1975, Rosen et al, 1975).   This assessment

is examined in depth in the appendix, where it is seen (Figures C5 and C7)

that patients whose tumours had high oestrogen receptor content fared

better than those whose tumours lacked oestrogen receptor.   This is in

agreement with the majority of other reports where such a prognostic

effect was sought (Knight et al 1977, Maynard et al 1978, Cooke et al 1979,

1980, Kern 1979, Humeniuk et al, 1980).   No such prognostic effect of ER

was found by Hilf and his colleagues (Hilf et al, 1980).   However, this

could be a chance error as it has been pointed out (Forrest et al, 1980)

that by moving the cut off point between oestrogen receptor rich (positive)

and poor (negative) tumours, the prognostic effect can be eliminated.   The

cut off point is one matter (amongst others) where agreement between

laboratories has not been reached.

In support of the hypothesis that ER status is an index of

biological activity is the recent finding by Cooke and his colleagues

(Cooke et al, 1980).   They showed that there was an inverse correlation

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - OESTROGEN RECEPTOR</u>

between ER value and the thymidine labelling index, i.e. tumours with low ER have high growth potential.

As reported elsewhere (Forrest et al 1980, Humeniuk et al 1980) the results in the appendix again show the curious <u>anomaly</u> that patients with <u>lowest rates of recurrence</u> were those with <u>low (positive) ER</u>. Amongst those with positive ER those with higher values did less well (Figure C5 in Appendix).

This is especially curious as the presence of (positive) ER has been correlated with tumour differentiation (by Maynard et al, 1978 and by Silverswärd et al 1980, though not by Rosen et al, 1975) which is of established prognostic significance (Bloom and Richardson 1957, Fisher et al 1975b, Blamey et al, 1979).

An explanation was sought for this anomaly, and although the results are not entirely conclusive, it seems possible that part of the explanation may be in the means of estimating and expressing the ER content. In Edinburgh, as in Chicago (Block et al, 1978) ER has been estimated as fm/mg (or g) of (wet) weight of tumour tissue. Elsewhere ER has been expressed as fm/mg cytosol protein (Rosen et al 1975, Maynard et al, 1978) or as fm/ug DNA (Silverswärd et al, 1980). It seemed possible that tumours with a large malignant cellular (as opposed to stromal) component might give higher values of ER compared with tumours of low (malignant) cellularity. After all, what is really of interest is the receptor content of individual malignant cells.

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - TUMOUR CELLULARITY</u>

An estimate of <u>cellularity</u> was therefore made in patients in whom histological material was available. The cellularity score was similar to that used by others (Rosen et al 1975, Masters et al, 1978) and most closely resembled the estimate of Roberts and her colleagues (Roberts et al, 1978). A 16 point scoring system, however, was used by multiplying the two components instead of adding them as in Roberts' 8 point system. Scores were graded from 0 to 4 for each component depending on the percentage (less than 25%, 25-50% etc.) of (a) neoplastic tissue compared with normal tissue, and of (b) malignant epithelial cells compared with stromal elements in the tumour itself.

The <u>tumour cellularity</u> scores were grouped as shown in the Appendix (Table CI). Computer analysis showed that the cellularity score itself was an important prognostic factor, tumours of high cellularity faring worse than those with low cellularity (Appendix Table CII (b) and Figure C6). It is of interest that Masters and his colleagues showed a significant association between cellularity and the level of oestrogen receptor activity in tumours in which such receptors were present (Masters et al, 1978). Modification of the oestrogen receptor value in our patients by means of the cellularity score altered the prognostic significance of oestrogen receptor level. Although patients whose tumours lacked ER still recurred early, the anomalous situation did not seem to be quite so apparent. After this modification, the level of ER seemed less important. There was no suggestion that patients with tumours of low (positive) ER status recurred at a slower rate than those with high ER content - in fact almost the reverse was evident (see Appendix Figures C5 and C7).

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - TUMOUR CELLULARITY</u>

Irrespective of the relationship between cellularity and oestrogen receptor content, these findings appear to establish that <u>cellularity</u> of the tumour is an important prognostic factor. Almost certainly, like tumour size and clinical node status, it is simply another measure of 'tumour burden', though it is possible also that it is a feature of growth potential or tumour 'biological activity'. Cellularity does not appear to have been compared in a strict way with <u>histological grade</u>, (or <u>different- iation</u>) of the tumour, which was not assessed in this study. Histological grade has been assessed in a number of ways. The most widely recognised grading method involves a scoring system, in which from one to three points are given for each of three separate features : (lack of) tubular or acinar differentiation; nuclear pleomorphism; and, nuclear hyperchrom- atic or mitotic activity (Bloom and Richardson 1957, Scarff and Torloni 1968, Bloom and Field, 1971). Blamey and his colleagues used similar grades (Blamey et al, 1979). Black and his colleagues used nuclear changes only (Black et al, 1975) while Fisher used the first two (Fisher et al, 1975b). All have shown a positive correlation with treatment failure. Bloom and Richardson (1957) took cellularity into account in assessing mitotic activity, but apparently increased the grade for tumours of low cellularity. It is of interest, therefore, that (high) ER content has been positively correlated with both (high) cellularity (Masters et al, 1978) and (low grade) tumour differentiation (Maynard et al, 1978). Thus, cellularity appears to be a prognostic factor which is independent of tumour differentiation, and may affect the prognostic importance of the (level of) ER.

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - 'SUPERSTAGING'</u>

The study described in Chapter 2 (supplemented in the Appendix), has demonstrated a number of useful clinical, biochemical, or histological indices of prognosis. However, it has also indicated that the 'superstaging tests' are of negligible help in predicting early recurrence. Almost certainly the earlier enthusiasm for these tests (Cant 1977, Cant et al, 1977) requires qualification.

In that earlier analysis patients were assigned to either a poor or good prognostic group depending not only on the 'superstaging' test results but also on the histological node status. The important histological node status may well have swamped the effect of the 'superstaging' test results. Thus, of the first 50 women studied there was no correlation between a positive 'superstaging' test and positive (metastatic) nodes (Cant et al, 1977). In the short term follow-up there was recurrence in 11 of 33 women with 'suspected metastases' (i.e. the group with positive tests and/or positive nodes) and no recurrence in the other 17 (negative tests and negative nodes).

However, closer inspection of the data (Cant 1977, Table 109) shows that the recurrence rate a little later, excluding node status, was : 6 in 22 patients with positive (abnormal) tests, and 6 in 28 with negative tests - not the sort of difference which would be expected to cause elation. The corresponding recurrences in those with positive and negative nodes were : 9 in 21 and 3 in 29 respectively. At follow-up in 1979 the results were : 22 patients with positive tests:12 recurrences, 6 dead; 28 with negative tests : 14 recurrences, 11 dead of cancer.

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - 'SUPERSTAGING'</u>

It is not easy to see why these 'superstaging' tests were of so little discriminatory potential. However, the poor predictive value of nuclear scans has been noted by many groups with respect to both liver (Sears et al 1975, Wiener and Sadis, 1978) and bone (Baker 1977, Bishop et al 1979, Burkett et al, 1979) despite a few enthusiastic reports (Galasko 1975, Spiessens et al, 1977). No attempt was made in this study (Chapter 2) to define the reason for false negative and false positive values. However, the non-specific nature of abnormal liver function tests (for example) is acknowledged, and certainly some of the patients with elevated gamma glutamyl transpeptidase and alkaline phosphatase were members of the drinking class ! One interesting false positive example of liver tests was patient 51 (Appendix Table A) whose abnormal scan, and subsequently detected abdominal masses were shown to be associated with polycystic kidneys and polycystic liver disease.

Although some predictive value for a <u>positive bone scan</u> was found its value was diminished because positive scans were so infrequent. A range of positive scans from 2% to 20% was shown in the collected series of the British Breast Group (1978). Other rates were : 7% in this series, 3% from Bishop (Bishop et al, 1979) and 1.5% from Baker (1977). Furthermore this study has shown, as did Kitchen (Kitchen et al, 1979), that patients with positive bone scans usually have other indices of high risk, viz. clinically enlarged or histologically proven metastatic axillary nodes. In Blamey's group there were only 9 positive scans in the first 192 women tested (5%) yet 94 were shown to be of poor prognosis on the basis of histological evidence of node metastases (Davies et al, 1977). It is of interest that those who have been encouraged by the success of bone scans have had a higher rate of positive tests, viz. 24% from

CHAPTER 7 : <u>DISCUSSION - PROGNOSIS - SITE OF RECURRENCE</u>

Galasko (1975) and 20% from Spiessens (Spiessens et al, 1977).

Both Baker (1977) and (Burkitt et al, 1979) recommend a restricted policy for bone scans, viz. preoperatively for patients with symptoms of bone or joint pain and for those with Stage III disease; and, post-operatively, as a baseline, for those with metastases in the axillary nodes. Such a policy would lead to follow-up scans. A subsequent conversion to positive has been associated with a high recurrence rate, viz. 14 out of 15 in one study (Furnival et al, 1980).

Although not part of the main study, the computer analysis has shown the profound effect, in terms of life expectancy, of the <u>site at which recurrence first occurs.</u> Table CII (c) and Figure C8 in the Appendix show the grave significance of systemic recurrence, especially liver metastases, compared with the relatively favourable outlook in those whose first recurrence is confined to the local skin flaps and/or axilla.

The comparatively slow progression of disease in those whose recurrence is purely local has been a 'clinical impression' (Forrest, personal communication). Published observations, on the other hand, have merely reflected on the (ultimately) grave significance of local recurrence (Dao and Nemoto, 1963) which most commonly occurs synchronously with dissemination (Bruce et al, 1970).

CHAPTER 7 : <u>DISCUSSION - AXILLARY LYMPHOSCINTIGRAPHY</u>

The work described in Chapters 3 and 4 was initially conceived in an attempt to confirm the work of Boak (Agwunobi and Boak, 1978). In the event, his results could not be reproduced. My concern initially was an inability to produce any evidence of colloid in the axillary nodes whatsoever, and a number of attempts were made to modify the method in order to produce more reliable results. It must be admitted that the method used initially differed from what may have been an important part of Boak's method (though not mentioned in his publication), namely the use of a mechanical device* to massage the breast after injection of the colloid. Apart from being cumbersome such vigorous massage did not seem to be ethically justified in patients with breast cancer. A gentle manual massage by the patient herself was suggested, but this did not seem to be an important factor in producing reliable results.

One other departure from Boak's technique was the choice of <u>colloid material</u>. The agent used was commercially available Technetium labelled Antimony Sulphide colloid (^{99}Tc^m A.S.C., 'Labelaid', Philips-Duphar, Holland), the same as that used by Ege. (Ege 1976, 1977, 1978). Boak's material was a 'home-made' colloid, alleged to have been prepared by the Pharmacy Department of the Hospital, though this claim was denied by that Department on questioning.

Apart from an inability to reproduce their results, one other problem was encountered, and that was the fact that a number of patients experienced moderate to severe pain with the injection (see Figure D2 in Appendix). Indeed it was noticed that the women who experienced most

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* It was apparently referred to as 'the wobbler' at its hospital of origin.

CHAPTER 7 : DISCUSSION - LYMPHOSCINTIGRAPHY

pain commonly produced the best images, a finding which suggested the possibility of injecting colloid by the intradermal route. By this means more meaningful and reproducible results were obtained, though this made it mandatory to precede the injection with local anaesthetic. The difficulty of demonstrating axillary nodes by lymphoscintigraphy has been referred to by Ege, who suggested that both mammary and interdigital injections should be given to produce good scintigrams of the axillary nodes (Ege, 1979). It was decided not to add injections into the hand as the nodes of interest were primarily those draining the breast. In the event, and with the modifications outlined above, interpretable scintigrams were obtained in 9 out of 10 of cases.

Even with these changes the disparity between the results in Chapter 3 and Boak's is not easily explained. It is possible that his fundamental aim may have been misguided. His claim (to distinguish scintiscan patterns of benign and malignant breast disease) was based on an hypothesis that lymph nodes responded in an immunological way to local malignancy and that such a response would be revealed by a qualitative or quantitative difference in the nodal scan. He felt that this was demonstrated in an experimental study using syngeneic mammary tumours in mice and VX_2 carcinomas in rabbits into whose footpads were injected $^{99}Tc^m$ A.S.C. (Boak and Agwunobi, 1978). In this paper the authors stated that there was a 'depression of labelled colloid uptake by regional lymph nodes draining tumour'. However, in these studies counts over regional nodes were expressed per milligram of node. Apparent depressions of uptake could have been due to enlargement of the nodes while the total count remained the same. What ever these studies

CHAPTER 7 : <u>DISCUSSION - LYMPHOSCINTIGRAPHY</u>

showed, and it seems somewhat perverse that inhibited 'phagocytic <u>activity</u> of lymph node medullary macrophages' should be the '<u>reaction</u>' to cancer revealed by depressed A.S.C. uptake, it is quite apparent from the clinical study in Chapter 3 that such subtle changes (if they occur) are not demonstrable in the majority of patients using his published method. (Agwunobi and Boak, 1978).

The results in Chapter 3 showed that axillary lymphoscintigraphy was quite unable to demonstrate differences between benign and malignant lesions (see Appendix Tables DI and DII, criteria A). However, in Chapter 4 it was shown that lymphoscintigraphy may be used with some reliability to predict the presence of <u>gross metastases</u> in the axillary nodes (Criteria B).

At present conventional treatment of operable breast cancer involves total mastectomy with lymph node sampling (Forrest et al, 1976, Forrest 1977). If axillary nodes are regularly examined histologically there may not be a place for pre-operative lymphoscintigraphy. However, lymphoscintigraphy could be useful in a number of circumstances. For example, in centres where only simple mastectomy is done, or there is a low yield of lymph nodes at mastectomy, (and in the prospective series, Chapter 2, it was only 81%) lymphoscintigraphy could be used in order to stage the patient accurately, so that appropriate adjuvant therapy (radiotherapy and/or chemotherapy) could be given.

Secondly, lymphoscintigraphy could find a future use under two sets of circumstances : (a) In patients with small primary tumours there is current interest in the possibility of minimal surgery, viz. 'lump-ectomy' only, with or without radiotherapy, and/or axillary node sampling.

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In such a patient pre-operative lymphoscintigraphy could add to the assessment of the patient by excluding, within limits, the presence of axillary node metastases. (b) Patients undergoing mastectomy in the future may well be offered immediate insertion of a prosthetic implant. Currently there is a prospective trial in Edinburgh to assess the place of this addition to conventional treatment. Although it is too early at present to judge the issue, it appears probable that radiotherapy after the insertion of the implant somewhat detracts from the appearance and feel of it. Such patients might perhaps benefit from the avoidance of the implant until the conclusion of radiotherapy. In that case pre-operative lymphoscintigraphy could be used to predict those with involved axillary nodes requiring post-operative radiotherapy.

If axillary lymphoscintigraphy should become an accepted pre-operative procedure, further attempts should be made to increase the rate of interpretable scans from the present 90%. Careful attention to the depth of injection may help in this respect. There is also the possibility that other <u>agents</u> will be found <u>which are more reliable.</u>

The most established agent is ^{198}Au, colloidal gold, (Thomas 1956, Turner-Warwick 1959, Kazem et al 1969, Hultborn et al 1970, 1974, Bechyne and Dienstbier 1976, Zum Winkel and Hermann, 1977) but it produces an unacceptable radiation dose. Goodwin has suggested that Indium would be suitable (Goodwin et al, 1970). However, when used intravenously it scarcely improved on clinical assessment (Silverstein, 1976). Osborne has recently used Technetium labelled liposomes to produce axillary lymphoscintigrams with results not superior to those in Chapter 4.

CHAPTER 7 : <u>DISCUSSION - INTERNAL MAMMARY LYMPHOSCINTIGRAPHY</u>

(Osborne et al, 1980). Other agents used include stannous phytate

(Osborne et al, 1979) though Ege (1979) is convinced of its inferiority

compared with A.S.C.

Ege (1976, 1977, 1978, 1979) has continued to advocate the use

of <u>internal mammary lymphoscintigraphy</u>, but it is difficult to know just

how helpful this investigation might be in planning treatment of patients

with operable breast cancer. Although such a technique undoubtedly adds

to the information obtained in a proportion of women with breast cancer,

it is not clear just to what extent this would alter treatment. One

difficulty is the fact that <u>abnormal</u> scintigrams are noted when there is

an <u>absence of uptake</u> in a particular area. The wide anatomical variation

(Ege, 1976) might make the interpretation of such changes difficult.

More importantly there is probably only a very small percentage of

patients in whom the findings of internal mammary scintigraphy would

alter management.

If one used the figures from the 1,000 cases studied by Handley

(1975) one might argue that internal mammary node involvement would be

found by scintigraphy in 20% of operable cases, thereby altering their

management. However, in only 7.7% of patients would such metastases be

demonstrated in the absence of involved axillary nodes (12% of medial

tumours, 3% of lateral tumours and 7% of central tumours). It might be

argued that internal mammary lymphoscintigraphy would also contribute

to the management of those with involved axillary nodes - 53.5% of Handley's

series. Of these 'node positive' patients 35% had involved internal mammary

nodes (48% with medial tumours, 22% with lateral tumours and 46% with

CHAPTER 7 : <u>DISCUSSION - NODE CORRELATION</u>

central tumours). However, patients with involved axillary nodes are known to have a poor prognosis from advanced disease, and such patients are usually offered adjuvant therapy (radiotherapy and/or chemotherapy) whether the internal mammary nodes are shown to be involved or not. It is also appreciated that the majority of these patients will not be curable. Internal mammary scintigraphic findings would not alter their management, nor their prognosis.

In other words the finding of involved internal mammary nodes by lyphoscintigraphy would only alter the staging (and management) of 7.7% of those with negative axillary nodes. The total number of such patients with positive internal mammary nodes in Handley's series was only 36 (3.6% of the total). In the case of outer quadrant tumours the figures were 9 of 475 or 2%. It appears that there is only a limited, if any, place in breast cancer management for internal mammary lymphoscintigraphy. A policy of performing internal mammary node biopsy (Haagensen 1974, Blamey et al, 1979) especially in those with medial quadrant tumours and/or negative axillary nodes, would appear potentially to be just as useful.

<u>CLINICO-PATHOLOGICAL CORRELATION OF NODE STATUS</u>

The lack of complete correlation between clinical findings on palpation of axillary nodes and on histological examination has been noted by a number of authors (e.g. Wallace and Champion, 1972) and summarised by Hughes and Forbes (1978). This, together with the findings of McNair and Dudley (1960) referred to in Chapter I, has led to the feeling by many that it is 'necessary to abandon conventional clinical staging as a measure of nodal involvement (Johnstone, 1972). Nevertheless,

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it has remained an accepted part of the TNM staging system (U.I.C.C.
1974, 1978).

Why the controversy ? One adversary of clinical staging by node
palpation, Hamilton, concluded that 'clinical (node) assessment was
useful ... only in so far as it reflected histological findings' (Ham-
ilton et al, 1974). Yet curiously enough, in his paper both
(histologically) node negative and node positive patients appeared to
do better if their nodes were impalpable. Haagensen (1974) had a similar
experience. Clinical node status, furthermore, must continue to be
important in places where simple mastectomy alone is practised - for
example the massive international trial co-ordinated in King's College
Hospital, London (Murray et al, 1976) - unless perhaps a technique such
as lymphoscintigraphy is employed.

Furthermore, as shown in Chapter 2 the clinical status of nodes
is as useful even as the pathological status (of a small node sample),
unless more careful note is taken of the histological node features than
the simple determination of whether metastases are present or not. It
was shown both in the retrospective series and in the prospective series
(Chapter 5) that there was a respectable <u>clinico-pathological correlat-</u>
<u>ion</u> (79%) in the group in whom nodes were clinically suspected of contain-
ing metastases. Against this was the finding that 32% of patients with
impalpable nodes had metastases. However, almost half of these were
only micrometastases, with less important influence on the patient's
prognosis. The experience of others in correlating clinical and path-
ological node status is in Table 7.1.

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CHAPTER 7 : <u>DISCUSSION - NODE CORRELATION</u>

<u>TABLE 7.1</u>

<u>Correlation between clinical and histological assessment of axillary</u>
<u>lymph nodes, expressed as percentage agreement.</u>

Author	Palpable - metastases suspected	Impalpable
Haagensen, 1957	82%	53%
Cutler et al, 1970	85%	58%
Majmudar et al, 1971	50%	90%
Atkins et al, 1972	75%	76%
Johnstone, 1972[+]	80%	63%
Wallace and Champion, 1972[*]	45%	74%
Roberts et al, 1973	53%	75%
Haagensen, 1974	74%	71%
Hamilton et al, 1974[*]	54%	70%
McDonald et al, 1976[*]	58%	69%
Schottenfeld et al, 1976	73%	63%
Co-operative Breast Cancer Group, 1978	75%	64%
Present series[*]	79%	68%

NOTE : (i) All were radical mastectomy series except those marked [*]
       (ii) Some patients were reclassified solely on the basis of internal mammary node involvement[+]
       (iii) Micrometastases are not distinguished from gross metastases.

In general these figures show that, where there was a good correlation in patients in whom axillary node metastases were suspected, there was a correspondingly poor correlation in patients with impalpable nodes, and vice versa. This probably reflects, not so much the sensitivity of the clinicians' fingers, but the determination of the pathologists to find small nodes in axillary fat and small metastases in axillary nodes. The overall results in this study are better than any of the other series, with the exception of the Guy's Hospital trial (Atkins et al, 1972). This

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is probably due to the fact that a number of experienced clinicians reached a concensus with respect to clinical node status. It is certainly an improvement on the other series from Edinburgh (Wallace and Champion 1972, Hamilton et al, 1974) of presumably comparable patients.

Unfortunately, in this study it was not possible to define a group of patients whose <u>palpable, non-suspicious nodes (N1a) confer an enhanced prognosis.</u> Indeed in Chapter 2 it was shown that this small group (N_{1a}) had a prognosis that was intermediate between those with impalpable nodes (N_0) and those with palpable nodes suspected of containing metastases (N_{1b}) (see also Appendix Figure C1). This appears to be in marked contrast with Cutler's findings (Cutler et al 1970). Furthermore, as shown in Chapter 5, though patients in this group (N_{1a}) had 'reactive' nodes in a large proportion of cases, the predominant 'reaction' was germinal centre predominance, which does not have prognostic advantage (Hunter et al 1975, and Chapter 2).

It is perhaps worth examining Cutler's data (Cutler et al, 1970) in more detail, as his observation that <u>palpable non-suspicious nodes carried a better prognosis</u> than impalpable nodes, has not been confirmed (see Chapter 1). There were two hospitals, and a large number of surgeons involved in Cutler's study. Nodes were assessed as palpable or not, whether they were mobile, and whether they were thought to contain metastases. Clearly not all surgeons assessed all these criteria. As a consequence a large number of subgroups (coded 1 to 10) were encountered (Table 7.2).

Group A included only those with impalpable nodes 'N_0' (593 patients). Those where palpability was not stated (46) were excluded. Group B included 27 with palpable mobile non-suspicious nodes 'N_{1a}'

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and 43 in whom suspicion was not stated, $'N_1$?'. Group C included 183 with palpable nodes whose mobility was not stated and where metastasis was not suspected, $'N_{1a}'$ (50) or not stated, $'N_1$?' (133). Group D had palpable suspicious nodes which were mobile, $'N_{1b}'$ (97) or fixed $'N_2'$ (21); and, Group E consisted of 197 patients with palpable suspicious nodes whose mobility was not stated $'N_{1-2}'$ and another 3 with fixed nodes. In other words there were 253 patients (Groups B and C) with palpable 'non-suspicious' (or not stated) nodes. However, it was only Group B which was shown to have an allegedly better prognosis than Group A. Group C did as badly as Group D, which included 21 patients with $'N_2'$ fixed nodes ! And even the difference between Groups A and B failed to reach statistical significance ($0.05 < P < 0.10$).

TABLE 7.2

Data from Cutler and his colleagues, concerning the prognostic effect of palpable axillary nodes (Cutler et al, 1970). Distribution of patients in the clinical assessment of the homolateral axillary nodes.

SUMMARY GROUP	CODE	PALPABLE	MOBILITY	METASTASIS SUSPECTED	NO. OF PATIENTS
A	1	NONE	–	–	593
	2	NS	NS	NS	46
B	3*	YES	MOVABLE	NO	27
	4	YES	MOVABLE	NS	43
C	5*	YES	NS	NO	50
	6	YES	NS	NS	133
D	7	YES	MOVABLE	YES	97
	8	YES	FIXED	YES	121
E	9	YES	NS	YES	197
	10	YES	FIXED	NS	3

NS = Not stated.

* These groups correspond with patients whose nodes are palpable and not suspicious. However, the group chosen in this report was summary Group B.

CHAPTER 7 : DISCUSSION - BILATERAL PALPABLE NODES

The way in which the groups were arranged in this paper are rather curious. It suggests the possibility of 'juggling' in order to find a favourable group. Why Groups B and C were separated the way they were is difficult to justify. Admittedly the U.I.C.C. (1974, 1978) classification followed this paper by some years. However, the group with unequivocally palpable, non-suspicious, nodes was to be found partly in Group B, which did better, and partly in Group C, which did worse than those with impalpable nodes (Group A).[*]

This paper (Cutler et al, 1970) followed two earlier publications (Cutler et al, 1969b, Black and Asire 1969) on the alleged prognostic advantage of bilateral palpable axillary nodes. They concerned follow-up data on over 2,000 patients from a number of centres. Palpable nodes in these studies had not been classified as to whether they were suspicious or not suspicious of metastases. Black and Asire reviewed the node histology of 121 selected patients, especially 43 patients with bilateral palpable nodes (Black and Asire, 1969), 20 of whom had no lymph node metastases. They found that there were more patients with nodes of high grade sinus histiocytosis in those with palpable nodes (10 of 16 with bilateral nodes palpable; 13 of 34 with ipsilateral nodes palpable; 6 of 23 with impalpable nodes). Curiously enough the group with bilateral palpable nodes (and without metastases) had more primary tumours with favourable nuclear grade, which in itself could have accounted for a better prognosis. It is also of interest that they showed no difference in the node (section) sizes of those with palpable and impalpable nodes. This suggests the possibility that the group with bilateral palpable nodes may have been less obese, which is in itself a prognostically advantageous

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[*] Group C was largely ignored. So also were patients in Group E with negative nodes. They apparently fared worse than those with negative nodes in Group A. Palpable 'benign' enlargement of nodes was clearly not protective in this group !

CHAPTER 7 : <u>DISCUSSION - BILATERAL PALPABLE NODES</u>

feature (Co-operative Breast Cancer Group, 1978).

The other paper (Cutler et al, 1969b) immediately preceded the above, in which Black had commented on Cutler's finding that bilateral palpable nodes were associated with 'more favourable survival ... in patients with and without metastases'. However, though that paper (Cutler et al, 1969b) purported to show that 'bilateral palpable nodes may be a manifestation of host defensive response', the data could be interpreted quite differently and certainly did not show what Black and Asire (1969) had claimed.

Firstly, it must be noted that there were some curious groupings in that paper also. Group A (ipsilateral nodes not palpable) was combined with Group E (clinical node status not stated) because they had similar survival experience. For a different reason, viz. to provide a large enough group, Group B (palpable and movable) was combined with Group C (palpable, mobility not specified). By doing this the prognosis of Group B was artificially shifted towards a poorer range. When they came to look at the group with <u>bilateral palpable nodes</u> it was found that their survival was better than those (in Group B) with only ipsilateral palpable nodes. However, it was virtually <u>identical with the group (A) in whom nodes were impalpable.</u> Why this should be interpreted as showing a host defensive response is far from clear. As stated above it could be interpreted that those with bilateral palpable nodes were thinner (or younger, or fitter) than those with impalpable nodes. Clearly those with only unilateral palpable nodes were likely to have had a greater proportion with node metastases than the other two groups. Indeed this was the case, as shown in a subsequent figure from the same paper.

CHAPTER 7 : DISCUSSION - BILATERAL PALPABLE NODES

The paper then went on to dissect the group with bilateral palpable nodes. Of those without metastases bilateral palpability was associated with marginally better outlook (not statistically significant) than impalpability. There was no difference in survival amongst those with nodal metastases between the impalpable and bilateral palpable group. Dissecting further into all patients with palpable nodes not containing metastases, patients were grouped according to primary tumour size. Amongst those with small tumours the mortality rate was actually better for those with impalpable nodes. They did not fit the hypothesis. They were excluded. Eventually a group of patients was found with tumours greater than 4 cm in diameter, without nodal metastases, in whom palpable nodes were associated with almost significantly ($0.05 < P < 0.1$) better survival. Yet in four of the five other groups the prognostic trend was in the reverse direction.

It seems extraordinary that such an authoritative group writing in a prestigious journal ('Cancer'), should have misused statistics in this way. That is, by progressive exclusion of groups which did not fit their hypothesis, they eventually defined a subgroup which did. Furthermore Black's claim (Black and Asire, 1969) that Cutler's work (Cutler et al, 1969b) showed that bilateral palpable nodes are associated with 'more favourable survival ... in patients with and without metastases' would appear to have gone unchallenged.

Returning now to the question of allegedly favourable outlook in those with palpable, not suspicious nodes, one should examine whether there is any published evidence to support Cutler's claim (Cutler et al, 1970).

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Unfortunately, in the majority of even recent large series, a group with palpable, not suspicious, nodes is not analysed separately (e.g. Atkins et al, 1972, Johnstone 1972, Roberts et al 1973, Hamilton et al 1974, Fisher et al 1975b, Murray et al 1976, Schottenfeld et al 1976, Co-operative Breast Cancer Group 1978, Langlands et al, 1979).

One is left then to draw inferences from Haagensen's (1957, 1974) series in which patients' node status was classified carefully into (the equivalent of) N_{1a} and N_{1b} categories. Table 7.3 shows the pathological node status in his papers, compared with Cutler's (Cutler et al, 1970), a 'comparable' group from Wallace and Champion (1972), and with the series from Chapter 2.

TABLE 7.3

Percentage of patients with histologically confirmed axillary node metastases.

| AUTHOR | PALPABLE NODES | | IMPALPABLE NODES (N_0) |
	MET. SUSPECTED (N_{1b})	MET. NOT SUSPECTED (N_{1a})	
Cutler et al, 1970	85%	40%	42%
Haagensen, 1957	82%	55%	47%
Haagensen, 1974	74%	40%	29%
Wallace and Champion, 1972 *	45%	0%[*]	26%
Present series	79%	10%	32%

* The comparable group is of those with palpable nodes shown following mastectomy to be free of metastases. The prognosis of this group was inferior to those with impalpable nodes (viz. 64% 5 year survival cf 75%).

CHAPTER 7 : PALPABLE, NOT SUSPICIOUS, NODES

In both Haagensen's series the N_{1a} group had a higher rate of metastatic nodes than did those with impalpable nodes (N_0). The implication (not proven) is that they would not have had a better prognosis. Though not strictly comparable, the experience of Wallace and Champion (1972) suggests the same conclusion, viz. that patients with palpable, not suspicious, nodes do not have an outlook that is better than those with impalpable nodes.

Furthermore, I have already commented on the finding (not statistically evaluated) that in two series (Haagensen 1974, Hamilton et al 1974) patients with impalpable nodes seemed to fare slightly better than those with palpable nodes whether metastases were confirmed or not. The same was true in four of the six groups from the series of patients in Cutler's study discussed above (Cutler et al, 1969b).

I conclude, therefore, that clinical evaluation of axillary nodes is a valuable exercise. However, if nodes are palpable and not suspicious of metastases, though such patients may not do as badly as those with suspicious nodes, there appears to be no support to Cutler's claim (Cutler et al, 1970) that they will do better than patients with impalpable nodes.

THE NATURE OF PALPABLE NODES

The work described in Chapter 6 has certainly indicated both the type of node (notably one with a metastatic deposit) and its order of magnitude, for it to be palpable. The data is insufficient to define

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exactly which node was palpable.[*]   However, most often the largest node
was found low in the axillary sample, and it seems probable that the
majority of palpable nodes are to be found low in the axilla. Cant's
work certainly supports this suggestion. In her carefully examined 50
patients (Cant, 1977) there was a remarkably consistent finding. All
patients with palpable nodes had nodal metastases, and with one exception,
a metastatic deposit was in the 'axillary tail' rather than in the
presumably higher 'pectoral' node which was removed by the surgeon at
operation after the breast had been excised.

It seems likely then, that palpable axillary nodes are most
commonly found in close relation to the breast or pectoral muscle
borders, i.e. the pectoral or anterior group, rather than in the central
group as suggested by Allen (1970) and Goldsmith (1977).

It is shown in Chapter 6 that, in order for nodes to be palpable
it is likely that they will not only contain gross metastatic deposits,
but that in all probability they will be considerably enlarged (greater
than 1.5 cm and/or greater than 1 gm in weight).

These figures are very different from those suggested by Wilson
(1979) who stated that 'One or two moveable, not particularly firm
lymph nodes 5 mm in diameter can frequently be palpated in the normal
axilla'. The present study suggests that the sensitivity of node

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* By comparing the sizes in Table E with the diagrams in Figures E
(Appendix) it can be seen, however, that in the majority of the 18
patients with palpable nodes, enlarged nodes ($\geq$ 1g; $\geq$ 1.5 cm) were
found in the lowest one or two of the sample. Possible exceptions were
patients 18 and 35.

CHAPTER 7 : <u>DISCUSSION - PALPABLE NODES</u>

palpation may be as high as 1.5 cm (or 1g). Furthermore, many '<u>reactive</u>'

<u>nodes</u>, and virtually all fatty nodes exceeding those criteria appear

to be impalpable. In Chapter 6 a size range of 'normal' (unstimulated)

<u>nodes</u> was defined. These are <u>mostly small</u> (up to 2.0 cm with a median

of 0.8 cm in maximum diameter, or up to 0.88 g with a median of 0.11 g)

<u>and impalpable</u>.

<u>'LYMPHADENOPATHY' OR 'LYMPHADENOMEGALY' ?</u>

In Chapter 1 I questioned the relative merits of these two terms.
The semantic question may be regarded as quite trivial by many, but I
would not agree. Perhaps McNair and Dudley (1960) fell into the trap of
assuming that, when colleagues could feel axillary nodes, they were
stating their belief that such nodes were abnormal or lymphadenopathic.
This is probably not so. They were merely saying that they were palpable
(for which a Greek word appears to be lacking !) and probably enlarged
(lymphadenomegalic).

The studies in this thesis have shown that in patients with
breast cancer palpable nodes are unquestionably enlarged (-megalic), but
in that most contain malignant deposits they are -pathic also. Furthermore
the fact that palpable nodes in these studies - and in most others with
the notable exception of Cutler's (Cutler et al, 1970) - had an index of
prognostic disadvantage, suggests that lymphadenopathy is the better term.
That is not to say, however, that it is the correct term to apply to
palpable nodes in otherwise normal individuals - lymphadenomegaly may be
preferable at least until a term for lymph-node-palpable-ness can be
devised.

CHAPTER 7 : <u>DISCUSSION - 'REACTIVE' NODES</u>

<u>THE NATURE OF 'REACTIVE' NODES</u>

The question remains as to whether any of the 'reactive' nodes should also be considered normal. Certainly Tsakraklides and his colleagues (Tsakraklides et al, 1975) have suggested that various forms of 'reaction' may be present throughout life, germinal centre predominance being commonest in children and young adults, while lymphocyte predominance is commonest in neonates.

Furthermore Symmers (1966) is of the opinion that nodes which are completely uninfluenced by exogenous factors are unlikely to be encountered after foetal existence. Of more importance perhaps is the question : which 'reactions' in the axillary nodes of patients with breast cancer are likely to have been engendered by processes occuring within the breast ?

This is a question which may be answered tentatively by studying the findings in Chapter 6 concerning the positions of different node categories (Figure 6.3 and Table 6.4). Quite clearly metastatic replacement of axillary nodes is determined by a process in the breast. Whether gross or microscopic, metastatic deposits occur most often in nodes which are geographically close to the primary neoplasm.

This position, which was referred to as 'focal' in Chapter 6 to avoid the ambiguity of the terms 'proximal' or 'distal', appears also to be the site where germinal centre predominance is most commonly found (Hunter et al 1975, and Chapter 6). This suggests that germinal centre predominance may well be a 'reaction' to the nearby carcinoma.

CHAPTER 7 : <u>DISCUSSION - 'REACTIVE'NODES</u>

However, the same cannot be said of the other 'reactions' sinus histio-
cytosis and lymphocyte predominance, which are found somewhat remote
from the neoplasm. If germinal centre predominance really is reactive
it is quite apparent that it is not a reaction which is protective.
Hunter has suggested that germinal centre predominance might be responsible
for enhanced tumour growth by the production of blocking antibodies. This
is, at present, simply speculation. There is, however, little doubt that,
as shown in Chapter 2, patients with germinal centre predominance did
worse than other patients with nodes free of metastases.[*] They even did
worse than those with micrometastases (though this was not statistically
significant and it should be noted that some of the latter received
adjuvant 5 fluoro uracil in the Edinburgh controlled trials).

Although they made little of the observation, Black and Speer
(1958) would also appear to have noted the relatively poor outlook in
patients whose nodes showed 'follicular prominence' (akin to germinal
centre predominance). Of 32 patients with marked follicular prominence,
the 5 year survival was only 36%, though only 17 of these patients had
axillary metastases. They concluded that 'follicular prominence ...
was not associated with the same (good) prognostic significance as was
sinus histiocytosis'.

In the studies in this thesis another feature of germinal centre
predominance was observed. Review of all the nodes with micrometastases
showed that the majority of patients with these also showed, in the same
or adjacent nodes, either germinal centre predominance or lymphocyte

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[*] The very small number with lymphocyte depletion did worst of all.

CHAPTER 7 : <u>DISCUSSION - 'REACTIVE' NODES</u>

depletion (see Appendix Table B). A close correlation between germinal

centre predominance and metastatic deposition was also noted by Hunter

(Hunter et al, 1975).

There is a strong implication, therefore, that <u>germinal centre</u>

<u>predominance is a reaction</u> either to <u>metastatic</u> deposition, or to some

agent (e.g. a deposit which has subsequently passed through the node)

which is microscopically invisible and which carries a similar <u>unfavour-</u>

<u>able prognostic significance.</u>

The 'B' lymphocyte response, then, appears not to be in any way

protective.

What about the 'T' cell response (lymphocyte predominance) and

the histiocytic response (sinus histiocytosis) ? Certainly the findings

of others (Black et al 1953, 1956, Black and Speer 1958, Cutler et al

1969a, Tsakraklides et al 1974, Hunter et al, 1975) that they are

'protective' is confirmed. However, the site in which these 'reactions'

are found suggests that they may well be normal features of axillary nodes,

rather than a protective reaction by the 'host' against the tumour. In

parenthesis it might be noted how often the terms 'tumour - host' and

'host response' may be found in published papers (e.g. Berg 1956, Black

et al 1956, Majmudar et al 1971, Syrjänen and Hjelt 1978) as if the

foreign nature of the tumour and the immunological defence mechanisms

against human cancer were established facts rather than attractive

hypotheses.

CHAPTER 7 : DISCUSSION - 'REACTIVE' NODES

There are of course hints of immunological effects in human breast cancer. For example there have been two careful recent studies of in vitro activity of cells obtained from axillary nodes of patients with breast cancer. In one study (Check et al, 1980) cytotoxicity against a human mammary cancer line was higher in the presence of sinus histiocytosis or paracortical hyperplasia (syn. lymphocyte predominance) than with germinal centre hyperplasia (predominance). The authors felt that germinal centre hyperplasia in nodes near an advancing tumour was associated with local suppression of cytotoxic cell activity.

In the other paper (Kiricuta et al, 1978) lymphocyte migration from node explants to (the patient's) tumour explants was studied. Migration was particularly apparent from nodes showing sinus histio-cytosis and/or paracortical hyperplasia, and least from nodes of patients with node metastases. The effect of germinal centre predomin-ance was not noted. Comparable immunological studies have been performed by Fisher (Fisher et al, 1973) with similar inferences but without details as to the histological features of the nodes studied.

Though all these studies could be interpreted as showing an immunological 'reaction' by regional lymph nodes with sinus histiocytosis (for example) it is of interest that the authors of the first paper were more impressed with the possibility that other factors were suppressing a normally 'protective' effect. They did not discount the possibility that sinus histiocytosis - and tumour cytotoxity - was normal, and that it was suppressed in the lymph nodes as the tumour spread.

Perhaps, as a basis for discussion, one should examine Symmers' suggestion that the fact that sinus histiocytosis is found in association

CHAPTER 7 : DISCUSSION - 'REACTIVE' NODES

with breast cancer 'may only reflect that' mastectomy with axillary node excision provides the commonest 'opportunity to examine axillary lymph nodes microscopically'. (Symmers, 1966). If this is the case, then the importance of sinus histiocytosis (and lymphocyte predominance) may lie not in the probability that they are protective in an immunological or similar way (the evidence in this thesis does not refute this possibility though it does not strongly support it), but rather that the finding of such 'reactions' implies an inverse probability of detecting unfavourable features, e.g. metastases. Note that in the retrospective group (Chapter 2) where only one or two nodes were sampled, a large number of patients with unstimulated nodes had a favourable outlook. They lacked sinus histiocytosis or lymphocyte predominance, but they also lacked germinal centre predominance or metastases. However, by comparison with the prospective group in Chapter 6, it is suggested that many of these patients would have shown a 'more favourable' reaction e.g. sinus histio-cytosis, had more nodes been sampled. Cutler's and Fisher's observations support these suggestions in that, (a) the more nodes that are examined, the greater the chance of detecting sinus histiocytosis (Cutler et al, 1969a), and (b) the absence of sinus histiocytosis is associated with the presence of (4 or more) nodal metastases (Fisher et al, 1975b, and others - see Table 7.4 below).

It is worth noting that the above 'reactions' are not unique to the axilla in patients with breast cancer. Sinus histiocytosis may be associated with gastric cancer (Black and Speer, 1958, Symmers, 1966) and colon cancer (Black and Speer 1958, Wartman 1959), lymphocyte and germinal centre predominance with cervical cancer (Tsakraklides et al, 1973) while similarly described increases in germinal centres and/or

TABLE 7.4

PUBLICATIONS PURPORTING TO SHOW AN EFFECT OF SINUS HISTIOCYTOSIS (SH) ON THE PROGNOSIS OF PATIENTS WITH BREAST CANCER

REFERENCE	NO.	PATIENTS INCLUDED (OR EXCLUDED)	NO. NODES	CLASSIFICATION OF SH	%GE HIGH GRADE SH	SURVIVAL DATA	CONCLUSIONS	COMMENTS
1 Black et al, 1953	226	Only 91 followed up.	NS	0-4 Highest SH grade.	41% 3-4	No SH 3-4 in those dead; 56% SH 3-4 in those alive at 5 yr.	'SH overshadows all other variables'.	Correlation with other variables not tested.
2 Black et al, 1956	321	14% excluded - nodes 'unreadable'.	NS	ditto	15% 3-4	5 year survival grade 3-4 92% grade 2 approx 65% grade 0-1 " 40%	SH independent of nuclear grade and lymphocyte infiltration.	Note different % grade 3-4 cf references 1 and 4
3 Berg, 1956	324	Data taken random from 100 only.	Avge 11 · examined of 16	0-4. Average grade per patient.	Approx. 35%	Not given.	SH inversely correlated with node metastases. It is not a host reaction.	A careful rebuttal of above.
4 Black & Speer, 1958	747	25% 'unreadable'	1-26	0-4. Highest SH grade.	11% 3-4	5 year survival +ve nodes / -ve nodes Gde 3-4 88% 97% Gde 2 50% 70% Gde 0-1 28% 57%	SH correlated with survival irrespective of node mets. There appeared to be a correlation between SH and nuclear grade.	Number and size of metastases (and effect of GCP) ignored.

NS = Not stated. GCP = Germinal centre predominance

TABLE 7.4 cont.

REFERENCE	NO.	PATIENTS INCLUDED (OR EXCLUDED)	NO. NODES	CLASSIFICATION OF SH	%GE HIGH GRADE SH	SURVIVAL DATA	CONCLUSIONS	COMMENTS
5 Wartman, 1959	66	? NS	Mean 6	+ve = moderate to marked -ve = minimal or absent	50%	7 year survival +ve 64% -ve 39%	SH correlated inversely with tumour grade, node metastases.	Though comparable with ref. 3 he felt SH was a 'host resistance'.
6 Moore et al, 1960	180	90 alive and 90 dead.	NS	0-4 (ref. 4)	Approx. 40%	17/90 SH in those alive. 15/90 in those dead.	'No useful prognostic feature in nodes'.	Study lacking in much 'data'.
7 Masse and Chassaigne 1962	78	NS	NS	0-4	42/78 3-4	SH 3-4 in 35/38 5 yr survivors. SH 3-4 in 7/40 dying early. Curiously mortality was greater in node -ve cases.	'SH is apparently the most important prognostic factor'.	* Some of the data appear spurious.
8 di Re & Lane, 1963	203	Operable cases after triple biopsy. (Only 1 'unreadable') Papillary and Intraduct Ca excluded	3-59 Mean 19	'minimal' to 'prominent'; patients classified according to %ge of nodes with SH.	one quarter 'prominent'	10 year survival minimal 44% moderate 46% prominent 51%	No significant effect of SH	However, the trend is the same as in refs. 1, 2, 4.

* In this paper patients with positive nodes appeared to have more high grade SH and to have better survival, viz. 12/39 dead cf. 28/40.

TABLE 7.4 cont.

REFERENCE	NO.	PATIENTS INCLUDED (OR EXCLUDED)	NO. NODES	CLASSIFICATION OF SH	%GE HIGH GRADE SH	SURVIVAL DATA		CONCLUSIONS	COMMENTS
9 Anastass- iades & Pryce, 1966	111	11 'unreadable'.	NS	+ = moderate to marked in any node. - = absent - trace.	64%+	Not given.		'SH prevents metas- tases'. 68% node +ve if SH- 33% node +ve if SH+	Converse is equally likely - see refs. 3 & 5
10 Cutler et al, 1969a	879	Nearly half ex- cluded - less than 6 nodes in mastectomy spec- imen.	6-37	I to III - Highest SH grade.	15% III 19% II	5 yr 10 yr survival I 81% 73% II 84% 81% III 93% 89%		'SH protects even with node mets.* %ge SH increases as more nodes exam- ined'.	Results show little effect of SH in favourable groups. Survival very high.
11 Kister et al, 1969	318	Haagensen's Stage A only.	6-71 avge 25	0-4 - highest SH grade	10% 3-4	10 yr survival Node +ve Node -ve Gde 3-4 58% 78% Gde 2 47% 70% Gde 0-1 46% 79%		'No effect of SH seen in this favour- able group of pat- ients.	Trend similar to reference 10.
12 Silverberg et al, 1970	366	32 excluded with less than 10 nodes.	10-66 avge 25	+ = SH II or III in any node. - = SH I or 'unreadable'	26% +	5 yr survival Nodes -ve any +ve 9+ve SH+ 80% 72% 17% SH- 70% 46% 13%		SH associated with small & well differ- entiated tumours; only 'protective' in intermediate prognostic groups.	See references 10 and 11.

* mets = metastases

TABLE 7.4 cont.

REFERENCE	NO.	PATIENTS INCLUDED (OR EXCLUDED)	NO. NODES	CLASSIFICATION OF SH	%GE HIGH GRADE SH	SURVIVAL DATA	CONCLUSIONS	COMMENTS
13 Majmudar et al, 1971	239	90% 'Halsted' mastectomy	avge 18	'significant' or not.	40%	Those with SH had 'slightly better survival'.	SH found most commonly with tumours 1-4 cm diameter.	Paper lacks data.
14 Hunter et al, 1975	57	Extended radical mastectomy.	13-60 Intl. mamm.+	Any high grade SH (or GCP)* in any node.	74% (half with GCP)	5 yr survival SH 16 out of 17 SH + GCP 17 out of 25 GCP 1 out of 6	GCP associated with more nodal mets. 'GCP enhances tumour growth'.	Tumour growth might equally well enhance GCP.
15 Syrjänen & Hjelt, 1978	302	NS	Mean approx. 2	Present or absent.	NS	SH associated with better survival at 5 years.	SH favourable because of its presence in cancer-free nodes.	There was also more SH with more differentiated tumours.
16 Chang et al, 1978	95	31 excluded – died of other illness, males etc.	NS	0 - III	38% II or III	10 yr survival 0 29% I 50% II 82% III 79% Survival not affected much with lobular, papillary Ca etc.	'SH represents a manifestation of cell mediated immunity'.	SH more common in those without node metastases (61% cf 26%).

* GCP = Germinal centre predominance
+ including internal mammary nodes

TABLE 7.4 cont.

REFERENCE	NO.	PATIENTS INCLUDED (OR EXCLUDED)	NO. NODES	CLASSIFICATION OF SH	%GE HIGH GRADE SH	SURVIVAL DATA			CONCLUSIONS	COMMENTS
17 Hu, 1979	228	Some excluded who received pre-* operative XRT etc.	avge 33	+ to +++ according to degree of SH in most lymph nodes.	44% +++		5 yr	10 yr	'Host immunity should be raised e.g. by traditional Chinese medicine'.	Ditto. (viz. 68 cf 24%) Hence profound effect of node mets. on prognosis ignored.
							survival			
						+	23%	13%		
						++	46%	39%		
						+++	83%	91%		

* XRT = Radiotherapy

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paracortical areas have been described in localised (Stage B) colorec-
tal cancer (Pihl et al, 1980).

Before leaving the question as to the nature of the various
node 'reactions', especially of sinus histiocytosis and lymphocyte
predominance which may be favourable, it is worth examining the published
data to see whether (a) the conflicting reports are in any way compat-
ible, and (b) whether they are consistent with the hypothesis that
sinus histiocytosis and lymphocyte predominance are normal features
of axillary nodes (Symmers, 1966) and are only protective in that they
represent the absence of unfavourable features.

In comparing published results there are a number of semantic
and practical difficulties : (i) variations in interpretation of sinus
histiocytosis etc.; (ii) classifications of patients (as opposed to
nodes) with sinus histiocytosis etc.; (iii) definition of the study
group, e.g. whether all stages of breast cancer or whether benign and
malignant nodes were considered; (iv) levels of statistical proof; and
(v) whether other, independent, prognostic factors were taken into account.

The majority of publications on sinus histiocytosis are
summarised in Table 7.4.

<u>Definition of 'reactions'</u>. It must be admitted that to some
extent the classification of node 'reactions' is a subjective assess-
ment. Although Tsakraklides has attempted definitions of lymphocyte
and germinal centre predominance etc. it is disconcerting that the
definitions in one publication (Tsakraklides et al, 1974) do not appear
in another (Tsakraklides et al, 1975). Furthermore, it is difficult to

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grasp what might be meant by 'increased numbers of lymphocytes', or

'... of germinal centres'. In this work a figure of 6 germinal centres

per node section was chosen - but this might have been too many or too

few. However, with the exception of lymphocyte predominance it seems

probable that germinal centre predominance, lymphocyte depletion and

the more gross examples of sinus histiocytosis can be easily recognised

(see Appendix Figures A).

Black, however, probably did his cause no good by the complicated

series of changes (13 in all) described in one paper, and by his subdivis-

ion of sinus histiocytosis into three types (Black and Speer, 1960) and

five grades (0 to 4, e.g. Black et al, 1956). Subsequently, this was

reduced to three (I, II and III), and as Grade I was a 'minimal or

absent reaction' (Cutler et al, 1966) it was really only two. Subsequently

others, noting even Black's inability to classify nodes into their same

grades more than 70% of the time (Cutler et al, 1966), elected simply

to indicate whether sinus histiocytosis was present or absent (e.g.

Silverberg et al, 1970). The definition used in this thesis has been very

similar - probably including Black's Grade III and perhaps some Grade II.

(See Appendix, Figure A1).

Classification of patients

From much published work it is not easy to identify how

patients were ascribed to the lymphocyte predominance classification (for

example) as opposed to another class. Tsakraklides classified each case

into 'the pattern that was present in the majority of the nodes'

(Tsakraklides et al, 1974). The results from the prospective series

(Appendix Table and Figures E) indicate that many patients showed a

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number of very obvious reactions, but not necessarily a single reaction

in the majority of the nodes (see for example patients 22 and 49).

Perhaps each reaction should be accepted as present in each patient in

whom it is found, to study its effect, as was done by Hunter (Hunter et

al, 1975). Only in this way can opposing effects (in terms of prognosis)

be revealed. Fortunately in the retrospective study only one or two nodes

were available, and classification of patients was not at all difficult

(see Appendix Table B). In that each patient was classified on the

basis of the node or nodes nearest the tumour perhaps this was the most

appropriate way. Hunter, on the other hand, classified a patient sinus

histiocytosis or germinal centre hyperplasia if this feature was present

in any one node. So did Black, Cutler, Kister etc., in that patients

were classified according to the highest grade of sinus histiocytosis in

any one node.

<u>Groups studied</u>

Reports have varied in the selection of patients. Differences

in results obtained could, no doubt, reflect these differences. Apart

from difficulties in the classification of patients (above) further

confusion (or lack of clarity) may be introduced by authors' failure

to recognise the presence or absence of other unfavourable features

which would otherwise affect the advantage conferred, for example, by

sinus histiocytosis. None of the publications have distinguished micro-

metastases from gross metastases, nor have authors commented on the

effect of germinal centre predominance on sinus histiocytosis - with the

exception of Hunter (Hunter et al, 1975) who found that germinal centre

(hyperplasia) decreased the prognostic advantage seen with sinus histio-

cytosis.

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<u>Statistical proof</u>

While Black's studies have shown a consistent advantage of sinus histiocytosis, others have stated there is no effect - even though the same trend was present but was not statistically significant (Di Re and Lane, 1963).

<u>Independent prognostic factors</u>

Many studies have omitted to take account of these. In the study described in Chapter 5 (see Table 5.1 and Appendix Tables A and B) sinus histiocytosis and lymphocyte predominance were more common in patients with impalpable nodes, or in the absence of nodal metastases. They were also found with smaller tumours (the statistical evaluation of these small groups is not shown, but this association is seen in the significant correlation between histological node status and tumour size in Appendix Table CIIa).

Table 7.4 shows in summary form the results of studies on the effect of sinus histiocytosis on prognosis - lymphocyte and germinal centre predominance studies amount to only two (Tsakraklides et al, 1974, Hunter et al, 1975). The following further comments may be made regarding the published results in Table 7.4.

Though at first sight the reports on sinus histiocytosis appear to be at conflict, there are differences in the structure of some investigations which suggest a reason for the different results obtained. Of the 15 papers with follow-up data only two (Moore et al 1960, Kister et al, 1969) showed no prognostic advantage in the presence of sinus

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histiocytosis; there was another (di Re and Lane, 1963) where the (advantageous) effect was not statistically significant. Two of these reports were from Columbia University, N.Y., (di Re and Lane 1963, Kister et al, 1969) and concerned Haagensen's personal cases. In one (di Re and Lane, 1963) patients were classified according to the percentage of nodes showing sinus histiocytosis rather than the highest grade of sinus hist-iocytosis in any one node. In both series a very large number of nodes was examined, suggesting the probability that sinus histiocytosis would be detected in the presence or absence of unfavourable features (e.g. metastases). In di Re and Lane's (1963) paper only one patient was 'un-readable' compared with between 14 and 25% in Black's series who were excluded for this reason. By comparison Wartman (1959) who studied only a small number of nodes per patient, found sinus histiocytosis predomin-antly in patients without nodal metastases. In other words, it may be that, by examining 'too many' nodes, sinus histiocytosis may be detected in cases where it is combined with an unfavourable feature (metastases and/or germinal centre predominance) thereby reducing the 'protective effect' of the presence of sinus histiocytosis.

There may be another reason why sinus histiocytosis was favour-able in most reports yet either ineffective (in two) or effective only in some groups of patients (Silverberg et al, 1970). It appears that it was ineffective in groups where prognosis was uniformly good (Silverberg's small tumours, Kister's Stage A) or where it was uniformly bad (Silver-berg's patients with more than 9 nodes containing metastatic deposits). It is quite possible that these groups were excluded in Black's and Cutler's series by excluding those with less than 6 nodes for examination (with probably less sinus histiocytosis and possibly less metastases) and

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also those with 'unreadable' nodes, i.e. nodes largely replaced by metas-
tases. These latter were also excluded by Anastassiades and Pryce (1966).

In 11 papers sinus histiocytosis was correlated with independ-
ently favourable factors : infrequency of node metastases (Black et al,
1953, Berg 1955, Wartman 1959, Anastassiades and Pryce 1966, Hunter et
al 1975, Chang et al 1978, Syrjänen and Hjelt 1978, Hu 1979); small tumours
(Berg 1956, Anastassiades and Pryce 1966, Silverberg et al 1970, Majmudar
et al 1971); and, low grade malignancies (Black and Speer 1958, Syrjänen
and Hjelt 1978, Silverberg et al 1970, Wartman 1959). In a recent study,
furthermore, a high frequency of marked sinus histiocytosis was recorded
in a series of patients with less aggressive cancer, viz. papillary cancer
(Fisher et al, 1980). It was also commoner with the more favourable
tumour types (papillary, mucoid, lobular, intraductal carcinoma) than
with the 'non specific cancers' from Chang's series (Chang et al, 1978).
Grade II or III sinus histiocytosis occurred in 16 of 33 patients in the
former category, compared with 20 of 62 in the latter.

The 'immunophilic' explanation for this would be that sinus
histiocytosis prevented node metastases (Anastassiades and Pryce, 1966)
and presumably kept primary tumours small - and of favourable histology
or well differentiated ! What is the 'immunophobic' (or agnostic) explan-
ation ? Clearly sinus histiocytosis could become lost as tumours spread,
producing metastases or the germinal centre predominance reaction in local
nodes.

In summary all the papers in Table 7.4 are <u>consistent with the</u>
<u>hypothesis</u> that it is not its presence so much as the <u>absence of unfavour-</u>
<u>able features</u> which <u>provides</u> the <u>favourable outlook associated with sinus</u>
<u>histiocytosis.</u>

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The evidence, furthermore, is in keeping with the hypothesis (Berg 1956, Symmers, 1966) that <u>sinus histiocytosis may be a normal feature of axillary nodes</u>. The evidence against this from Black and Speer (1958) is not entirely convincing. They studied a 'control' sample of nodes from various regions excised for diagnostic or other reasons or at autopsy. They found only 3% of 29 cases had sinus histiocytosis of Grade 2 or more in axillary nodes, and concluded that it was not a normal feature. However, they did not examine <u>all</u> nodes in each axilla (as they had done with the radical mastectomy specimens) and could not, therefore, allocate each case to the 'highest grade of sinus histiocytosis in any node'. They would not appear to have confined their study, moreover, to female axillae.

In a subsequent report (Black and Speer, 1960) which included 117 autopsy examinations of axillary nodes 'regular' sinus histiocytosis was also not encountered. However, in this study a different staining technique was used (silver). Curiously half of those dying of 'cirrhosis uraemia' showed syncytial histiocytosis (i.e. a reaction included in other papers as high grade sinus histiocytosis), though it was not seen in the remaining patients. No explanation was offered for this anomalous finding.

Black and Speer (1958, 1960) supported their thesis that sinus histiocytosis was not normally found in axillary nodes by quoting evidence from studies in mice and rats. Clearly it is high time that a study was done to assess the extent to which sinus histiocytosis occurs in normal axillae - if a satisfactory control group can be found.

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Though it is difficult to feel confident that his 'Proliferation der
sog. Sinus endothelien' is entirely comparable with sinus histiocytosis
it is of interest that Gnirs (1954) who examined nodes from 65 patients
with breast cancer and 7 with chronic cystic mastopathy concluded : 'Die
Sinus-reaktion tritt mit genau den gleichen Befunden und in gleicher
Stärke bei Carcinom und bei Mastopathie auf'. The sinus reaction
occurred in exactly the same way and to the same degree with carcinoma
as with mastopathy.

One quite inexplicable finding in the above publications
(Table 7.4) is the considerable variation in the proportion of patients
with high grade sinus histiocytosis. Whereas over half had (high grade)
sinus histiocytosis in some series (Masse and Chassaigne 1962, Hunter et
al, 1975) in others it was as low as 10% (Kister et al, 1969). Even
allowing for differences in classification of patients, in definitions of
pathologoists, and in the number of nodes examined, it is hard to see why
even Black's papers should have varied by as much as from 11% (Black and
Speer, 1958) to 41% (Black et al, 1953).

<u>TOTAL MASTECTOMY. HOW SIMPLE IS A NODE SAMPLE</u> ?

Current management of operable breast cancer accepts that
simple or total mastectomy is no less effective than radical mastectomy
in terms of survival (see for example Murray et al 1976, Forrest et al
1977, Stewart 1977) and that excision of axillary nodes is not performed
for therapeutic reasons. Excision of, or sampling of nodes, is added to
simple (total) mastectomy in order to obtain an accurate estimate of the

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extent or stage of the disease, so that additional treatment may be

planned if necessary (Forrest, 1977).

<u>How many nodes should be sampled at mastectomy, and examined</u>

<u>by the pathologist</u> ?   The final word cannot be said on this subject.

However, although some would advocate a total or near total excision of

nodes within the axilla (Hultborn et al 1974, Kitchen et al 1980),

 together with minute examination for small nodes, and serial sections,

it would appear from the work in this thesis that such elaborate and

obsessive examination is unnecessary.

In Chapter 5 it was shown that in all probability the only

important additional finding obtained by <u>sampling more nodes</u> was the

demonstration of <u>more nodes showing, inter alia, the 'favourable reactions'</u>

<u>of sinus histiocytosis and lymphocyte predominance</u>.   There was no evidence

that increasing the node sample size increased the number in whom

metastases were found (gross or microscopic), nor the number showing

germinal centre predominance.[*]   Furthermore it is seen that both of

these features (metastases and germinal centre predominance) increase

the probability of early recurrence (cf sinus histiocytosis, lymphocyte

predominance or unstimulated nodes), and each could therefore be used as

a prognostic index if there is a perceived need to give adjuvant therapy

to patients with a less favourable outlook.   The finding that <u>node</u>

<u>metastases could be detected as readily in a small sample as in a</u>

<u>moderate sized one</u> is in agreement with the Cardiff-St. Mary's breast

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[*] While these comments appear valid in general terms, there will of course
be individual exceptions. See, for example patient 33 (Table and Figure
E, Appendix) in the prospective group. Upper lymph nodes had gross deposit
(and were very large, 'though impalpable) while lower ones showed micro-
metastases and germinal centre predominance.

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cancer trial (Roberts et al 1973, Forrest et al 1977). In this random-
ised controlled trial the proportion of patients in whom nodal
metastases was detected was actually higher (though not significantly)
in the group who had a simple mastectomy, with node sampling, than in
those undergoing radical mastectomy.

Fisher's work, furthermore, shows the relative unimportance of
slavishly searching the axillary fat for small nodes and microscopic
deposits. In one study (Fisher and Slack, 1970) he and his colleagues
followed over 2,000 patients from 46 institutions using different methods
(and determination ?) to identify nodes after radical mastectomy. The
number of nodes identified in the mastectomy specimen varied significantly
between institutions. Nevertheless the <u>important prognostic factor</u>,
irrespective of the size of the sample, was the <u>number</u>, not the proport-
ion, of <u>nodes with metastases</u>. Patients with two positive nodes out of
5 did no worse than those with 2 out of 30, and patients with 5 negative
nodes did no worse than those with 30 free of tumour. In a second study
(Fisher et al, 1978) the detection of <u>micrometastases</u> by serial sectioning
added <u>little or no prognostic information</u> to that obtained after each
node had been examined by a single section. This latter view was also
held by Pickren (1961) and Huvos (Huvos et al, 1971), and is supported
by the findings in Chapter 2.

Against these findings, which suggest the validity of lower
axillary node sampling in determining the patient's prognostic status,
are two recent non-controlled reports (Smith et al 1977, Kitchen et al,

CHAPTER 7 : DISCUSSION - NODE SAMPLING

1980). Kitchen found that in 33 (modified) radical mastectomy specimens 7 (21%) had 'upper nodal involvement with negative lower nodes'. However, knowing the difficulty in orientation of some axillary specimens, even dissecting all myself, I would not feel completely confident as to the validity of this claim as a large number of surgeons and pathologists was involved. It is of interest to note also that the number of nodes identified after the more radical dissection (2 to 26, mean 9) was not very different from the studies in Chapter 5 (1 to 18, median 6, mean 7), in which only the lower axilla was sampled.

Similarly in Smith's series of radical mastectomy specimens from 385 patients, a number of pathologists dissected the specimens (Smith et al, 1977). Nodes identified at three levels varied greatly, but there was a median of two positive nodes at each level suggesting a most diligent search for metastases. Metastases occurring at one level only were found in 29% of patients low in the axilla and in 10% each for high and middle levels. They felt that their findings 'generally supported the contention that breast cancer metastasizing to the axilla does so in an orderly manner' (Smith et al, 1977). Another conclusion from this careful study was that the number of nodes involved, rather than the level, was the important prognostic index (i.e. findings in agreement with Fisher and Slack 1970, see above). In neither of these studies were micrometastases distinguished from gross deposits. It may be that some of the higher deposits, in the absence of lower axillary involvement were only micro-scopic. Such deposits are less prognostically important but they could have been missed in the Cardiff trial (above) as well as in the studies from Chapter 6 as less node sections were taken from the higher nodes.

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It can be seen that, in general the evidence suggests that a lower axillary sample will be sufficient to determine the patients' nodal state with respect to metastases and/or germinal centre predominance. However, examination of a larger number of nodes, while not disclosing greater numbers in categories of poor prognostic significance, appears likely to uncover more examples of sinus histiocytosis and lymphocyte predominance (as in Chapter 5 and as described by Cutler et al, 1969a). It is suggested that the explanation for this is a 'geographical' one, i.e. sinus histiocytosis and lymphocyte predominance are more likely to be found in nodes higher in the axilla than in the ones closest to the primary tumour. A similar conclusion was reached by Hunter (Hunter et al, 1975).

An alternative, and in my opinion a much less likely, explanation is that the histological criteria in Chapters 2, 5 and 6 were too strict, and that sinus histiocytosis and/or lymphocyte predominance were being overlooked in the retrospective series (with the smaller node sample). Certainly, the less favourable 'reactions' of germinal centre predominance and lymphocyte depletion (Figures A3 and A4 in Appendix) are quite easily recognised with minimal experience. Similarly sinus histiocytosis in its more obvious forms (or grades - see Figure A1, Appendix) is easily recognised. The most difficulty is experienced in distinguishing unstimulated nodes from nodes showing lymphocyte predominance (Figure A2, Appendix) and it is possible that this latter category may have been recognised less frequently than it should. Fortunately, it appears from Chapter 2 that unstimulated and lymphocyte predominant nodes carry a similar prognosis (at least in the small sample). It is

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therefore unnecessary to distinguish between the two providing the other 'reactions' (especially germinal centre predominance and lymphocyte depletion) can be excluded.

As explained above, it does appear to be necessary to remove more than just the <u>axillary tail</u>, as up to 40% of patients in whom this alone is removed will have no nodes for examination (Cant, 1977). It is probably worth examining Cant's results more closely, as the recommendations from that study (Cant et al 1975, Cant 1977) are perhaps misleading. Patients in that series were treated by 'simple mastectomy and pectoral node biopsy' (Forrest et al, 1976). Nodes were obtained in this way in approximately 90% of cases. However, the yield from the axillary tail was only from 32 of 45 cases (71% Cant et al, 1975) or 36 of 60 (60% Cant 1977). In her study results she stated that the number of nodes identified 'within the breast parenchyma' (axillary tail, not otherwise defined) were 'from 1 to 13, on average 5' (Cant et al, 1975) or 'from 1 to 13, average 4' (Cant, 1977). In fact the raw data (Appendix, Cant 1977) suggest a very different interpretation. The total number of nodes so identified (141) from 60 individual patients varied from zero (not one) to 13 with a mean (from all 60 patients, not the 36 in whom nodes were found) of 2.4 (not 4 or 5). The median was 1 and the mode zero ! In other words if only the axillary tail is dissected it is very likely that no nodes (or perhaps one) will be found. It then seems pertinent to ask whether the 'up to 13' nodes were really in the breast parenchyma at all, or in the axillary fat - the evidence that they were in the parenchyma was not presented. Previous publications suggest that strictly intramammary lymph nodes are very rarely found (Hyman and Aberella, 1974).

CHAPTER 7 : <u>DISCUSSION - AXILLARY TAIL NODES</u>

Obviously one <u>cannot always rely on obtaining an adequate node</u> <u>sample if only the axillary tail is examined.</u> Leaper and Pollock (1977) have described an ingenious method of ensuring that an adequate sample of nodes is excised. By injecting 1 ml of disulphine blue dye beneath the areola 1 to 2 hours before mastectomy they were able, easily, to detect nodes and lymphatics in the axilla in all cases except one patient in whom all nodes were replaced by tumour.

Apart from Cant's publications, there are no data indicating just how many nodes will be obtained in total mastectomy including the axillary tail. A policy of simple mastectomy has been used in the Cancer Research Campaign trial centred at King's College Hospital (Murray et al, 1976, 1977). Though they presumably expected nodes to be evaluable in a large proportion of cases, they have not presented data to indicate how effective such a procedure was in sampling axillary nodes. In the second paper (Murray et al, 1977) it was stated that lymph nodes were obtained for study in 350 women, but it is unclear just to what extent they were selected from the overall number of 2,268 patients.

The results in Chapter 2, and in the Appendix (Table CIIb and Figures C3 and C4) suggest that there may be an <u>advantage in removing and</u> <u>defining at least two nodes</u>, as a prognostic 'cut-off' point with gross metastases may be as low as one rather than four as used by others (Fisher et al, 1975b, Attiyeh et al, 1977). An adequate sample of axillary nodes would appear to have been achieved by the operation employed in the prospective series described in Chapter 6. Although the operation lacked strict definition, an attempt was made to obtain a moderate sample of nodes.

CHAPTER 7 : DISCUSSION - AXILLARY TAIL NODES

Dissection did not go above the lateral border of pectoralis minor, and although often identified, no attempt was made to 'clean' the axillary vein. In this way a median of six nodes was obtained, and in only two patients (10 and 27 in Table E, Appendix) was just a single node examined.

The data presented in this thesis (Chapters 2, 5 and 6), together with Fisher's work, (Fisher et al, 1978) very strongly imply that examining the smallest nodes is unlikely to yield important additional findings, and that if serial sections of nodes are to be performed (in this study 10 were taken from 1 node) then the node that should be most carefully examined should be the node apparently closest to the primary tumour. Almost certainly this will be very close to the breast ('axillary tail') or is the node previously referred to as the 'pectoral' node (Forrest et al, 1976). It would not appear necessary to extend the axillary dissection to include nodes above the lateral border of pectoralis minor muscle, as dissection of the axilla below and lateral to this as in the prospective series in Chapter 6 provided sufficient nodes (2 or more) in the vast majority of patients.

CHAPTER 8

CONCLUSIONS : SOME QUESTIONS ANSWERED

CHAPTER 8

CHAPTER 8 : <u>CONCLUSIONS - SOME QUESTIONS ANSWERED</u>

In Chapter 1 eight questions were posed, questions of practical importance in the management of patients with breast cancer. Though some could perhaps have been answered from previous studies, the answers would not have been unanimous. These questions therefore needed re-examination.

As a result of the studies in this thesis it is possible to answer all questions except one.

1   <u>The value of axillary node palpation</u>

This is confirmed as an extremely valuable predictor of node metastases and hence a valuable prognostic index, provided that the clinical status is assessed by a competent observer, preferably with a colleague's confirmation. It is no less valuable than the histological determination (simply) of whether or not metastatic deposits are present in a small node sample, excised at (non-radical) mastectomy.

2   <u>Methods of improving pre-operative clinical node assessment</u>

Axillary lymphoscintigraphy has been shown to be well tolerated and simple to perform. At present it is reliable in only 9 out of 10 patients. However, it is superior to palpation - it corrected 5 of 6 clinical misclassifications in 31 patients.

3   <u>'Reactive' nodes</u>

It is confirmed that all the so-called 'reactions' in lymph nodes can be seen in British women undergoing mastectomy for carcinoma. With the possible exception of lymphocyte predominance, all 'reactions'

CHAPTER 8 : <u>CONCLUSIONS - SOME QUESTIONS ANSWERED</u> cont.

are identifiable without difficulty, once strict criteria for their identification are agreed upon. Both sinus histiocytosis and lymphocyte predominance are apparently 'advantageous reactions' (but see 7 below).

4   <u>Benign node enlargement</u>

Difficulties are encountered in defining what is enlarged and what is normal. However, it is shown that the size of 'reactive' nodes of all types exceed the size of unstimulated nodes, with the proviso that sinus histiocytosis may render the node heavier without appreciably altering its diameter. A valid reference range of (lower) axillary lymph node sizes has been determined.

5   <u>Node palpability</u>

Though 'reactive' nodes are often enlarged they only occasionally become palpable. No particular 'reaction' appears to predominate in the group of patients with palpable benign nodes. The majority of palpable nodes in breast cancer patients are both invaded by metastatic cancer, and enlarged to a considerable degree, viz. 1.5 cm maximum diameter and/or 1 g in weight.

6   <u>Prognostically advantageous, palpable nodes</u>

Regretably, I cannot confirm that there is such a group. The relatively small experience with patients whose palpable nodes were 'not suspicious' suggests that their prognosis is not better than those with impalpable nodes. Furthermore, the 'reaction' which was found most commonly (germinal centre predominance), is an unfavourable one. The prognostically advantageous node 'reactions' of sinus histiocytosis and lymphocyte predominance are commoner in patients with impalpable nodes.

CHAPTER 8 : <u>CONCLUSIONS - SOME QUESTIONS ANSWERED</u> cont.

7   <u>The site of 'reactive' nodes</u>

Careful dissection and 'mapping' suggests that different 'reactions' occur at different sites. Germinal centre predominance is found in nodes close to the tumour (as are metastases) whereas lymphocyte predominance and sinus histiocytosis are found at relatively random sites. Though germinal centre predominance may be a reaction to the nearby primary tumour (or to adjacent metastases) it seems less likely that sinus histiocytosis and lymphocyte predominance are. They may be features of axillary nodes in normal subjects.

8   <u>Clinical, pathological, or 'super'-staging</u> ?

Clinical staging, viz. careful assessment of the size of the primary tumour, and of axillary node status, is of fundamental importance in determining the likelihood of early recurrence. Histological confirmation of the axillary node status (positive or negative with respect to metastatic deposits) is as useful, but is not superior unless other histological features are assessed. In negative nodes germinal centre predominance and lymphocyte depletion are unfavourable features, conferring a prognostic disadvantage not less than that associated with micrometastases. In positive nodes micrometastases are associated with a prognosis indistinguishable from that seen with (the total group) of negative nodes. Gross metastases, on the other hand, are of grave prognostic significance when found in any of the nodes.

However, even with gross metastases, the prognosis is significantly better in patients whose gross metastasis is confined to a single node. The importance of node sampling at mastectomy, preferably obtaining more

CHAPTER 8 : <u>CONCLUSIONS - SOME QUESTIONS ANSWERED</u> cont.

than one node, is thus underlined.

The 'superstaging' tests are shown to be non-discriminatory, (non-specific and/or insensitive) and hence misleading. Their aim of determining the presence of occult metastases has singularly failed. There is perhaps one exception, the nuclear bone scan which, if positive, is predictive of early recurrence. However, the low rate of positive scans (7%) and their association with other adverse features (node metastases) suggests that bone scans could well be restricted to an otherwise high risk group.

APPENDICES

ADDITIONAL TABLES AND FIGURES

TABLE A   Clinical details and 'superstaging' results of 172 patients with operable breast cancer.

FIGURE A   Histological features of lymph node 'reactions'.

TABLE B   Retrospective histological review of nodes excised at mastectomy from 172 patients with operable breast cancer.

TABLE C   Statistical analysis of survival and recurrence-free intervals in 172 patients treated by mastectomy for cancer of the breast.

TABLE D   Clinical and pathological correlation in patients undergoing axillary lymphoscintigraphy.

FIGURE D   Representative lymphoscintigrams.

TABLE E   Axillary lymph node sizes in 50 patients undergoing mastectomy for breast cancer.

FIGURE E   Axillary node plots, showing the relative position of metastatic and reactive nodes.

TABLE F   Statistical analysis of node sizes.

CLINICAL DETAILS, AND "SUPERSTAGING" RESULTS OF 172 PATIENTS WITH
OPERABLE BREAST CANCER, FOLLOWED REGULARLY FOR TWO YEARS OR MORE

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
1	2.6.76	-	-	18.6.79	4.5	$T_2N_0M_0$	-	A and W
2	12.12.74	8.12.77	-	9.8.79	5.0	$T_2N_0M_0$	-	First recurrence axilla; currently on Tamoxifen for S/C node.
3	6.7.76	11.4.77	7.6.78	7.6.78	3.0	$T_2N_0M_0$	-	Medial tumour; node recurrence, later mediastinum, pleura.
4	11.5.77	-	-	12.11.79	2.5	$T_2N_0M_0$	-	A and W
5	22.10.73	-	-	13.11.78	2.0	$T_2N_0M_0$	-	A and W
6	4.7.77	-	-	9.7.79	5.0	$T_2N_0M_0$	-	A and W
7	5.9.74	2.2.77	-	14.8.79	3.0	$T_2N_{1A}M_0$	-	Medial tumour. First recurrence bone. Liver free at laparoscopy. Oox 15.12.77.
8	27.5.75	27.5.75	13.5.75	13.5.75	5.0	$T_2N_{1B}M_0$	Bone scan; UOHP; Bone ALP	Retrospective X-ray recurrence at time of masrectomy.
9	7.9.76	-	-	10.9.79	5.5	$T_2N_0M_0$	-	A and W

A and W = alive and well; S/C = supraclavicular; Oox = oophorectomy; UOHP = urinary hydroxproline; ALP = alkaline phosphatase

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
10	20.7.76	-	-	30.7.79	4.0	$T_3N_{1B}M_0$	-	A and W
11	16.3.76	31.8.78	10.8.79	10.8.79	?	$T_?N_{1A?}M_0$	-	Bx, elsewhere; first recurrence axilla and scar, later disseminated; oox; later ChemoRx. Suspected mets, brain and liver.
12	31.8.76	-	-	22.10.79	3.0	$T_2N_0M_0$	-	A and W
13	23.5.74	4.12.78	-	10.8.79	4.5	$T_3N_{1B}M_0$	UOHP; liver scan	First recurrence in scar; later wide spread; on Chemo Rx.
14	9.9.75	-	-	24.9.79	1.0	$T_1N_{1B}M_0$	-	A and W
15	8.2.77	-	-	22.10.79	4.0	$T_2N_0M_0$	GGT	A and W
16	24.2.76	-	-	13.3.79	2.5	$T_2N_0M_0$	-	A and W
17	20.12.76	-	-	10.9.79	2.0	$T_1N_0M_0$	-	A and W
18	20.12.76	-	-	9.7.79	2.0	$T_2N_0M_0$	GGT	A and W
19	28.9.77	-	-	1.10.79	3.0	$T_2N_{1B}M_0$	-	A and W
20	24.6.77	-	-	25.6.79	1.5	$T_1N_0M_0$	Bone scan	Recent fractured femur, not metastatic.

Bx = biopsy; Rx = therapy; mets = metastases; GGT = gamma glutamyl transpeptidase

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
21	9.3.76	-	-	19.11.79	2.0	$T_1N_0M_0$	-	A and W; scar nodule biopsy negative.
22	10.9.74	30.6.75	13.4.78	13.4.78	4.5	$T_2N_0M_0$	Bone scan	Bony dissemination.
23	2.11.77	7.8.78	-	10.9.79	3.1	$T_2N_{1B}M_0$	-	Scar recurrence.
24	18.10.77	-	13.10.78	13.10.78	3.5	$T_3N_{1B}M_0$	UOHP; bone ALP	Post mortem : died of myo-cardial infarction.
25	25.2.77	-	-	20.8.79	2.2	$T_2N_0M_0$	-	A and W
26	1.6.76	-	-	23.7.79	3.0	$T_2N_0M_0$	-	A and W
27	20.7.76	-	-	23.7.79	1.5	$T_1N_0M_0$	-	A and W
28	18.2.75	5.9.75	11.2.76	11.2.76	7.0	$T_3N_{1A}M_0$	-	Recurrence in bone and scar; Post mortem : bone confirmed; no liver mets.
29	13.8.74	-	-	20.8.79	0.5	$T_1N_0M_0$	-	A and W
30	5.9.77	-	-	10.9.79	3.5	$T_2N_{1B}M_0$	UOHP	A and W
31	7.10.77	-	-	15.10.79	3.8	$T_2N_0M_0$	UOHP	A and W until Feb. '79 - CVA.

CVA = cerebro-vascular accident

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
32	7.2.77	-	-	10.9.79	3.0	$T_2N_0M_0$	-	A and W
33	2.1.75	4.3.75	-	20.7.79	3.0	$T_2N_0M_0$	Bone ALP	Local recurrence, with further local recurrences 1976/77.
34	10.10.74	27.9.77	20.1.78	20.1.78	2.0	$T_2N_0M_0$	-	Disseminated recurrence to liver and bone.
35	7.9.76	-	-	10.9.79	3.0	$T_2N_0M_0$	-	A and W
36	2.4.76	-	-	2.7.79	4.5	$T_2N_2M_0$	Bone scan	A and W
37	3.9.74	1.12.75	11.11.77	11.11.77	4.5	$T_2N_{1B}M_0$	-	First recurrence local and in bones; oox; Post mortem : mets in ovary, bone; not liver.
38	7.10.75	-	-	1.10.79	3.5	$T_2N_0M_0$	-	A and W
39	16.9.75	-	-	24.9.79	4.5	$T_2N_0M_0$	UOHP	A and W
40	14.2.77	-	-	3.9.79	?	$T_?N_0M_0$	-	Diffuse invasive lobular carcinoma; size not measureable.
41	22.6.76	-	-	25.6.79	4.0 4.0	$T_2N_{1B}M_0$ $T_2N_0M_0$	-	Bilateral mastectomy. A and W

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
42	15.11.76	-	-	18.6.79	3.5	$T_3N_0M_0$	-	A and W
43	2.7.74	-	-	2.7.79	2.5	$T_3N_{1B}M_0$	-	A and W
44	12.1.77	-	-	28.5.79	3.0	$T_2N_{1B}M_0$	GGT	A and W
45	23.4.74	3.1.75	27.1.76	27.1.76	4.0	$T_2N_{1B}M_0$	Bone scan; UOHP & GGT	First recurrence in bone; Post mortem : mets in bone, liver, brain.
46	13.6.77	-	-	5.11.79	2.0	$T_1N_0M_0$	-	A and W
47	15.11.77	-	-	19.11.79	?	$T_?N_0M_0$	Bone ALP	A and W. Primary lesion unmeasurable - diffusely infiltrating.
48	25.8.76	-	-	20.8.79	4.0	$T_2N_0M_0$	-	A and W
49	6.1.77	-	-	30.7.79	1.0	$T_1N_0M_0$	-	A and W
50	27.2.75	6.2.78	5.6.78	5.6.78	3.5	$T_2N_0M_0$	-	Disseminated recurrence (liver confirmed).
51	17.8.76	-	-	18.10.79	7.0	$T_3N_{1B}M_0$	Liver scan & GGT	Subsequent abdominal mass.= polycystic kidneys (and liver).

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
52	22.8.77	-	-	27.8.79	4.0	$T_2N_{1B}M_0$	-	A and W
53	4.4.77	-	-	1.10.79	3.5	$T_2N_{1A}M_0$	-	A and W
54	7.10.77	-	-	8.10.79	3.5	$T_2N_0M_0$	UOHP and GGT	A and W (? alcoholic)
55	28.3.77	10.2.78	14.3.78	14.3.78	5.0	$T_3N_{1B}M_0$	-	Medial quadrant tumour; disseminated to liver, peritoneum.
56	2.11.77	-	-	24.9.79	5.9	$T_3N_{1B}M_0$	-	A and W
57	18.10.77	-	-	1.11.79	3.0	$T_2N_{1A}M_0$	UOHP	A and W
58	22.5.75	13.5.77	-	23.10.79	3.0	$T_2N_{1A}M_0$	Liver scan	Local recurrence in scar; rhizotomy for pain.
59	6.12.76	14.11.77	? 6.79	? 6.79	4.0	$T_2N_{1A}M_0$	-	Bony dissem; oox; Adrex.
60	13.12.76	-	-	13.3.79	3.0	$T_2N_0M_0$	-	Contra-lateral mastectomy 1977.
61	19.11.74	29.11.76	19.6.79	19.6.79	4.5	$T_2N_{1B}M_0$	-	Scar at node recurrence; oox; Y90 pituitary; Chemo Rx. Brachial plexus palsy.

Adrex = Adrenalectomy; Y90 = Yttrium irradiation

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
62	5.10.77	-	-	8.10.79	4.0	$T_2N_0M_0$	Bone scan and GGT	A and W
63	1.11.77	8.12.78	5.2.79	5.2.79	4.7	$T_2N_{1B}M_0$	UOHP	Disseminated to bone and lung.
64	2.12.75	13.6.77	6.9.79	6.9.79	3.0	$T_2N_{1B}M_0$	-	Disseminated to bone; died hepatic failure.
65	4.12.75	2.8.77	1.7.78	1.7.78	2.0	$T_2N_0M_0$	-	Scar recurrence, later bones.
66	3.8.77	-	-	6.3.79	3.0	$T_2N_0M_0$	-	A and W
67	9.5.77	20.2.79	16.3.79	16.3.79	4.5	$T_2N_{1B}M_0$	-	Metastasis in breast; ? second primary. Clinical liver mets.
68	29.4.75	3.5.76	5.9.77	5.9.77	3.5	$T_2N_{1B}M_0$	-	Inner quadrant tumour bone recurrence; Post mortem : mets in bone & liver.
69	21.9.76	28.5.79	-	27.9.79	4.0	$T_2N_{1B}M_0$	-	Recurrence in scar and breast; later bone; Rx Tamoxifen.
70	2.4.74	-	-	4.6.79	3.5	$T_2N_0M_0$	-	A and W

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
71	26.3.75	-	-	16.4.79	2.5	$T_2N_{1B}M_0$	-	A and W
72	13.5.75	-	-	12.11.79	2.0	$T_2N_0M_0$	-	A and W
73	29.9.77	-	-	29.10.79	3.7	$T_3N_0M_0$	UOHP	A and W, arm swelling.
74	31.1.77	? 5.79	-	8.11.79	6.5	$T_3N_0M_0$	-	Bone recurrence; K nail, XRT and Tamoxifen.
75	5.11.74	-	-	12.11.79	3.0	$T_2N_0M_0$	-	A and W
76	24.2.76	17.10.77	4.9.78	4.9.78	2.0	$T_2N_{1B}M_0$	-	Recurrence in scar and nodes; later bone and liver.
77	28.3.77	29.1.79	-	27.7.79	3.0	$T_2N_0M_0$	-	Recurrence in cervical spine very dubious.
78	28.2.77	-	-	3.9.79	3.0	$T_2N_{1A}M_0$	-	A and W
79	25.5.77	-	-	28.5.79	2.0	$T_2N_0M_0$	-	A and W
80	22.10.75	25.4.77	30.5.78	30.5.78	3.0	$T_3N_0M_0$	-	Disseminated bone, ovary and liver at oox; later in brain.
81	21.2.77	-	-	20.8.79	3.0	$T_2N_0M_0$	Bone ALP	A and W

K nail = Kuntschner intramedullary rod insertion to femur; XRT = radiotherapy

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
82	17.6.77	15.9.79	-	15.9.79	?	$T_?N_1M_0$	-	Initial treatment and follow-up elsewhere. Recurrence in S/C node. Rx Tamoxifen.
83	3.8.77	14.5.79	-	5.11.79	1.0	$T_1N_0M_0$	-	Recurrence in axilla Rx XRT.
84	14.10.75	16.7.79	-	3.9.79	4.0	$T_2N_{1B}M_0$	GGT	Node recurrence. Rx Tamoxifen.
85	20.7.76	-	2.12.76	2.12.76	4.0	$T_2N_{1B}M_0$	-	Died from suicide while on holiday. Previous history of depression.
86	18.5.76	-	-	4.6.79	4.0	$T_2N_0M_0$	UOHP	A and W
87	22.4.75	-	-	23.4.79	4.0	$T_2N_{1B}M_0$	Liver scan	A and W
88	15.8.77	-	13.11.77	13.11.77	2.5	$T_2N_{1B}M_0$	UOHP	Died of psychiatric disease without evidence of metastases.
89	27.1.76	-	-	9.4.79	4.0	$T_2N_0M_0$	-	A and W. Follow-up in Northumberland.
90	18.10.76	-	-	22.10.79	3.0	$T_2N_{1A}M_0$	-	A and W
91	1.6.76	-	-	11.6.79	2.0	$T_1N_0M_0$	-	A and W

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
92	2.5.77	-	-	6.8.79	0.8	$T_0N_0M_0$	-	A and W. Pathologically 8 mm in diameter. Symptomless lump discovered on breast screening by mammography.
93	12.3.74	-	-	12.3.79	1.5	$T_1N_0M_0$	UOHP; liver scan; GGT & ALP	A and W
94	8.8.77	-	-	24.8.79	3.5	$T_2N_0M_0$	-	A and W
95	28.10.76	31.10.77	8.11.79	8.11.79	5.0	$T_3N_{1B}M_0$	-	Recurrence in axilla; further recurrence in axilla. Rx Tamoxifen.
96	6.12.76	-	-	28.9.79	7.0	$T_3N_{1B}M_0$	-	A and W
97	11.6.76	-	-	18.6.79	4.0	$T_2N_{1B}M_0$	-	A and W
98	29.11.76	-	-	29.11.78	1.0	$T_1N_0M_0$	-	Follow-up by letter from GP.
99	7.2.77	-	13.8.79	13.8.79	4.0	$T_2N_{1B}M_0$	-	Died in motor vehicle accident. Shortly before death superstaging tests repeated prior to prosthetic implant.
100	22.4.77	-	-	29.10.77	1.2	$T_1N_0M_0$	-	A and W

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
101	22.11.76	-	-	28.5.79	3.0	$T_2N_0M_0$	-	A and W
102	26.6.77	-	-	15.10.79	4.0	$T_2N_{1B}M_0$	-	A and W
103	17.8.76	-	-	23.8.79	2.0	$T_1N_0M_0$	-	A and W
104	16.2.77	-	-	20.8.79	5.5	$T_3N_{1B}M_0$	UOHP	A and W
105	14.1.75	-	-	19.1.79	1.5	$T_1N_{1A}M_0$	-	A and W
106	21.10.75	-	-	5.11.79	3.0	$T_3N_{1B}M_0$	-	A and W
107	15.6.76	-	-	18.6.79	1.0	$T_3N_{1B}M_0$	-	A and W
108	7.3.77	8.10.79	-	5.11.79	3.5	$T_3N_{1B}M_0$	Bone ALP	Node recurrence; bone pain and positive scan subsequently.
109	25.7.77	-	-	30.7.79	4.0	$T_2N_2M_0$	ALP	A and W
110	4.5.76	20.2.78	-	11.10.79	3.5	$T_1N_{1B}M_0$	-	Local recurrence; subsequently pleural effusion; Rx Aminoglutethimide; ChemoRx.
111	20.4.77	-	-	10.9.79	2.0	$T_1N_0M_0$	UOHP	A and W

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
112	26.7.74	-	-	? 9.79	4.0	$T_2N_{1B}M_0$	-	A and W
113	28.10.75	3.10.77	-	24.9.79	5.5	$T_3N_{1B}M_0$	-	Recurrence in axilla; Rx Tamoxifen.
114	27.4.76	23.6.77	23.6.77	23.6.77	2-3.0	$T_2N_0M_0$	GGT	Death certificate included breast cancer; recurrence not confirmed histologically.
115	18.10.77	-	-	22.10.79	4.0	$T_2N_0M_0$	-	A and W
116	18.6.74	28.2.77	26.10.78	26.10.78	5.3	$T_3N_{1B}M_0$	-	Recurrence opposite axilla; clinical mets in liver; no PM
117	19.2.75	16.2.77	-	27.8.79	2.0	$T_2N_{1B}M_0$	Bone scan	Node recurrence. RX XRT; subsequently ChemoRx.
118	25.10.77	? 7.78	30.4.79	30.4.79	6.0 / 7.0	$T_3N_{1B}M_0$ / $T_3N_0M_0$	UOHP; ALP	Bilateral carcinoma; died of MI; rib mets accepted from X-ray.
119	16.9.74	16.11.77	11.8.79	11.8.79	5.0	$T_2N_2M_0$	GGT	Local and bone recurrence; no response to Tamoxifen etc; died of CVA.
120	21.10.75	11.8.78	11.8.78	11.8.78	2.5	$T_2N_{1B}M_0$	-	Died of CVA; suspected cerebral mets.

MI = myocardial infarction

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
121	12.11.74	-	-	12.11.79	2.0	$T_2N_{1A}M_0$	-	A and W
122	6.11.74	-	-	12.11.79	3.0	$T_2N_0M_0$	-	A and W
123	15.8.74	? 9.77	2.12.78	2.12.78	2.0	$T_2N_{1B}M_0$	-	Colonic cancer; subsequently accepted as died of breast cancer.
124	18.6.74	30.6.75	3.2.77	3.2.77	5.5	$T_3N_{1B}M_0$	-	Lung recurrence, also bone.
125	9.10.74	-	-	22.10.79	2.0	$T_1N_0M_0$	Liver scan; GGT	A and W. Liver enlarged, diabetes.
126	26.11.74	5.9.75	13.9.76	13.9.76	7.0	$T_3N_{1B}M_0$	-	Recurrence in lungs, also bone and liver.
127	25.7.77	13.11.78	17.11.79	17.11.79	4.5	$T_2N_0M_0$	-	Bone recurrence; oox; liver mets suspected; no PM.
128	30.9.75	-	-	10.9.79	4.0	$T_2N_0M_0$	Bone scan	A and W
129	20.4.76	1.11.76	-	25.9.79	5.0	$T_2N_0M_0$	-	Scar recurrence; later lungs; oox. No liver mets; currently ChemoRx.
130	17.12.74	-	-	11.6.79	4.5	$T_2N_0M_0$	-	A and W

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
131	3.2.76	3.10.77	4.5.78	4.5.78	3.5	$T_2N_{1B}M_0$	-	Recurrence in bone and liver; no PM.
132	15.12.76	-	-	10.9.79	2.0	$T_1N_0M_0$	-	A and W
133	20.8.74	-	-	27.8.79	3.0	$T_2N_{1B}M_0$	Liver scan	A and W
134	24.7.74	-	-	6.8.79	2.0	$T_2N_{1B}M_0$	UOHP	A and W
135	22.11.76	22.1.79	-	3.9.79	7.0	$T_3N_{1B}M_0$	-	Recurrence in opposite breast, bone; laminectomy for extradural met; oox.
136	30.6.76	-	-	9.7.79	2.0	$T_2N_{1B}M_0$	-	A and W
137	3.12.76	-	-	23.4.79	2.5	$T_2N_{1A}M_0$	-	A and W
138	12.11.74	17.1.77	15.8.78	15.8.78	6.5	$T_3N_{1B}M_0$	-	Recurrence lung, bone & liver; no PM.
139	13.7.77	-	-	30.7.79	0	$T_1N_0M_0$	-	Inpalpable primary lesion (dimpling only). A and W.
140	10.6.75	-	-	.6.79	2.0	$T_1N_0M_0$	Liver scan	A and W

DETAILS OF 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
141	28.1.75	-	-	4.6.79	7.5	$T_3N_0M_0$	UOHP	A and W
142	29.7.75	29.3.77	30.11.77	30.11.77	?	$T_?N_2M_0$	-	Local recurrence; later liver at oox; presented initially with axillary mass.
143	15.8.77	-	-	20.8.79	1.5	$T_2N_0M_0$	UOHP	A and W
144	15.11.77	-	-	18.6.79	4.0	$T_2N_0M_0$	-	A and W
145	4.11.75	6.3.78	17.9.78	17.9.78	2.0	$T_1N_{1B}M_0$	Bone scan; ALP	First recurrence in liver; later in bones.
146	22.4.77	-	-	22.10.79	2.0	$T_1N_0M_0$	-	A and W; lobular carcinoma.
147	4.2.75	8.2.78	-	18.10.79	4.0	$T_3N_{1B}M_0$	-	First recurrence liver; regression with Medroxyprogesterone and later oox (mets in ovaries).
148	26.10.77	30.4.79	-	18.10.79	6.7	$T_3N_{1B}M_0$	-	First recurrence S/C node; later brachial plexus palsy; ChemoRx.
149	27.6.77	-	-	29.10.79	3.0	$T_2N_{1B}M_0$	-	A and W
150	28.9.77	23.8.78	11.1.79	11.1.79	7.0	$T_3N_{1B}M_0$	Bone scan	Bone recurrence

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
151	11.3.75	-	13.1.77	13.1.77	1.0	$T_1N_0M_0$	-	Died of myocardial infarction.
152	29.11.77	-	-	11.6.79	0	$T_0N_0M_0$	-	A and W. From screening clinic; primary impalpable.
153	15.7.74	-	-	16.7.79	2.8	$T_3N_{1B}M_0$	UOHP; liver scan	A and W
154	28.10.75	-	-	29.10.79	3.0	$T_2N_0M_0$	-	A and W
155	29.6.76	-	-	2.7.79	2.0	$T_1N_{1B}M_0$	-	A and W
156	10.6.77	-	-	18.6.79	4.8	$T_2N_0M_0$	-	A and W
157	18.3.75	23.9.75	31.1.78	31.1.78	2.0	$T_1N_0M_0$	UOHP	Recurrence in scar and node; later lung, pleura, liver but not bone; no PM.
158	4.11.75	1.3.78	30.9.79	30.9.79	2.5	$T_2N_0M_0$	-	Recurrence in chest wall; Rx XRT; later pleura; Rx Tamoxifen, Aminoglutethimide.
159	8.3.74	-	-	22.3.79	3.0	$T_2N_0M_0$	UOHP	A and W

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
160	16.7.74	-	-	16.7.79	3.0	$T_2N_0M_0$	Bone scan	A and W
161	3.6.77	-	-	8.10.79	4.5	$T_2N_{1B}M_0$	-	A and W
162	26.3.74	19.2.75	2.3.75	2.3.75	6.0	$T_3N_{1A}M_0$	-	Recurrence in liver; no PM.
163	12.9.77	-	-	24.9.79	0	$T_?N_0M_0$	-	Impalpable primary lesion. A and W.
164	8.10.74	? 2.78	-	11.10.79	3.0	$T_2N_{1B}M_0$	UOHP	Scar recurrences; Rx Tamoxifen.
165	28.9.76	6.2.78	21.5.78	21.5.78	4.0	$T_2N_0M_0$	-	PM : mets in lung, pleura, nodes.
166	27.5.77	-	-	29.10.79	6.5	$T_3N_{1B}M_0$	-	A and W
167	3.6.77	-	-	5.9.79	?	$T_?N_{1B}M_0$	UOHP; GGT; liver ALP	Follow-up and initial biopsy elsewhere. A and W
168	30.4.74	2.5.77	8.12.78	8.12.78	2.5	$T_2N_{1B}M_0$	UOHP; liver scan	Recurrence in bone; later in scar; no PM.
169	29.10.76	-	-	5.11.79	4.0	$T_2N_0M_0$	-	A and W
170	21.2.77	-	-	20.8.79	5.5	$T_3N_0M_0$	-	A and W

PATIENT NO.	MASTECTOMY	DATE OF RECURRENCE	DEATH	LAST VISIT	TUMOUR SIZE (CM)	STAGE	ABNORMAL SUPERSTAGE TESTS	COMMENTS
171	12.9.77	-	-	24.9.79	5.5	$T_3N_0M_0$	-	A and W
172	30.4.76	4.11.78	31.3.79	31.3.79	5.0	$T_2N_{1B}M_0$	-	Death from pneumonia and pleurisy; recurrence accepted from chest X-ray evidence.

HISTOLOGICAL FEATURES OF LYMPH NODE "REACTIONS"

FIGURE A1 SINUS HISTIOCYTOSIS (S.H.)

(Black et al, 1956; Cutler et al, 1966, 1969a)

"Dilatation of sinusoids by large elongated cells with eosinophilic cytoplasm and indistinct cell boundaries.

Grade I	- minimal or absent
Grade II	- 3-4 cells across sinuses
Grade III	- more than 4 cells across sinuses"

Figure shows a gross example of marked (++ or Grade III) S.H., at least 10 cells across sinus (arrowed). Only nodes showing Grade III changes throughout most or all of node were classed as S.H. in analyses. Haemorrhagic sinuses containing cells showing erythrophagocytosis only were not classed S.H. Syncytial histiocytosis (less eosinophilic, larger nuclei) were included, but degenerative S.H. (vacuolation of histiocytes, prominent cell borders) was excluded. The latter was often a feature of exhausted nodes (see A4, Black & Speer, 1960).
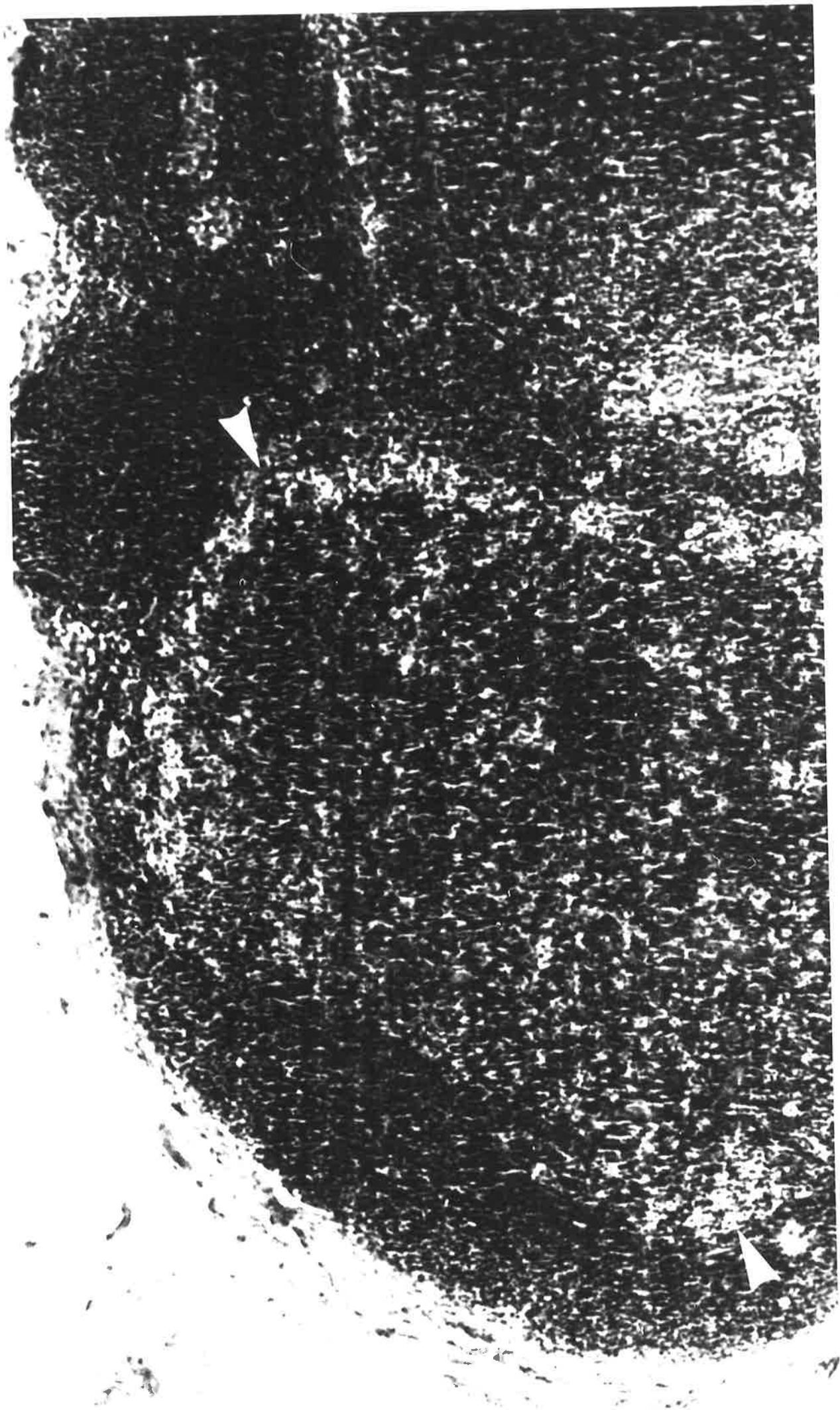
LYMPH NODE REACTIONS

FIGURE A2   LYMPHOCYTE PREDOMINANCE (L.P.)

(Tsakraklides et al, 1974)

"Large numbers of lymphocytes throughout cortex and
medulla, and especially deep cortex (paracortex) which
is expanded and shows prominent large lymphocytes and
post capillary venules".

In this example the greatly expanded and "lighter"
paracortex is easily distinguished (between arrows)
from the "compressed" darker (outer) cortex without
prominent secondary follicles (germinal centres).

Minor examples of this reaction could have been missed
and nodes classed as unstimulated.

LYMPH NODE "REACTIONS"

FIGURE A3   GERMINAL CENTRE PREDOMINANCE (GCP)

(Tsakraklides et al, 1974)

"Increased numbers of nypertrophic germinal centres in the cortex or throughout the node".

Germinal centres (between arrows) were accepted as such if there were spherical or oval structures surrounded by a dense cuff of small lymphocytes, and consisting predominantly of large lymphocytes. Especially light, large cells (macrophages) within the germinal centres may produce a "starry sky" appearance (Symmers, 1966). At least six germinal centres in any one node was required to designate it GCP.
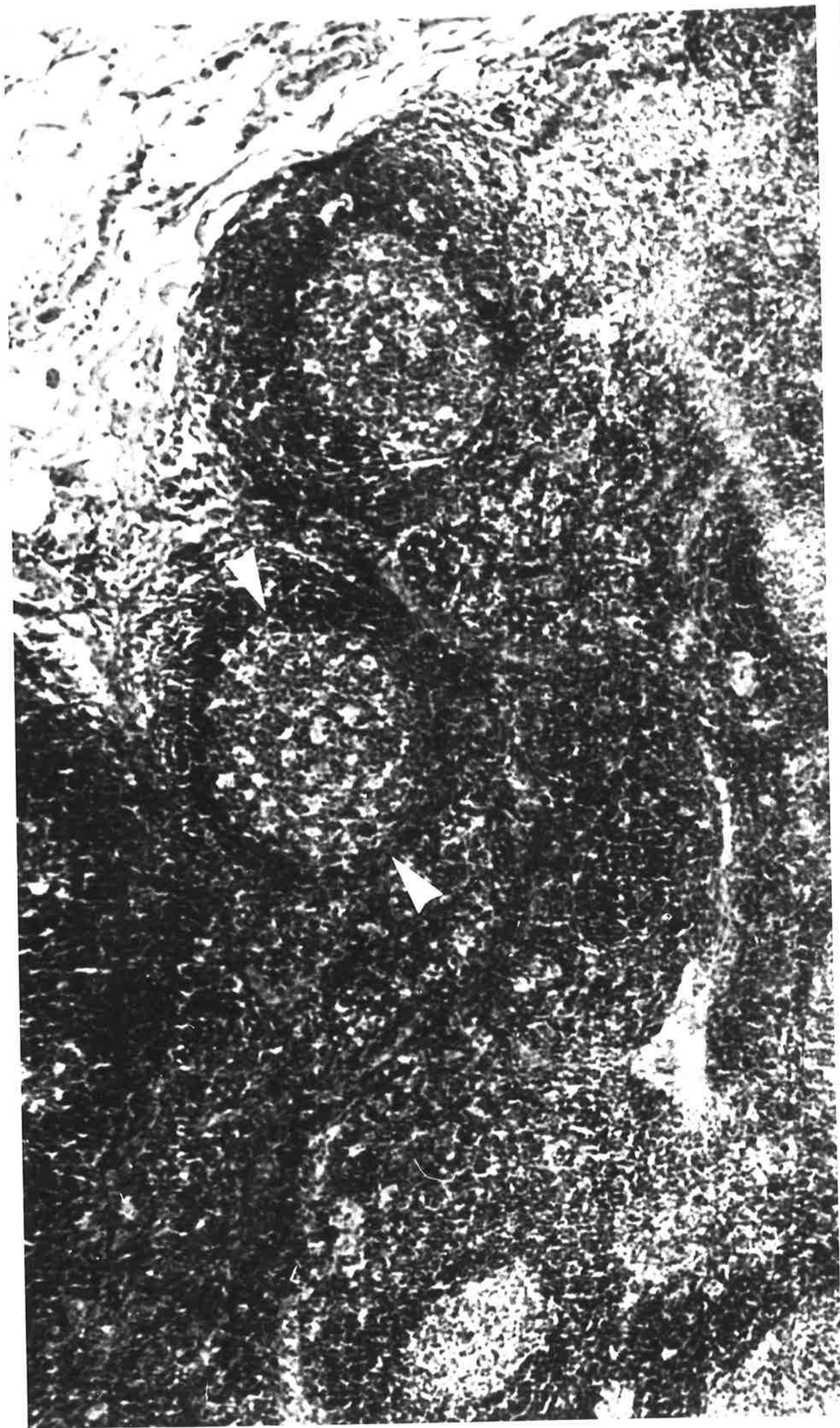
LYMPH NODE REACTIONS

FIGURE A4   LYMPHOCYTE DEPLETION (L.D.)

(Tsakraklides et al, 1974)

This reaction also fits the description of "exhausted" (Black and Speer, 1960).

"Decreased numbers of lymphocytes, absence of germinal centres, and increase in fibrosis".

A fibrotic, relatively structureless node is illustrated. Towards the bottom right hand side, the node shows areas of hyaline deposition, a feature also of this type of node (Tsakraklides et al, 1975).

LYMPH NODE "REACTIONS"

FIGURE A5   SINUS HISTIOCYTOSIS AND FATTY INFILTRATION

Grade III S.H. is clearly visible in this node. To the
left the cortex has been partly lost in preparation,
(it is virtually non-existent), while to the right
prominent fat cells replace the remaining medulla and
hilar region (not shown), merging in to extra nodal fat.
In this case fat occupied more than 80% of the entire
node which was represented by a crescentic rim of contex
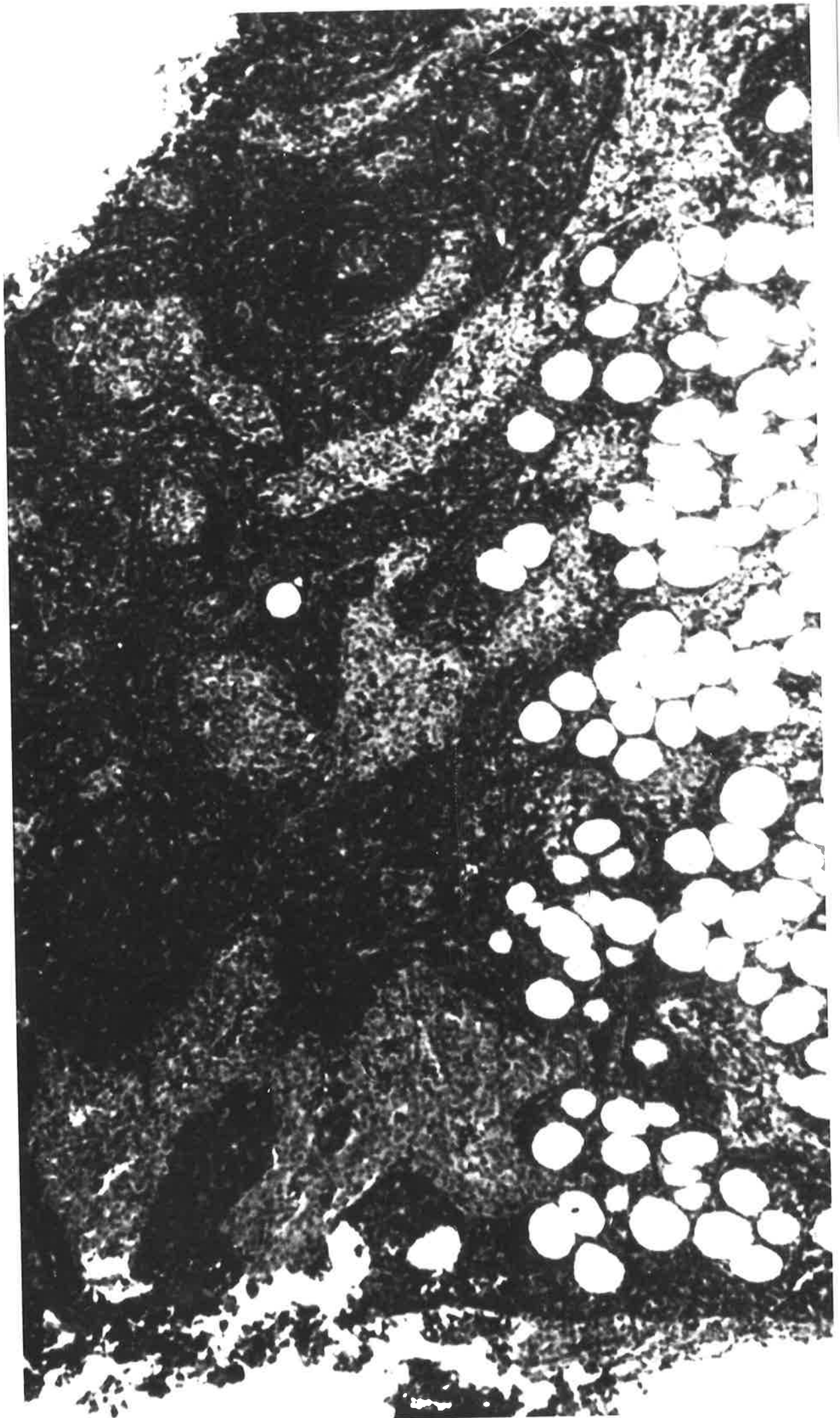and medulla.

LYMPH NODE "REACTIONS"

A6   GERMINAL CENTRE PREDOMINANCE WITH MICROMETASTASES

Prominent pale germinal centres are seen in this node, together
with clumps of metastatic carcinoma (arrowed). This node was
classified "micrometastasis" rather than "GCP". GCP or LD were
"reactions" seen frequently in patients with micrometastases
either in the same node (as here) or in adjacent nodes.

RETROSPECTIVE HISTOLOGICAL REVIEW OF NODES EXCISED AT MASTECTOMY FROM 172 PATIENTS WITH OPERABLE BREAST CANCER

PATIENT NO.	NO. NODES EXAMINED/ EXCISED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE-ACTION"
1	1	GCP
2	0	-
3	2	20%; GCP
4	0	-
5	0	-
6	1	GCP
7	1	GCP (SH$^+$)
8	1	100%
9	1	GCP (SH$^+$)
10	4	US (SH$^+$)
11	0	-
12	2	US; micrometastasis
13	3	20%; GCP; US
14	2	80%; LP & SH
15	2	SH^{++}; 10%
16	2	US; 50%
17	0	-
18	1	70%
19	1	GCP
20	0	-

LP = Lymphocyte predominance; GCP = Germinal centre predominance;
SH = Sinus histiocytosis; US = Unstimulated.

PATIENT NO.	NO. NODES EXAMINED/ EXCISED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE-ACTION"
21	2	LD; micrometastasis
22	1	90%
23	0	-
24	0	-
25	2	SH^{++}; US
26	2	GCP (SH$^+$)
27	2	US
28	2	90%; 100%
29	1	GCP
30	1	GCP (SH$^+$)
31	3	70%; 70%; US
32	2	SH^{++}
33	1	LD
34	0	-
35	2	US
36	1	100%
37	1	30%
38	1	100%
39	1	GCP
40	0	-

PATIENT NO.	NO. NODES EXAMINED/ EXCISED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE-ACTION"
41	1 + 1*	80%; SH^{++}
42	0	–
43	0	–
44	3	20% - 100%
45	3	100%
46	0	–
47	1	micrometastases
48	1	SH^{++}
49	0	–
50	1	US
51	5	5%; 40%; 90%; US
52	1	10%
53	1	GCP
54	2	fatty; 20%
55	3	10% - 100%
56	1	100%
57	1	US
58	1	fatty
59	2	GCP
60	3 + 2	GCP; US; SH^{+}; GCP

* bilateral mastectomy

PATIENT NO.	NO. NODES EXAMINED/ EXCISED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE- ACTION"
61	1	100%
62	2	US (SH$^+$)
63	1	100%
64	2	70%; US
65	1	>90%
66	1	US
67	3	40%; >90%; >90%
68	2	50%; US
69	1	100%
70	1	US (SH$^+$)
71	1	US (SH$^+$)
72	1	LP
73	1	GCP + micrometastases
74	2	LD; US
75	0	-
76	4	US; 100%; 100%; 100%
77	2	SH^{++}; fatty
78	1	GCP
79	0	-
80	2	SH^{++}; LP

PATIENT NO.	NO. NODES EXAMINED/ EXCISED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE-ACTION"
81	1	GCP
82	0	-
83	0	-
84	3	US; 100%; 100%
85	3	40%; 40%; >90%
86	1	GCP
87	1	>90%
88	1	90%
89	1	US
90	1	SH^{++} with LP
91	0	-
92	1	US
93	2	GCP
94	1	90%
95	1	GCP
96	1	GCP + micrometastasis
97	1	GCP + micrometastasis
98	1	GCP
99	1	LP (SH^{+})
100	2	GCP

PATIENT NO.	NO. NODES EXCISED/ EXAMINED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE-ACTION"
101	0	-
102	0	-
103	2	LP: US (SH$^+$)
104	1	US
105	2	US; GCP
106	2	100%; US
107	0	-
108	2	GCP; 50%
109	3	US; GCP; micrometastasis
110	1	$>$90%
111	1	LP
112	1	90%
113	1	100%
114	0	-
115	2	US
116	1	$>$90%
117	0	-
118	2 + 1	70%; $>$90%; US
119	3	LD; $>$90%; 90%
120	2	60%; GCP

PATIENT NO.	NO. NODES EXCISED/ EXAMINED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE- ACTION"
121	0	-
122	6	GCP; US; LD
123	3	50% - 100%
124	7	LD; 20 - 100% (6)
125	1	US
126	1	100%
127	1	>90%
128	1	US
129	0	-
130	0	-
131	2	100%
132	0	-
133	1	fatty
134	3	SH^{++}; US; LP
135	1	100%
136	2	LD; micrometastasis
137	2	SH^{++}; LP
138	2	50%; 90%
139	5	90%; 80%; 60%; 90%; >90%
140	0	-

PATIENT NO.	NO. NODES EXCISED/ EXAMINED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE-ACTION"
141	1	> 90%
142	1	100%
143	7	80%; 20%; LD; US (4)
144	3	fatty; US; GCP
145	0	-
146	1	US
147	0	-
148	1	> 90%
149	3	50%; US; GCP
150	7	US (2); 20% - 100% (5)
151	1	LD
152	1	GCP
153	1	US
154	2	US; 50%
155	3	US; fatty (2)
156	2	LP; US
157	0	-
158	4	micrometastasis; 40%; 40%; 90%
159	7	US (1); fatty (6)
160	2	90%; GCP

PATIENT NO.	NO. NODES EXCISED/ EXAMINED	% METASTATIC REPLACEMENT AND/OR HISTOLOGICAL "RE-ACTION"
161	1	$>$90%
162	3	GCP
163	3	US (2); GCP
164	1	GCP
165	3	fatty (2); LD (1)
166	1	100%
167	1	metastatic [*]
168	3	$>$90%
169	4	GCP
170	3	US (2); GCP
171	0	–
172	1	$>$90%

* Slides not reviewed – biopsy elsewhere

TABLE C

STATISTICAL ANALYSIS OF SURVIVAL AND RECURRENCE - FREE INTERVAL
IN 172 PATIENTS TREATED BY MASTECTOMY FOR CANCER OF THE BREAST

I COMPUTER INPUT

The following details were recorded on punch card for each patient.

Columns 1 - 3 = pt number
       4, 5 = age
       6 = maximum diameter primary tumour (cm) e.g. 1 = $\leqslant$ 1 cm;
            9 = unknown
       7-12 = date of first treatment, viz. mastectomy
       13-18 = date of first recurrence; 999999 = free, as yet, of
            recurrence
       19-24 = date of death from cancer; 999999 = still alive or died
            of other cause
       25-30 = date of last follow-up (or death)
       31 = clinical status of nodes, viz. 1 = impalpable
                                2 = palpable but not
                                   suspicious
                                3 = palpable, suspicious
                                   of metastases
                                9 = unknown
       32 = pathological node status, viz. 1 = sinus histiocytosis
                                2 = lymphocyte predominance
                                3 = unstimulated
                                4 = germinal centre
                                   predominance
                                5 = lymphocyte depleted
                                6 = micrometastases
                                7 = gross metastases in
                                 only one node
                                8 = gross metastases in
                                 only node sampled or
                                 $>$ 1 node
                                9 = unknown - no nodes
                                 sampled or histology
                                 uninterpretable
       33-38 = result of 'superstaging' tests : 1 = -ve, 2 = +ve, 9 = not
            done
              (bone tests = 33 bone scan 34 bone Alk PO_4 ase 35 urine
              OH proline)
              (liver tests = 36 liver scan 37 liver Alk PO_4 ase
              38 gamma GT)
       39 = site of recurrence, viz. <u>local</u> : 1 = scar only,
              2 = axillary nodes
              <u>systemic</u> : 3 = disseminated, not otherwise specified
              4 = disseminated, including bone
              5 = disseminated, including liver
              6 = disseminated, including liver and bone
              9 = no recurrence

TABLE C cont.

STATISTICAL ANALYSIS : SURVIVAL ETC. AFTER MASTECTOMY

I   COMPUTER INPUT cont.

Column 40   = Oestrogen receptor content of tumour
             "negative", i.e. $<$0.1 fm/mg wet wt = 1
             "positive', i.e.   0.1-0.5 fm/mg wet wt = 2
                               0.5-1.0 fm/mg wet wt = 3
                               1.0÷2.0 fm/mg wet wt = 4
                               $>$2.0 fm/mg wet wt = 5
                               unknown = 9

       41   = Cellularity score graded (1-4) x (1-4)
             1 i.e. 1 x 1 = 1
             2 i.e. 1 x 2 (or 2 x 1) = 2
             3 i.e. 1 x 3 (or 3 x 1) = 3
             4 i.e. 1 x 4 (or 4 x 1) or 2 x 2 = 4
             6 i.e. 2 x 3 (or 3 x 2) = 5
             8 i.e. 2 x 4 (or 4 x 2) = 6
             9 i.e. 3 x 3 = 6
             12 i.e. 3 x 4 (or 4 x 3) = 7
             16 i.e. 4 x 4 = 8
             unknown = 9

       42   = Adjusted oestrogen receptor score w.r.t. cellularity,
             viz. $\frac{(\text{column } 40) \times 16}{(\text{column } 41)}$
             "negative", i.e. "zero" = 1
             "positive" but $<$2 = 2
                           2-5 = 3
                           5-10 = 4
                           $>$10 = 5
                        unknown = 9

TABLE C cont.

STATISTICAL ANALYSIS : SURVIVAL ETC. AFTER MASTECTOMY

II   COMPUTER ANALYSIS (Dr R. Prescott and Mrs K. Bers)

    (a)   Correlation between variables

(Chi^2 analysis)

	Chi^2	Degrees of freedom	P
Age (decades) v Tumour size	21.4	35	0.97
Age " v Clinical node status	11.2	8	0.19
Age " v Pathological node status	32.5	28	0.25
Tumour size v " " "	68.6	49	0.03*
Tumour size v Year of mastectomy	24.9	28	0.64
+ Age (whether $\geqslant$50 or <50) v oestrogen receptor status (ER)	22.2	4	0.0002*
Age as above v Adjusted ER	12.9	4	0.01*
Tumour size v Cellularity	26.7	42	0.97

    *   Statistically significant
    +   See Table C II (d)

    (b)   Recurrence-free interval (log rank analysis)

The following variables showed a significant effect :

	Chi^2	Degrees of freedom	P
Tumour diameter	37	7	0.0001
* Clinical node status	17.6	2	0.0002
Pathological node status (all groups)	51.4	8	0.0001
* Ditto grouped 1-3 v 4-6 v 7-8 v 9	28.8	3	0.0001
Ditto grouped 1-3 v 4-5 only	4.2	1	0.041
* Ditto grouped 7 v 8 only	6.0	1	0.015
* ER	11.1	4	0.026
* Adjusted ER	11.7	4	0.020
* Cellularity	14.6	7	0.041

    *   See Figures C1 to C7

The following variables showed no significant effect :

Age (by decade or whether $\geqslant$50); "superstage" test results; site of recurrence.

The best "superstage" results were as follows :

	CHi^2	Degrees of freedom	P
Bone alkaline PO_4 ase	3.6	1	0.057
Bone scan	3.1	1	0.079

TABLE C cont.

STATISTICAL ANALYSIS : SURVIVAL ETC. AFTER MASTECTOMY

II   COMPUTER ANALYSIS cont.

(c)   Survival time (log rang analysis)

	Chi^2	Degrees of freedom	P
Tumour diameter	20.9	7	0.004
Clinical node status	7.8	2	0.021
Pathological node status (all groups)	34.1	8	0.0001
Ditto grouped 1-3 v 4-6 v 7-8 v 9	28.6	3	0.0001
Ditto grouped 1-3 v 4-5 only *	0.53	1	0.46
Ditto grouped 7 v 8 only *	2.23	1	0.14
ER *	8.1	4	0.09
Adjusted ER *	5.6	4	0.23
Cellularity *	5.9	7	0.55
Bone alkaline PO_4 ase *	0.84	1	0.36
Bone scan *	2.83	1	0.09
+ Site of recurrence	18.8	5	0.002

*   These and all other variables had no statistically significant effect.

+   See Figure C7.

(d)   Correlation between age (greater than 50 or not, i.e. $\equiv$ menopausal status) and oestrogen receptor status (ER).

	ER (fm/mg wet weight)					
	<0.1	0.1 - 0.5	0.5 - 1	1 - 2	>2	Totals
Age less than 50	5	11	7	16	7	46
Age 50 and over	21	13	7	10	40	91
	26	24	14	26	47	137

$Chi^2 = 22.18$

4 degrees of freedom   P = 0.0002

Comment : The older ('post menopausal') patients had a significantly increased proportion of either high levels or very low levels.

FIGURE C

SURVIVAL AND RECURRENCE-FREE INTERVAL IN 172 PATIENTS
TREATED BY MASTECTOMY FOR BREAST CANCER (Chapter 2 etc)

FIGURE C1

Recurrence-free probability in patients according to clinical node status.

Group 1 : Impalpable nodes (No.) 85 pts.

Group 2 : Palpable nodes not suspected of containing metastatic deposits (N1a) 12 pts.

Group 3 : Palpable nodes, metastases suspected 74 pts.

Chi^2 = 17.6, 2 degrees of freedom, P = 0.0002.

DISEASE FREE PROBABILITY ——— CLINICAL NODE STATUS

100%

80

60

40

20

0

months   4   8   12   16   20

impalpable nodes N_0 1
palpable, not suspicious N_{1a} 2
palpable, metastasis suspected N_{1b} 3

1

2

3

FIGURE C cont.
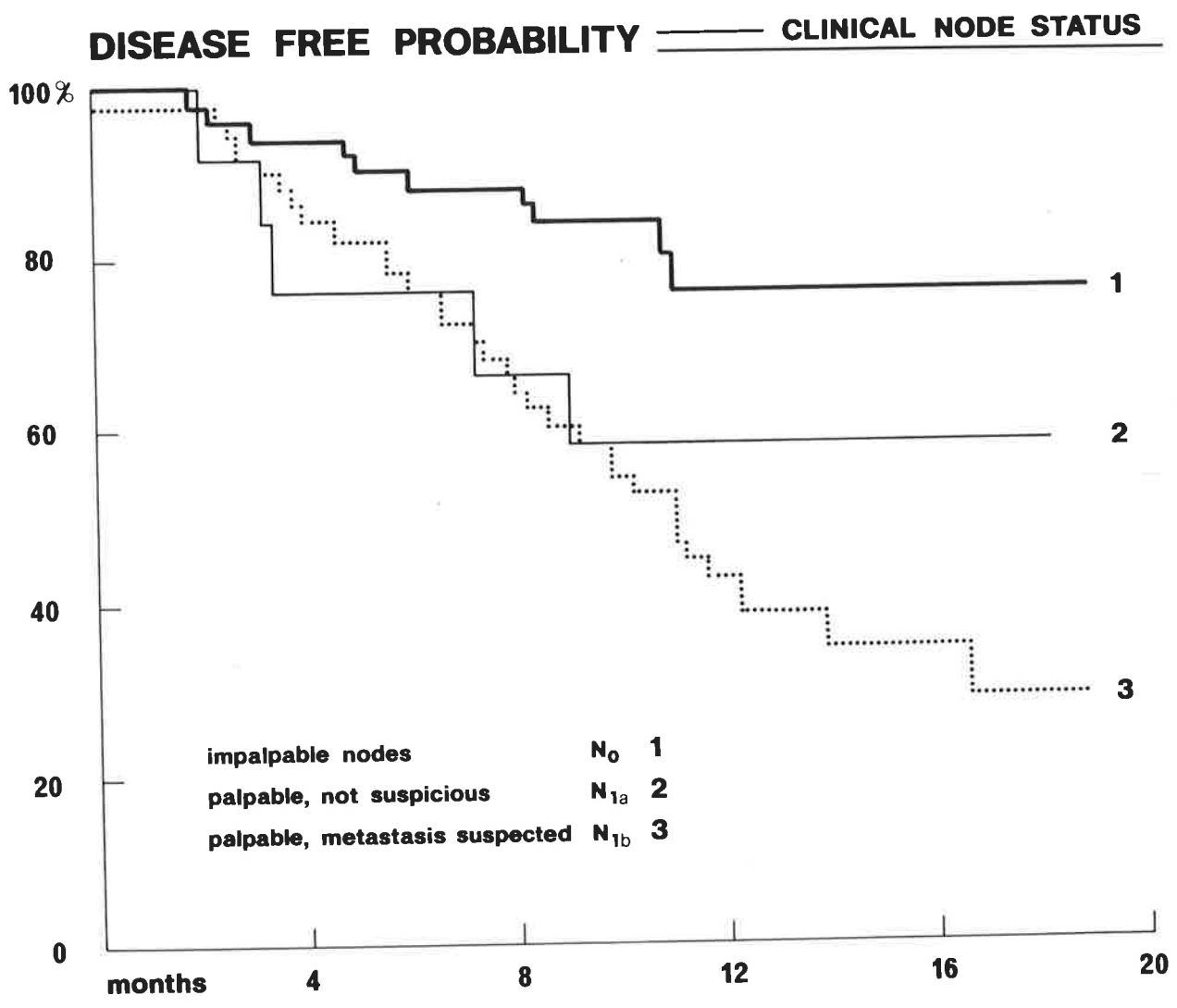
SURVIVAL ETC. AFTER MASTECTOMY

FIGURE C2

Recurrence free probability in patients according to Node Histological Status

Group 1 : Sinus histiocytosis, lymphocyte predominance or unstimulated nodes. (36 patients)

Group 2 : Germinal centre predominance, lymphocyte depletion or micrometastases. (44 patients)

Group 3 : Gross metastases in one or more nodes. (60 patients)

Group 4 : Nodes not excised at mastectomy. (32 patients)

Chi^2 28.75; 3 degrees of freedom; $P < 0.0001$

DISEASE FREE PROBABILITY – PATHOLOGICAL NODE STATUS

SH LP or US   1
GCP LD or micrometastases 2
Gross metastases   3
Nodes not examined   4
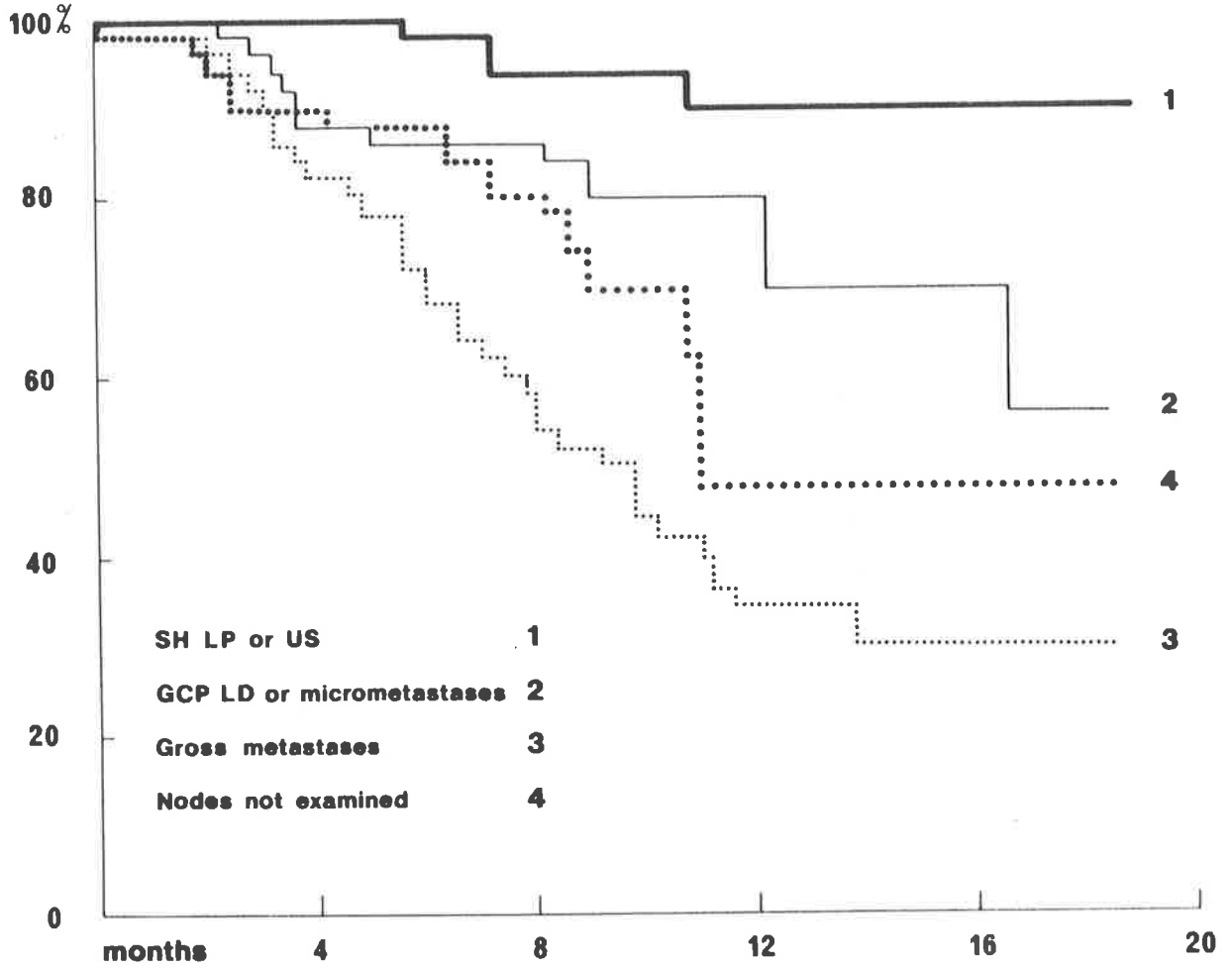
FIGURE C cont.

SURVIVAL ETC. AFTER MASTECTOMY

FIGURE C3

Recurrence free probability in patients with gross node metastases

Group 1 : Metastases in only 1 node of two or more. (13 pts)

Group 2 : Metastases in the only node removed, or in more than one node. (47 pts)

Chi^2 5.96; 1 degree of freedom; P = 0.015

DISEASE FREE PROBABILITY — GROSS NODE METASTASES

Mets. in only one node of two or more 1

Mets. in the only node – or in more than one node 2
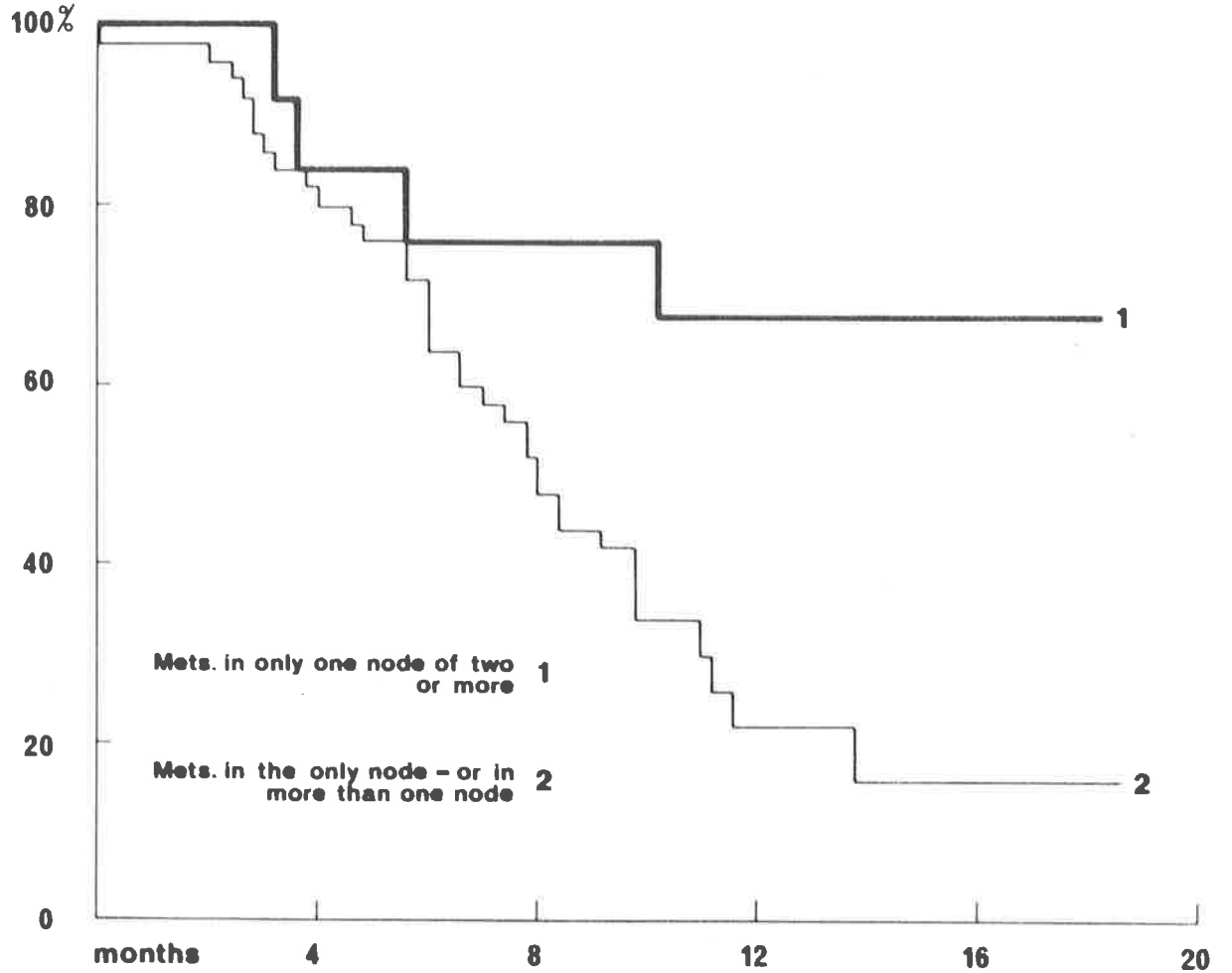
FIGURE C cont.

SURVIVAL ETC. AFTER MASTECTOMY

FIGURE C4

Recurrence free probability in all patients with node metastases on histological examination

Group 1 : Micrometastases only. (12 pts)

Group 2 : Metastases in only 1 node of two or more. (13 pts)

Group 3 : Metastases in the only node examined or in more than one node. (47 pts)

DISEASE FREE PROBABILITY ——————— NODE METASTASES

100%

80

60

40

20

0

Micrometastases only ········ 1

Mets. in only one node of two 2
or more

Mets. in the only node – or in 3
more than one node

months   4   8   12   16   20

1

2

3

FIGURE C cont.
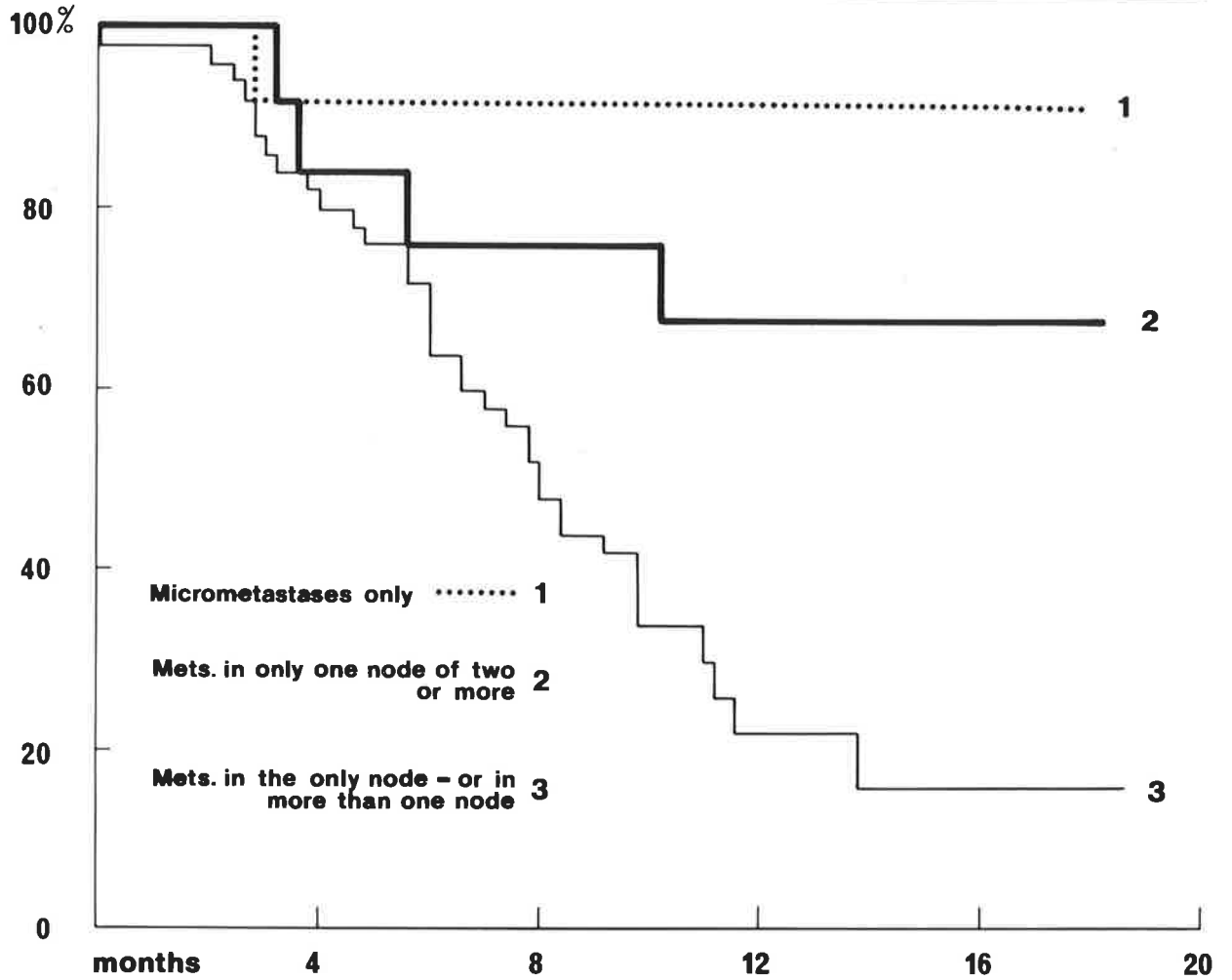
SURVIVAL ETC. AFTER MASTECTOMY

FIGURE C5

Recurrence free probability according to oestrogen receptor status

Group 1 : "negative" i.e. $<$ 0.1 fm/mg wet wt. (26 pts)

Group 2 : 0.1 - 0.5 fm/mg. (24 pts)

Group 3 : 0.5 - 1.0 fm/mg. (14 pts)

Group 4 : 1.0 - 2.0 fm/mg. (26 pts)

Group 5 : $>$2.0   fm/mg. (47 pts)

$$Chi^2 = 11.1; \ 4 \text{ degrees of freedom}; \ P = 0.026$$

FIGURE C cont.
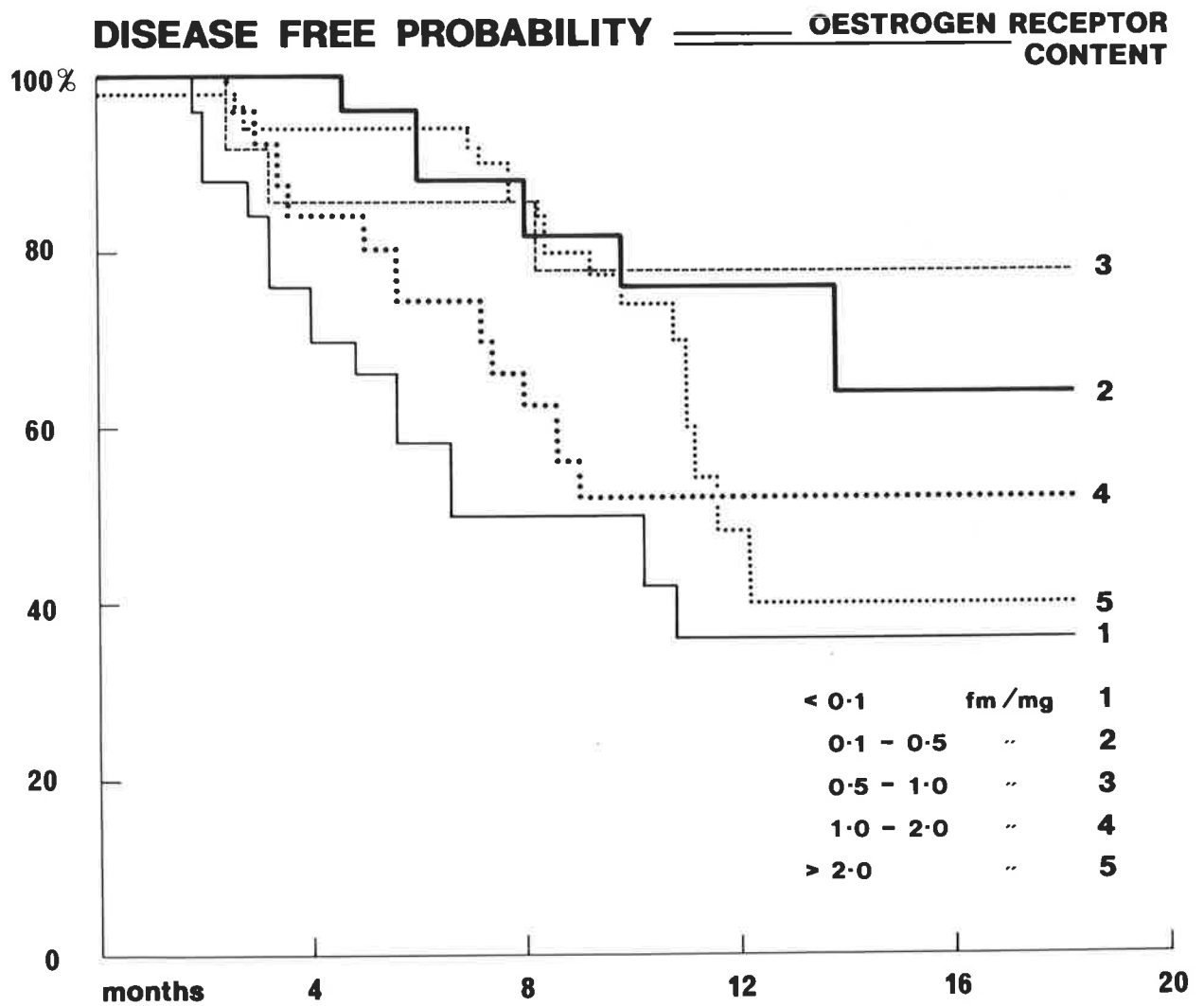
SURVIVAL ETC. AFTER MASTECTOMY

FIGURE C6

Recurrence free probability according to cellularity scores graded from 1 to 7.

(See Table C1, column 41, for explanation).

No. of patients in each group : 1:6; 2:6; 3:12; 4:23; 5:7; 6:24; 7:10.

$Chi^2 = 14.6$; 7 degrees of freedom; P = 0.041

DISEASE FREE PROBABILITY ———— CELLULARITY SCORES

FIGURE 6 cont.

SURVIVAL ETC. AFTER MASTECTOMY

FIGURE C7

Recurrence free probability according to adjusted oestrogen receptor score

(See Table CI column 42 for explanation)

Group 1 :   "zero" or "negative". (21 pts)

Group 2 :   "positive", but <2. (16 pts)

Group 3 :   2 - 5 (17 pts)

Group 4 :   5 - 10 (18 pts)

Group 5 :   >10 (19 pts)

$Chi^2 = 11.7$; 4 degrees of freedom; $P = 0.02$

DISEASE FREE PROBABILITY adjusted **OESTROGEN RECEPTOR SCORE**

0	1
0 – 2	2
2 – 5	3
5 – 10	4
> 10	5

FIGURE C cont.
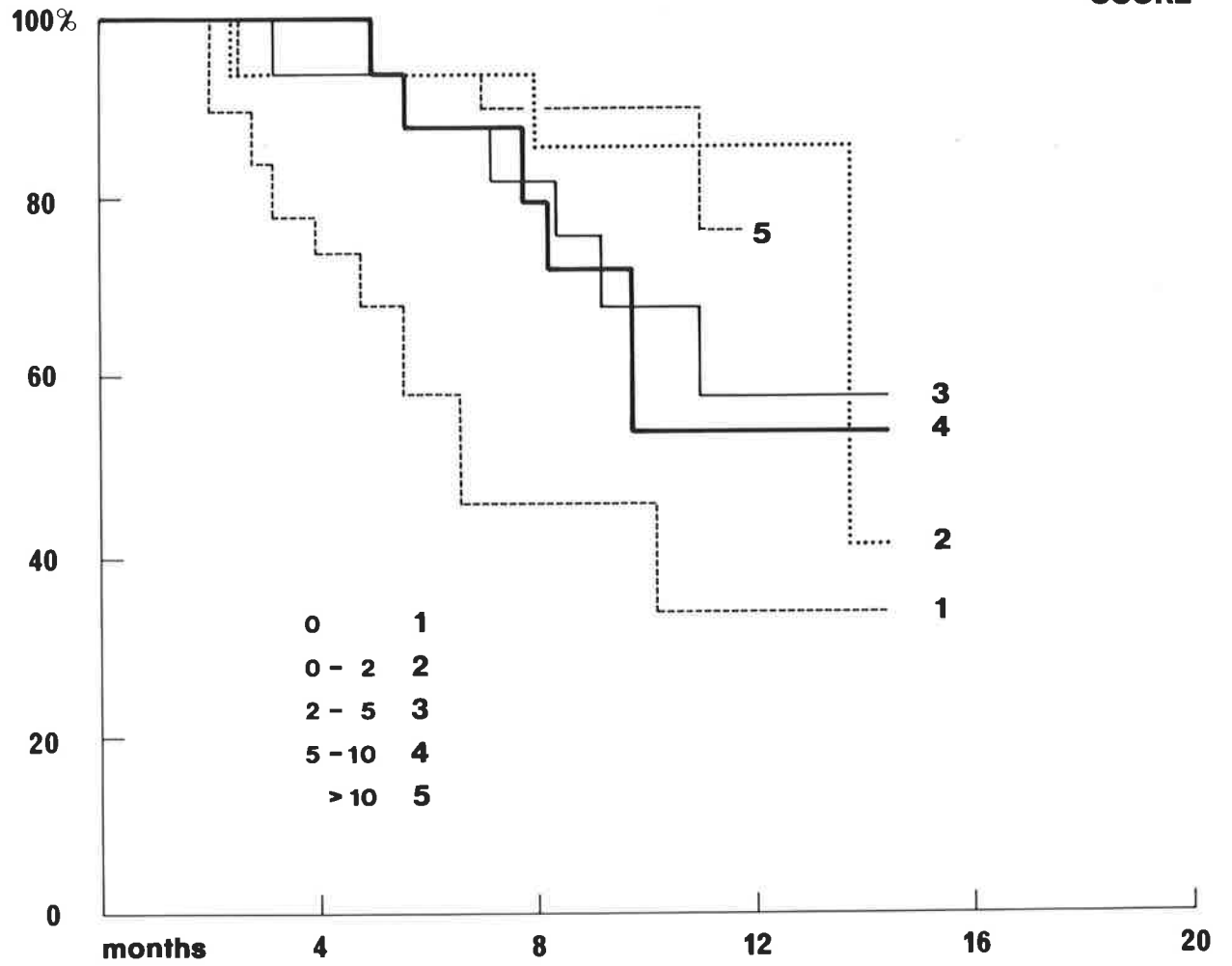
SURVIVAL ETC. AFTER MASTECTOMY

FIGURE C8

Survival probability - interval from 1st recurrence to death - according to site of 1st recurrence

Local recurrence alone

    1 - scar, flaps etc. only. (3 pts)

    2 - axilla $\pm$ 1. (6 pts)

Disseminated ($\pm$ local) recurrence

    3 - not otherwise specified. (12 pts)

    4 - including bone. (19 pts)

    5 - including liver. (9 pts)

    6 - including bone and liver. (11 pts)

$$Chi^2 = 18.8; \text{ 5 degrees of freedom; } P = 0.002$$

SURVIVAL PROBABILITY ═══════ SITE OF FIRST RECURRENCE
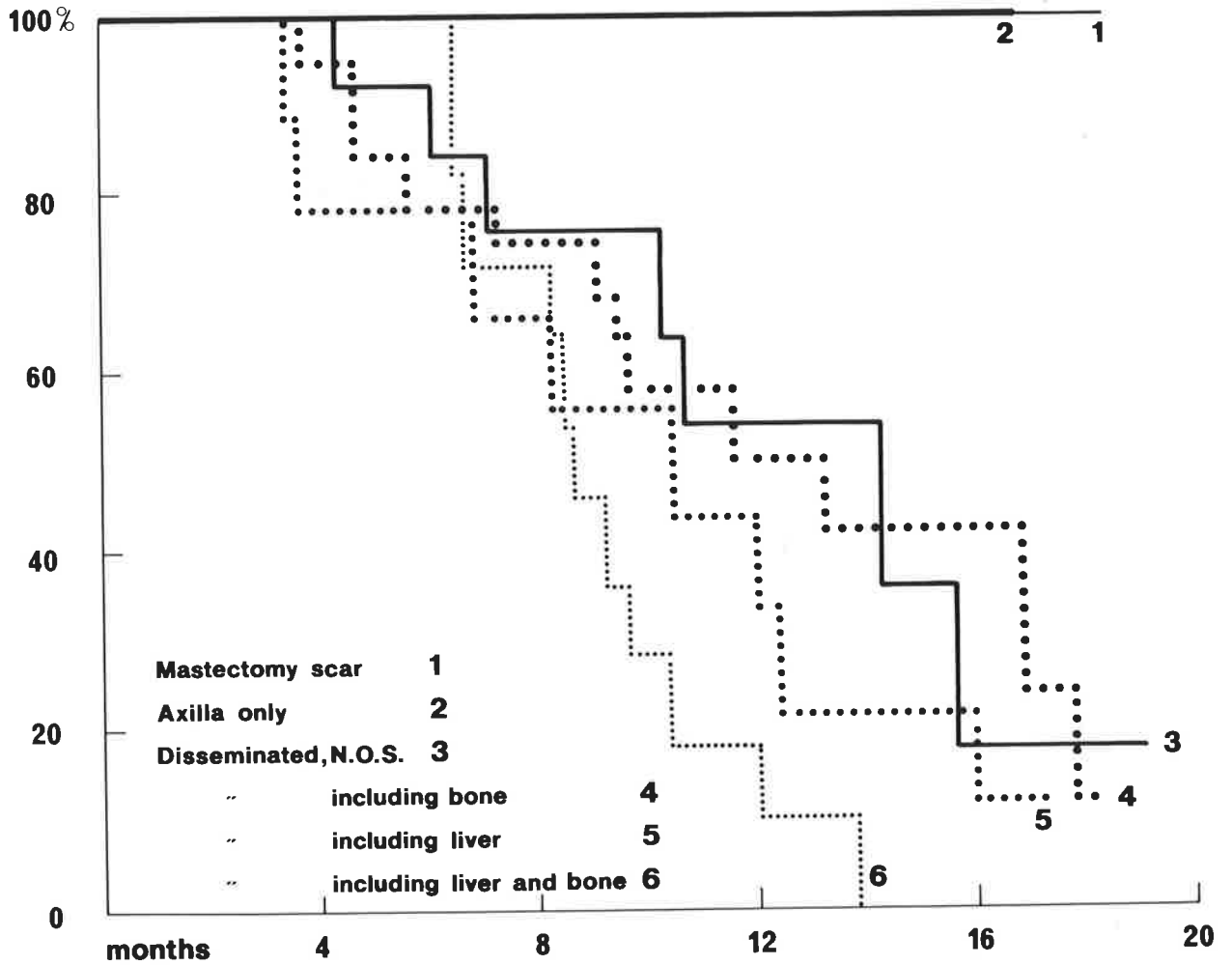
Mastectomy scar   1
Axilla only   2
Disseminated, N.O.S.   3
  „   including bone   4
  „   including liver   5
  „   including liver and bone 6

CLINICAL AND PATHOLOGICAL CORRELATION IN PATIENTS UNDERGOING AXILLARY LYMPHOSCINTIGRAPHY

I   CARCINOMA

PATIENT		CLINICAL NODE STATUS	LYMPHOSCINTIGRAPHY			NODE HISTOLOGY
			METHOD*	R E S U L T CRITERIA A+	CRITERIA B+	
JH	3	No	1	0	U	2/2 reactive
RF	1	No	1	B	N	2/18 reactive
AF	2	N1b	1	0	U	4/4 metastatic
MH	4	No	1	0	U	4/5 reactive
HW	5	N1b	1	M	Met	5/5 metastatic
GH	6	No	1	0	U	5/8 reactive
JW	7	No	1	0	U	1/7 metastatic; 1 reactive
HL	8	No	1	0	U	5/13 reactive
KB	10	N1b	1	0	U	3/5 metastatic
IW	9	N1b	1	0	U	1/9 metastatic; 1 reactive
AG	11	No	1	B	N	0/1 metastatic
CW	12	N1b	1	0	U	1/16 metastatic 1 reactive
AH	13	N1b	1	0	U	1/18 metastatic 7 reactive
LG	14	N1b	1	0	U	2/3 reactive
MMcD	15	No	1	M	Met	1/6 metastatic
JB	16	N1b	1	B	N	6/7 reactive

Patient numbers refer to numbers in Table E , ie those subsequently undergoing detailed histological node studies.

*   Method 1 = subcutaneous injection of ASC
    Method 2 = intradermal injection of ASC
+   Criteria A = those of Agwunobi and Boak (1978)
    Criteria B = those of Ege (1978) and others
M = malignant; B = benign; U = uninterpretable; N - No abnormality detected;
Met = metastatic nodes; 0 = negligible uptake by nodes

CLINICAL AND PATHOLOGICAL CORRELATION WITH LYMPHOSCINTIGRAPHY

PATIENT		CLINICAL NODE STATUS	LYMPHOSCINTIGRAPHY			NODE HISTOLOGY
			METHOD*	R E S U L T CRITERIA A[+]	CRITERIA B[+]	
AH	18	N1b	1	0	U	1/6 metastatic
LB	17	N1b	1	0	U	0/
EW	19	No	1	0	U	0/7 metastatic
CP	20	No	1	0	U	0/7 metastatic
JC		No	1	0	U	Nil. Bone metastases
EE	21	No	1	0	U	1/11 metastatic
JM	26	N1b	1	0	U	3/3 metastatic
JL	22	No	1	0	U	5/19 reactive; no mets.
MN	25	No	1	0	U	2/6 mets; 1 reactive
DM	23	N1b	1	0	U	2/5 mets; 1 reactive
MB	24	N1b	1	0	U	5/7 metastatic
JB		N3	1	0	U	Nil. XRT
JMcN	27	No	1	B	N	1/2 reactive; no mets
AH	28	No	1	0	U	0/7 metastatic
AR	30	No	1	0	U	3/6 reactive; no mets
NA	29	N1b	1	M	Met	3/3 metastatic
CMcF	31	No	1	B	N	1/11 micrometastasis
DF	34	N1b	2	0	U	1/3 metastatic
AB	33	No	2	M	Met	5/12 mets; 3 reactive
HM	32	No	2	B	N	0/3 mets; 1 reactive
ES	35	N1b	1	0	U	2/5 mets; 2 reactive

CLINICAL AND PATHOLOGICAL CORRELATION WITH LYMPHOSCINTIGRAPHY

PATIENT		CLINICAL NODE STATUS	LYMPHOSCINTIGRAPHY			NODE HISTOLOGY
			METHOD*	RESULT CRITERIA A+	CRITERIA B+	
AR		N3	1	0	U	Nil. XRT and Chemo Rx
LM	36	N1b	1	0	U	3/6 metastatic
CS		No	1	0	U	Nil. XRT for infra mammary tumour
NH	38	No	2	B	N	0/4 mets; 3 reactive
IL	37	No	2	B	N	0/6 mets; 1 reactive
SA	40	No	2	B	N	0/6 metastatic
AT	41	No	2	0	U	1/7 reactive; no mets
LC	39	No	2	M	Met	2/4 metastatic
AB	42	No	2	B	N	1/10 micromet; 2 reactive
CS	43	No	2	B	N	1/7 mets; 4/7 micromets.
MA	44	No	2	B	N	0/4 mets; 1 reactive
JS	45	No	2	B	N	0/3 mets
JB	48	No	2	B	N	1/5 micrometastatic
MS	47	No	2	B	N	0/9 mets; 3 reactive
MM	49	No	2	B	N	0/11 mets; 4 reactive
AMcL	46	No	2	B	N	0/6 mets
DC	50	N1b	2	M	Met	1/6 met; 1 reactive
OC	52	No	2	B	N	0/6 mets; 2 reactive

CLINICAL AND PATHOLOGICAL CORRELATION WITH LYMPHOSCINTIGRAPHY

| PATIENT | CLINICAL NODE STATUS | LYMPHOSCINTIGRAPHY | | | NODE HISTOLOGY |
		METHOD*	CRITERIA A+	CRITERIA B+	
MMCQ 51	No	2	B	N	0/4 mets
EO 54	No	2	0	U	2/13 micromets; 1 reactive
AY	N3	2	M	Met	Supraclavicular node metastatic
MT 55	No	2	M	Met	2/10 mets; 2 reactive
HB 53	N1b	2	M	Met	1/4 met; 1 micromet; 1 reactive
SW	N1b	2	M	Met	Nil. Biopsy only.
SMcK	N1b	2	M	Met	Nil Stage 4 (marrow mets)
CP	N1b	2	M	Met	Mets
JMcK	N1b	2	M	Met	Mets
RG	No	2	B	N	All nodes fatty
SH	No	2	B	N	reactive
DR	No	2	B	N	reactive
MF	No	2	B	N	reactive

CLINICAL AND PATHOLOGICAL CORRELATION IN PATIENTS UNDERGOING AXILLARY LYMPHOSCINTIGRAPHY

II BENIGN

| PATIENT | CLINICAL DIAGNOSIS | LYMPHOSCINTIGRAPHY | | | FINAL DIAGNOSIS* |
		METHOD	RESULT CRITERIA A	CRITERIA B	
IT	Fibro-adenosis	1	B	N	Inflammatory
IMcK	Fibro-adenosis	1	0	U	Mammary dys-plasia+
ER	Fibro-adenosis	1	0	U	Fibrosis and atrophy
SMcK	Mastalgia	1	0	U	Mammary dys-plasia+
IR	Fibro-adenosis	1	0	U	Mammary dys-plasia+
MD	Mastalgia	1	B	N	Mammary dys-plasia+
AH	Fibro-adenosis	1	B	N	Mammary dys-plasia+
JE	Fibro-adenosis	1	M	N	Mammary dys-plasia+ cyst
SM	Carcinoma	1	M	U	Cyst+
MC	Carcinoma	2	B	N	Mammary dys-plasia
MB	Carcinoma	2	B	N	Mammary dys-plasia

* Based on clinical, cytologic and mammographic criteria, and confirmed histologically except in cases marked +

LYMPHOSCINTIGRAMS (see Table D for explanation)

In all scans the large dark mark on each side is the injection
site. A marker has been used to outline the patient's (neck
and) shoulders.

FIGURE D 1

Patient S.M. 47 years (Table DII); hard mass left breast
? cancer.

Lymphoscintigrams by Method 1.

Result : Uptake by nodes on right side only.

Interpretation :

Criteria A   Malignant

Criteria B   Uninterpretable

Final diagnosis : cyst

FIGURE D 2

Patient J.E. 37 years (Table DII); thickening in left breast,
both breasts small and tender.

Lymphoscintigram by Method 1. (Painful injection).

Result : Uptake in both axillae (R greater than L) and
by L internal mammary nodes also.

Intepretation :

Criteria A   Malignant

Criteria B   Normal

Final diagnosis : mammary dysplasia + cyst
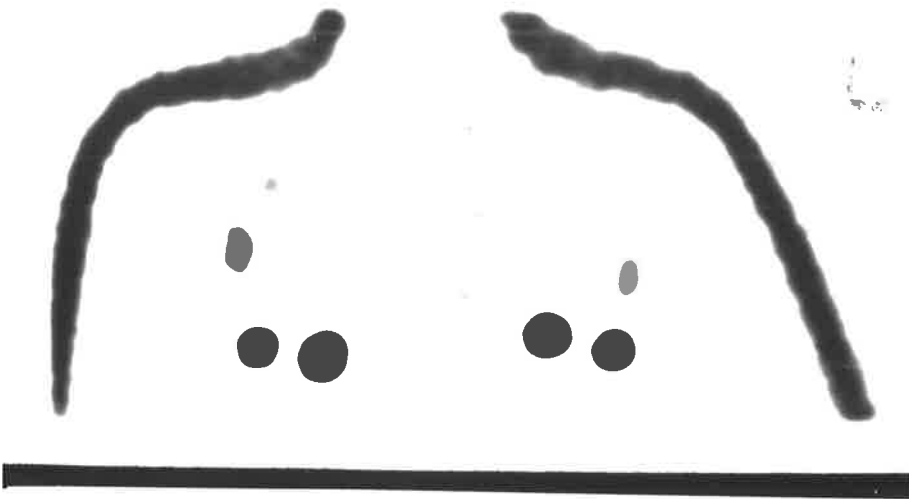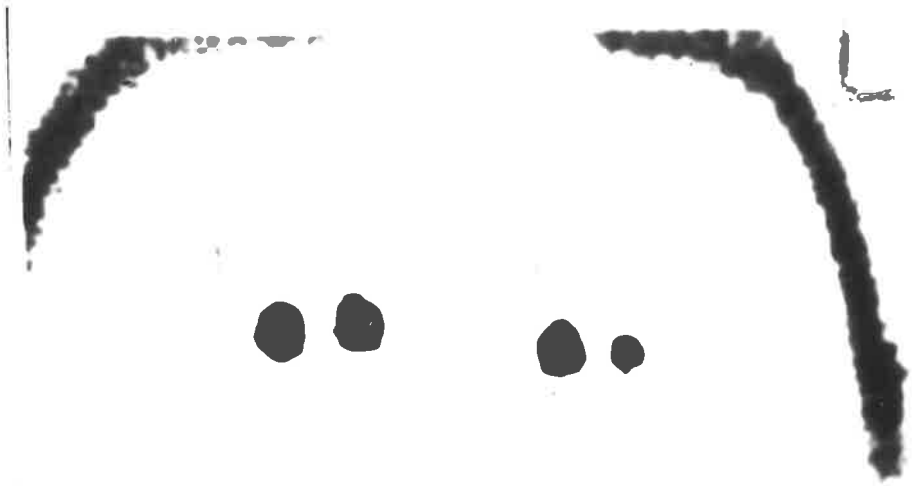
FIGURE D 3

Patient D.R. 56 years (Table DI, not numbered); 3 cm lump upper outer quadrant left breast; probable carcinoma, Stage $T_2N_0M_0$.

Lymphoscintigram by Method 2.

Result : Good uptake in each axilla (L greater than R)

Interpretation :

Criteria A   Benign

Criteria B   No abnormality (negative for metastases)

Final diagnosis : Invasive cancer; nodes free of metastases histologically.

FIGURE D 4

Patient N.A. 58 years (Table DI, No. 29); tethered mass R breast; probable carcinoma, Stage $T_{2b}N_{1b}M_0$.

Lymphoscintiscan by Method 1.

Result : Uptake by nodes in each axilla, but not by lower nodes on right. Uptake greater on left.

Interpretation :

Criteria A   Malignant

Criteria B   Node metastases

Final diagnosis : Invasive cancer; 3 nodes excised at mastectomy, all replaced by metastatic deposits.
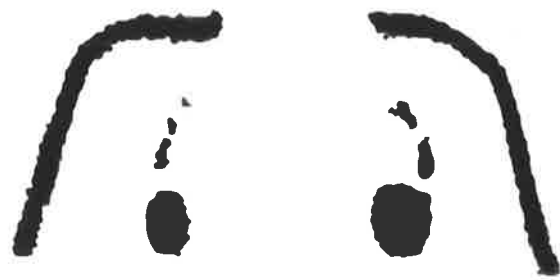
ANT

AXILLARY LYMPH NODE SIZES[+] IN 50 PATIENTS UNDERGOING MASTECTOMY FOR
BREAST CANCER

+ shown as mass (G)/maximum diameter (cm)

PATIENT	CLINICAL NODE STATUS	NODE HISTOLOGY					
		METS	SH[++]	GCP	LP	U/S	FATTY
RF 1	No		.06/.6 .02/.2 .02/.2 .04/.4 .03/.4	.72/2*	.40/1.2	.10/.8 .17/1 .03/.2 .02/0.4 .03/.3 .03/.3 .04/.4	.05/.5 .02/.2 .04/.4 .03/.3 .06/0.6
AF 2	N1b	.25/1.5 .26/1 .24/1.0 1.56/2.5*					
JH 3	No		? /1.0	? /.8			
MH 4	No		.29/1.1		.65/2	.29/1.2 .10/.8	1.75/3.5*
HW 5	N1b	.85/1.5 1.67/2.5* .34/1.5 .45/1.5 ? /0.8					
GH 6	No		.44/2 .50/2 .20/.8 .61/1.5	1.13/2.3*	1.13/2.3*	.84/2 .28/1.1 .30/1	
JW 7	No	.73/1.8*			.42/1.5	.16/.9 .75/1.7	.66/1.8 .52/1.5 .41/1.5

Nodes marked * are the largest node from each axilla
Mets = Metastasis (gross or microscopic)
SH = Sinus histiocytosis
GCP = Germinal Centre Predominance
LP = Lymphocyte Predominance

U/S = Unstimulated
LD = Lymphocyte depleted

PATIENT	CLINICAL NODE STATUS	NODE HISTOLOGY					
		METS	SH++	GCP	LP	U/S	FATTY
HL 8	No		.17/1			.16/1	
			.09/.8			.11/.6	
			.08/.3			.14/.5	
			.25/1			.14/.5	
			.31/1.3*			.08/1.6	
						.06/.5	
						.20/1	
						.07/.6	
IW 9	N1b	.45/1.5	.50/1	.50/1		.24/.8	1.5/2.5* (LD)
						.18/1.1	
						.46/1.5	
						.08/.5	
						.04/.5	
AG 10+	N1a					? /0.3	
CW 12	N1b	2.83/2.4*	.10/.5			.23/1.2	? /.8 (LD)
						.04/.2	? /.8 (LD)
						.05/.3	.11/.5 (LD)
						.05/.4	.75/3.2 (LD)
						.12/1	.05/.4 (LD)
						? /.4	
						.22/1.2	
						.13/1	

+ NB This patient is not included in the node sizes (chapter 6) statistics. Mastectomy was not performed according to the protocol and the node(s) was not processed by me.

PATIENT	CLINICAL NODE STATUS	NODE HISTOLOGY					
		METS	SH^{++}	GCP	LP	U/S	FATTY
AH 13	N1b	2.09/3.1*	.17/1	2.09/3.1* .89/1.9 .31/1	.35/1.8 .38/1.3 2.09/3.1* .31/1 .32/1.3	.08/.6 .07/.6 .20/.8 .10/.6 .08/.7 .13/.5 .29/1.5 .15/1 .16/1	
LG 14	N1b		.88/2		.23/1.5 4.29/5*		4.29/5*
MMcD 15	No	.12/1	.56/2			.88/2*	.30/1.2
JB 16	N1b		.75/1.5 .98/2*	.75/1.5	.85/2 .26/1 .96/1.5 .10/.8	.08/.5	
LB 17	N1b		1.32/1.5 * .16/.8	1.32/1.5 *	1.32/1.5 * .28/1 .54/1.5 .76/1	.16/1	.56/1.5 1.19/2 (LD)
AH 18	N1b	15.5/5*				.10/.6 .05/.6 .22/1	.16/.9 .25/1.2
EW 19	No				0.32/1	.13/.8 .21/1 .16/.8 .12/.8 .18/1	1.08/2*

PATIENT	CLINICAL NODE STATUS	NODE HISTOLOGY					
		METS	SH++	GCP	LP	U/S	FATTY
CP 20	No				.45/1.5	.14/.5	.76/2
						.11/.5	1.00/2.5
							.71/2.5
							2.55/3 *
ES 21	No	1.37/2 (micro)				.11/.5	3.45/3*
						.10/.4	1.56/2
						.12/1	.11/.5
							.06/.5
							.05/.5
							.55/2
JL 22	No			.55/1.5	.11/1	.12/.5	1.68/2.5*
				.13/.5	.11/1	.06/.5	.57/2
				.68/1.5	.11/1	.23/1	.64/2
				.17/1.5	.15/.5	.07/.5	
					.49/1.5	.09/?	
						.05/.5	
						.08/.5	
						.09/.5	
DM 23	N1b	1.65/2*		.69/2		.26/1	1.65/2*
		0.33/1					1.46/3
MB 24	N1b	1.02/1.5				.22/1	
		0.33/1				.05/.5	
		.22/1					
		1.34/2.5*					
		2.19/2					
MN 25	No	.85/1.5*	.12/1			.08/1	0.38/2 (LD)
		.38/2 (micro)				.05/.8	
						.05/1	
						.05/1	
						.68/2	
JM 26	N1b	⌀ 9.15/4*					
JMcN 27	No		.30/1 *				

⌀ (3 matted nodes)

PATIENT	CLINICAL NODE STATUS	NODE HISTOLOGY					
		METS	SH^{++}	GCP	LP	U/S	FATTY
AH 28	No					.25/1 .10/.5 .10/5	4.01/3(LD) .30/1 (LD) .15/1 (LD) .10/.8 (LD
AR 30				0.5/1 0.35/1.5 0.30/0.5		.4/1.5 .2/1	1.8/2.5*
CMcF 31	No	.25/1.2 (micro)				.3/1.5 .15/1 .10/1 .35/1.5 .10/.5 .30/1.2	.25/2.5* (fibrotic) .4/1.6 (fibrotic) .5/1.4 .10/1 (fibrotic)
HM 32	No				.52/1.8*		.29/1 .48/2*
AB 33	No	.39/1.3 .12/1 1.01/1.8 8.67/4* 1.06/1.5		.13/.6 .21/1 .41/1.5		.07/.4 .04/.5 .03/?	.36/1
DF 34	N1b	1.45/2*					.22/1.5 (fibrotic) .26/1.4(LD
ES 35	N1b	.42/1 .06/.8		.42/1.3 1.01/2*		.13/.8	
LM 36	N1b	.70/1 .55/1 2.45/2.2*					1.05/1.2 .25/.8 .10/.5
IL 37	No			0.8/1.6		.26/1.3	.17/1 .89/1.5 1.02/1.5 .87/3*

PATIENT	CLINICAL NODE STATUS	NODE HISTOLOGY					
		METS	SH++	GCP	LP	U/S	FATTY
NH 38	No				0.30/1 0.11/0.8		0.44/0.5 0.81/1.4*
LC 39	No	0.44/1.2* 0.07/0.8				0.15/1	.06/.8 (LD)
SA 40	No					.03/0.4 .22/1.3 .07/0.6 .10/0.8 .06/0.5 .06/0.8	2.69/3.5*
AT 41	No			.21/1.5		.19/1.3 .05/.8 .02/.6 .02/.5	.24/1.5*
AB 42	No	2.38/2.5* (micro)			2.38/2.5* .81/3	.15/1 .05/1 .08/0.5	.21/1.3 .95/2 .04/0.5 .21/1 .38/1.5
CS 43	No	0.30/1 0.10/.6 (micro) 2.11/2.5 (micro) 0.18/1 (micro) 0.29/1.5 (micro)				.05/.5 .03/.4	2.11/2.5* (LD)
MA 44	No				.06/0.8	.06/0.7 .64/1.5	.72/1.5*
JS 45	No					0.04/0.3	1.53/2.6* 0.42/1.5

PATIENT	CLINICAL NODE STATUS	NODE HISTOLOGY					
		METS	SH++	GCP	LP	U/S	FATTY
AMcL 46	No					0.03/0.5 0.23/1.0 0.06/0.8 0.20/1.0	0.64/2.0* 0.35/1.5 (LD)
MS 47	No			0.44/? 0.18/0.8 0.09/?	0.44/?	0.20/0.8 0.04/? 0.61/1.5*	0.04/? 0.02/? (LD)
JB 48	No	3.36/3 (micro)					3.36/3 4.41/3* 0.73/1.5 2.28/1.0 0.60/1.0
MM 49	No		0.23/0.6 0.44/1.2 0.46/1.2	0.73/2.0*	0.35/1.0 0.73/2.0*	0.20/0.4 0.16/0.4	0.16/0.7 0.68/1.8 0.49/1.3 0.07/0.4
DC 50	N1b	17.6/4.0*	1.01/2.7	0.25/0.8		0.71/1.0	1.01/2.7 0.12/0.5 (LD)
HB 53	N1b	2.35/1.5* 0.5/0.8 (micro)		0.7/1.0			1.8/2.0 (LD)
EO 54	No	0.1/0.5 (micro) 0.2/0.7 (micro)		1.0/1.5*		0.2/0.6 0.3/0.8 0.2/0.4 0.1/0.3 0.7/1.3 0.2/1.0 0.1/0.3 0.5/1.0 0.3/0.6	

NB   Patients 11, 29, 51, 52 and 55 are excluded as the node diameters were not assessed.

AXILLARY NODE PLOTS, SHOWING THE RELATIVE POSITION OF METASTATIC
AND REACTIVE NODES

In all diagrams the apex of the dissection is shown uppermost, the
contents being viewed from the anterolateral aspect.

Unstimulated nodes shown.

Fatty nodes shown.

Nodes with sinus histiocytosis shown.

Lymphocyte predominant nodes shown.

Germinal centre predominant nodes shown.

Lymphocyte depleted nodes shown.

Gross metastases shown.

Micrometastases shown.

Axillae in which all or most nodes show the same feature are not
illustrated.

AXILLARY NODE PLOTS

1   RF   RIGHT
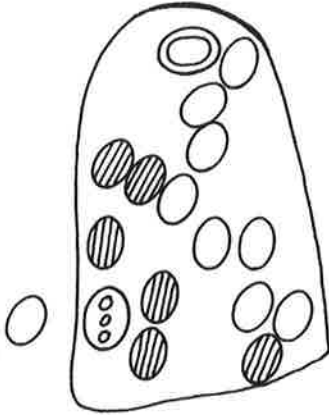
6   GH   LEFT
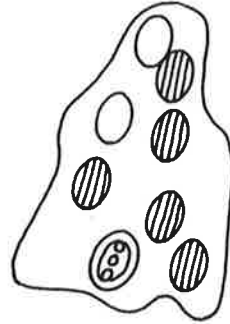
4   MH   RIGHT
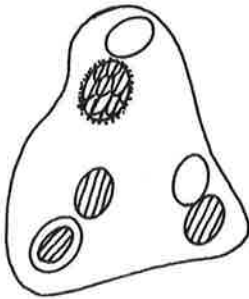
7   JW   RIGHT
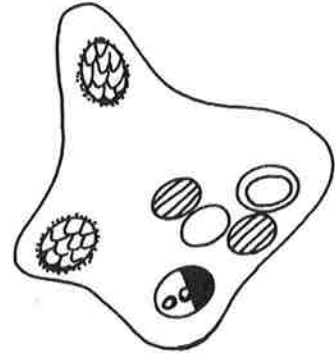
5   HW   LEFT

8   HL   LEFT

AXILLARY NODE PLOTS
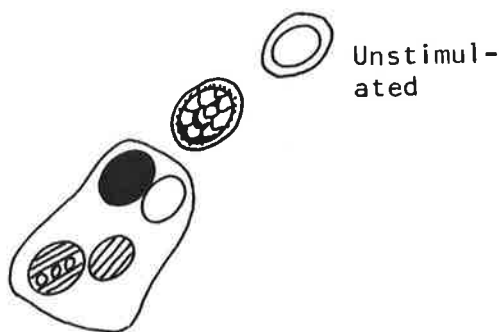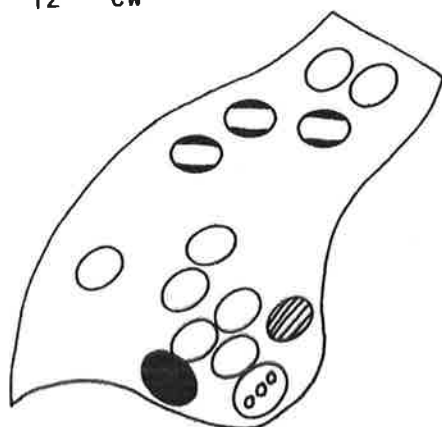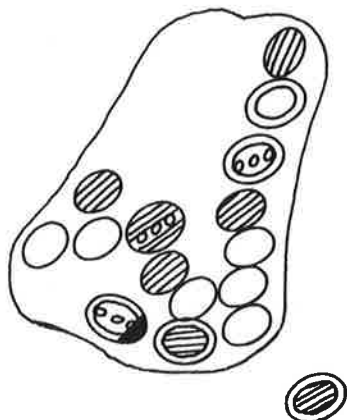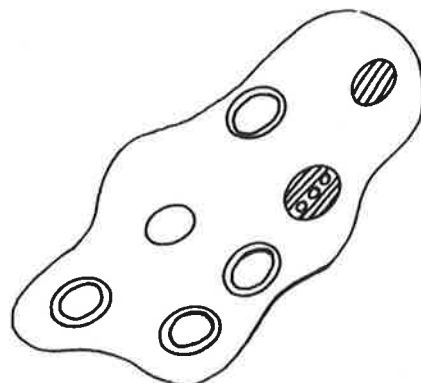
AXILLARY NODE PLOTS

17   LB   LEFT
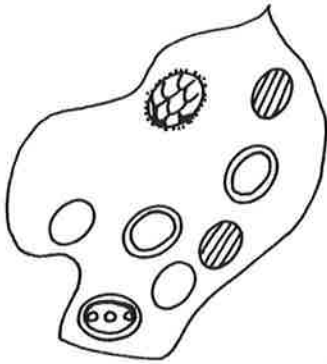
20   CP   RIGHT
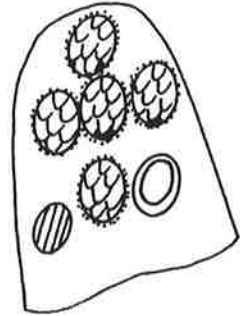
18   AH   LEFT
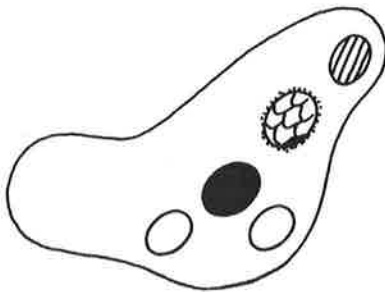
21   EE   RIGHT
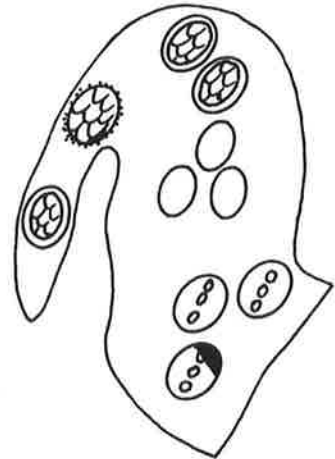
19   EW   LEFT
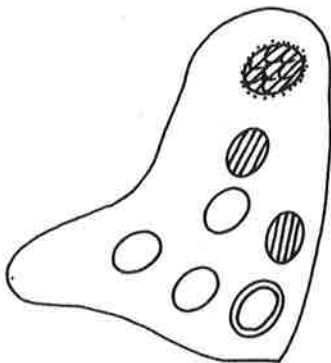
22   JL   RIGHT
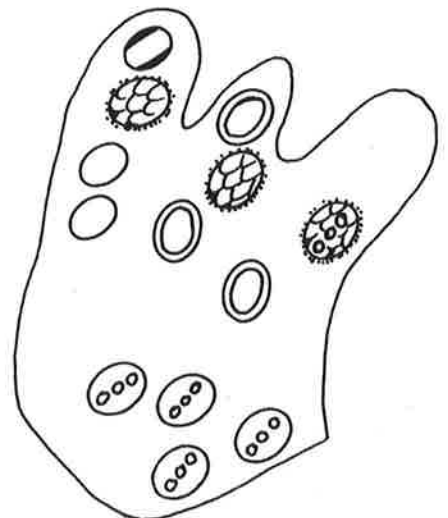
AXILLARY NODE PLOTS

23   DM   LEFT
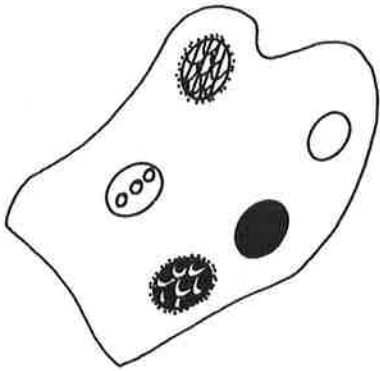
28   AH   LEFT
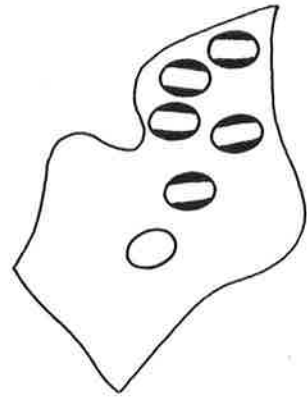
24   MB   RIGHT

30   AR   LEFT
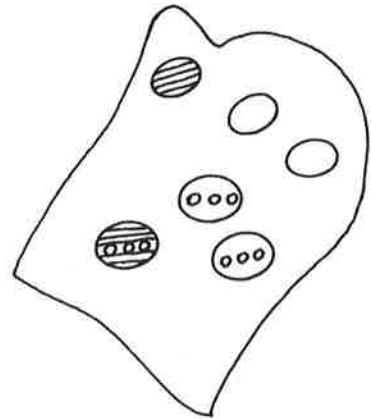
25   MN   RIGHT
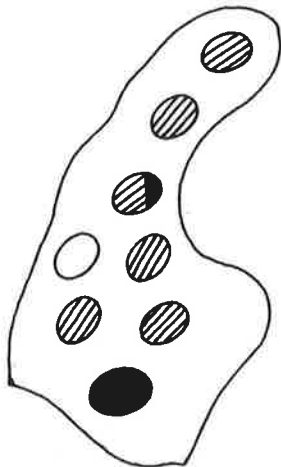
31   CMcF   LEFT
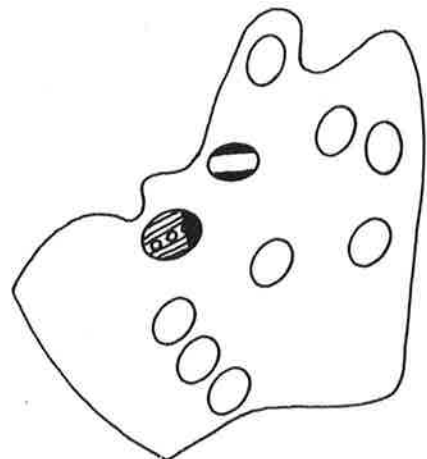
32   HM   RIGHT
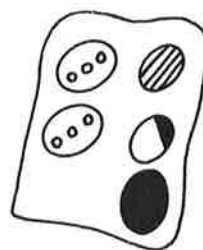
33   AB   LEFT
(Radical mastect-
omy)

34   DF   LEFT

35   ES   RIGHT
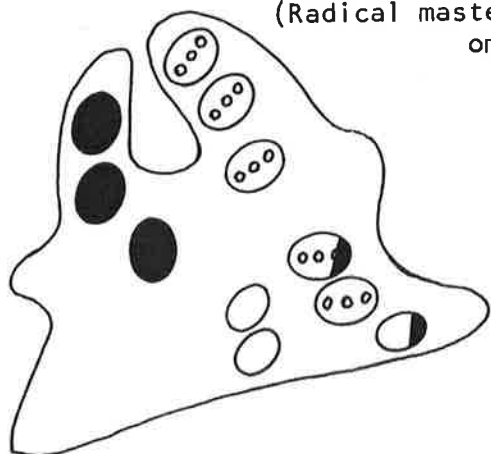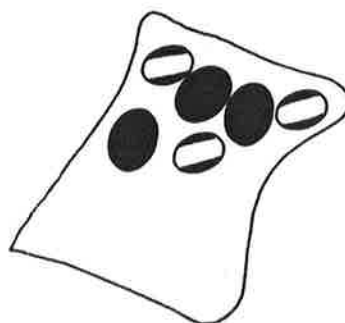
36   LM   LEFT

37   IL   RIGHT
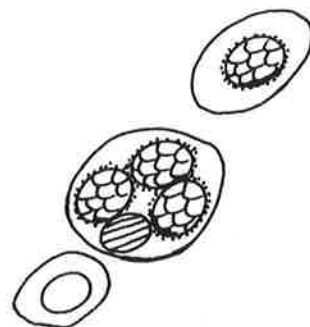
AXILLARY NODE PLOTS

38   NH   RIGHT
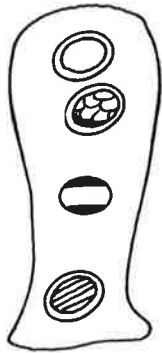
42   AB   LEFT
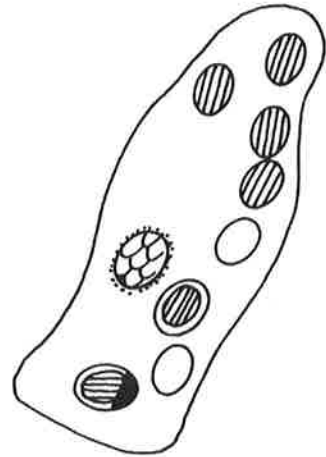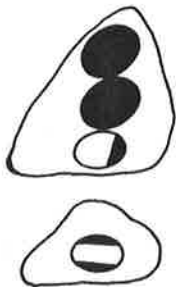
39   LC   RIGHT
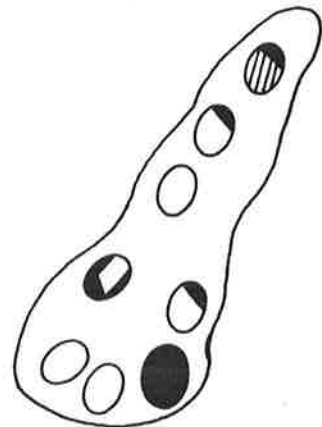
(NB   Uncertain which part was prox-
          imal)

43   CS   RIGHT

40   SA   RIGHT
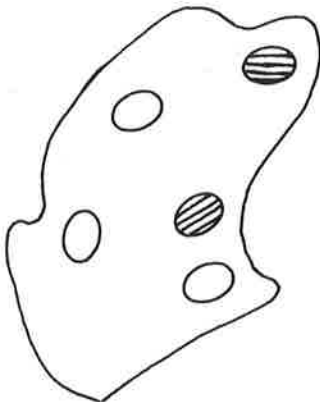
44   MA   LEFT

AXILLARY NODE PLOTS

45   JS   LEFT
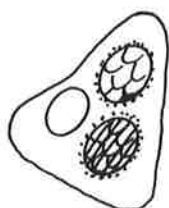
46   AMcL   LEFT

47   MS   LEFT

48   JB   LEFT
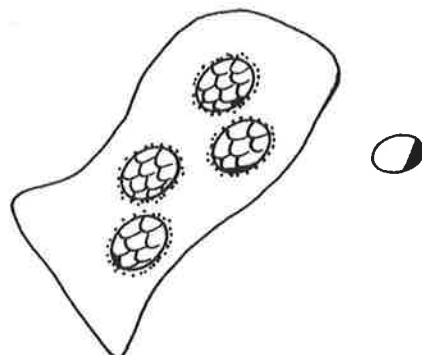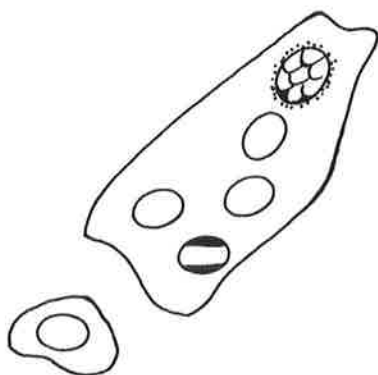
49   MM   LEFT
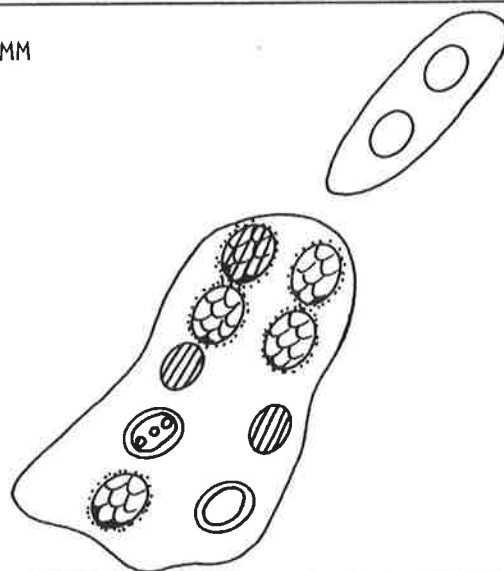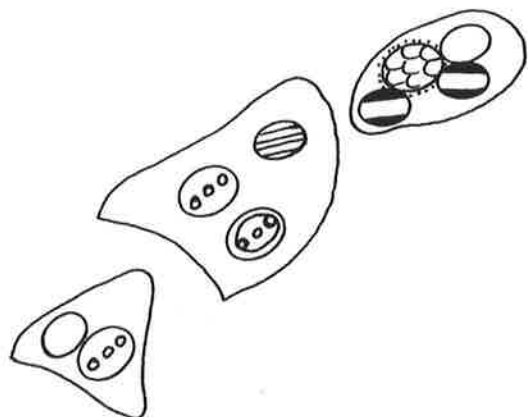
50   DC   LEFT
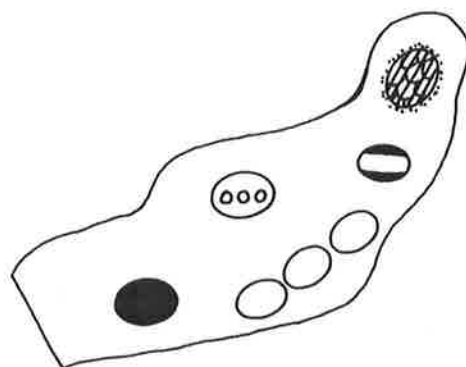
STATISTICAL ANALYSIS OF NODE SIZES

Significance (P) of differences comparing the median sizes of all categories of nodes with unstimulated nodes. *

NODE CATEGORY (Median size mass G/diameter cm)	MASS			DIAMETER		
	Wilcox on Rank Sum Test	Sign Test	Wilcox on Signed Rank Sum Test	Wilcox on Rank Sum Test	Sign Test	Wilcox on Signed Rank Sum Test
Metastatic nodes 0.45G/1.5 cm	< 0.01	< 0.01	ND	< 0.01	< 0.01	ND
Sinus histiocytosis 0.25G/1.0 cm	$0.05 < P^+$ < 0.10	< 0.05	< 0.05	$0.05 < P^+$ < 0.10	$0.05 < P$ < 0.10	> 0.10
Germinal centre predominance 0.55G/1.5 cm	< 0.01	< 0.01	ND	< 0.01	< 0.05	ND
Lymphocyte predominance 0.40G/1.5 cm	< 0.01	< 0.05	ND	< 0.01	< 0.01	ND
Fatty nodes 0.64G/1.5 cm	< 0.01	< 0.01	ND	< 0.01	< 0.01	ND

* Median size 0.11G/0.8 cm
ND = Test not done to confirm the other significant tests.
+ using alternate values, i.e. only half data, as Tables for this test have insufficient numbers.

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