STUDIES IN BREAST CANCER

With special reference to histological grading and treatment by simple mastectomy and radiotherapy

THESIS SUBMITTED FOR THE DEGREE OF

Ch.M.

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By

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SECTION/

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INTRODUCTION

Almost one hundred years ago the belief that cancer was from the beginning a constitutional disease was giving place to the view that it began as a local condition. The object of surgery ceased to be palliation and began to be cure.

The stimulus to surgical development was immense and indeed the modern concept of cancer surgery dates from that time.

In the surgery of cancer of the breast the evolution of the radical mastectomy took little more than 20 years. Its general adoption in the succeeding decades led to striking improvements in the results of treatment.

Gains have not ceased to be made in the treatment of breast cancer but they have become marginal gains and are obtained with increasing difficulty.

Twenty-five years ago the established radical mastectomy was replaced in Edinburgh as the basis of treatment by simple mastectomy and radiotherapy. At first this seemed to achieve a major gain.

As time has passed however numerous comparisons have been made between the results obtained in Edinburgh and those obtained in centres using radical mastectomy. In many cases the differences have been small and in consequence a great deal of controversy has surrounded and continues/

continues to surround the problem.

It has in fact become clear that such comparisons between different centres are incapable of demonstrating the relative merits of the two policies.

Some years ago it was suggested to me by Professor Sir John Bruce that more light might be shed on the problem by studying in detail a large group of the cases treated in Edinburgh.

The basic assumption of the policy adopted in Edinburgh is that radiotherapy is an effective means of dealing with local spread beyond the limits of the operation. This, it seemed to me, could well be tested by studying the internal evidence provided by our own cases. Central to this theme is the study of the pattern of local recurrence.

The results of treatment depend of course on many factors other than the treatment itself. In such a study these must be analysed to determine, where possible, their effect. Of these factors one of considerable importance which has not hitherto been studied in relation to the Edinburgh method is histological grading.

Since the differences between the two main methods of treatment are small in terms of results it becomes relevant to enquire into the relative cost in terms of morbidity. Without this the picture is incomplete. Again internal evidence provides one with a useful basis on which to assess this factor.

In/

In any study of this size and nature the opportunity is afforded of collecting data not strictly related to the central theme, but providing nevertheless material of ancillary interest. This opportunity has been taken and such data have been considered.

The material on which this study has been based consists of all the cases of carcinoma of the breast admitted to five surgical units in Edinburgh during a twelve year period from 1946 to 1957.

HISTORICAL NOTE

HISTORICAL NOTE

References to cancer of the breast and to its treatment are to be found recorded as far back as Egyptian papyri of the fourth millenium B.C. (Gordon-Taylor, 1948). Numerous records of surgical treatment appear in the medical literature of the Middle Ages and some of the operations described were quite extensive (Lewison, 1955).

It was mainly in their extent however, rather than in their concept that these early operations anticipated the treatment of today; and their extent was determined by the extent of the disease rather than by any general principle.

The beginnings of a rational approach can be found in the surgical writings of the eighteenth century. It had been observed, for example, that when enlarged axillary nodes were present early recurrence was the rule. The removal of such nodes was suggested at the beginning of the century (D'Arcy Power, 1934) and a monograph, dated 1746, by Angelo Nannoni describes an operation comparable with the present radical mastectomy (Mustacchi and Greco, 1961). Bell in Edinburgh advised the removal of axillary nodes and, with an insight far in advance of his time, stated "cancer, on its first appearance, is perhaps, in every instance, a local affection only.....the cancer diathesis is produced not by an original affection in the constitution but by absorption/

absorption from a local ulcer.....every cancerous sore should be removed by immediate amputation, wherever this can be practised." (Bell, 1785).

It was nearly a hundred years after Bell wrote these words that the constitutional theory of cancer was finally displaced. Astley Cooper in 1837 expressed the view that the constitutional nature of the disease would cause its recurrence "unless it be changed by a medical treatment," and prescribed various remedies for the after-treatment of patients operated on for cancer of the breast. But he nevertheless condemned the use of a separate incision to remove enlarged axillary nodes advising that if they were removed it should be in continuity with the breast tissue.

Even Sir James Paget, as late as 1853, upheld the old theory and concluded with a pessimism fully justified by his own carefully recorded experience of the condition, that one may "dismiss all hope that the operation will be a final remedy for the disease."

Then in 1867 the now well-known paper by C.H. Moore was published. Moore's description of the operative technique of mastectomy is generally regarded as the foundation on which the modern radical mastectomy was built. He advocated complete excision of the breast with wide margins of healthy tissue including a generous area of skin and, where necessary, of underlying muscle, removal of involved axillary/

axillary nodes en bloc and in continuity with the breast, and even anticipated modern wound chemotherapy in his use of a zinc chloride irrigation prior to closure.

Of far greater importance, however, than such matters of technique were the reasons which led Moore to adopt them. The title of his paper "On the Influence of Inadequate Operations on the Theory of Cancer" is significant. The paper itself is largely devoted to a study of local recurrence following surgery for breast cancer - surgery which ranged from local excision through segmental resection to mastectomy. From his observations he concluded that cancer was not a constitutional disease nor yet a disease process affecting a whole region, but a local condition which spread centrifugally from its point of origin. Consequently, he considered, local recurrence was due to inadequate surgery.

From this point onwards the history of the surgical treatment of breast cancer is that of the strivings to achieve this goal of adequate surgery - attempts now supported by the belief in the potential curability of the disease.

Moore himself had not gone so far as to recommend routine removal of the axillary contents whether invaded by tumour or not, but this was strongly advocated some years later by Mitchell Banks of Liverpool, an Edinburgh graduate (Banks, 1883).

Meanwhile/

Meanwhile, in America, William Halsted of Baltimore had begun to practise routine excision of pectoralis major in his mastectomies for breast cancer. This he was led to do on the basis of his own microscopic findings that the muscle was frequently involved even in early tumours. It appears that at first he removed the muscle after completing the dissection of the breast and axilla (Halsted, 1891) but from this evolved the full radical mastectomy (Halsted, 1895) essentially as practised today.

The new operation, as it was termed, was rapidly adopted. Meyer of New York, unaware of Halsted's work, evolved a similar procedure which he published in 1894. Watson Cheyne in London was claiming in 1896 even better results than those of Halsted. Stiles in Edinburgh, again on the basis of pathological studies, recommended the removal of both pectoral muscles (Stiles, 1899).

As the closing decades of the nineteenth century witnessed the perfecting of surgical techniques and their widespread adoption in the treatment of carcinoma of the breast, so also did they see the development of the means by which the effect could be measured. Statistical studies of the results of treatment began to appear towards the end of the century particularly from continental clinics. Volkmann has in fact been credited with presenting the first systematic/

systematic follow-up of treated cases in 1875 (Lane-Claypon, 1924). Earlier writers such as Paget, however, tabulated case records and survival times, suggesting that the importance of such data had already been recognized (Paget, 1853) and indeed the dawn of medical statistics dates back to the recording of mortality figures in the reign of Henry VIII (Benjamin, 1959). Paget as a matter of fact was able to demonstrate from his own figures that the treatment of his day had no effect on the expectation of life of a patient with breast cancer.

Many of these early series have been collected by Lane-Claypon. They form a useful yardstick against which later progress can be measured and also demonstrate the superiority of radical mastectomy. For less extensive operations the three-year survival rate was about 30-40 per cent excluding palliative procedures, while that for radical mastectomy was around 50 per cent. The operative mortality however was formidable ranging between 10 per cent and 15 per cent.

Within/

Within a year of Roentgen's discovery of X-rays in 1895 and closely following upon the evolution of radical surgery, attempts were made to utilize radiotherapy in the treatment of breast cancer. These initial attempts were purely empirical, for there was at first a tendency to try out the new weapon in almost any disease (Portmann, 1933). Within a very short time however treatment by X-rays was being seriously applied to malignant disease.

Few successes were reported in these early years but in spite of this Portmann relates that radiotherapy given post-operatively to supplement surgery in carcinoma of the breast was tried as early as 1901. There was little evidence of its value. Coley reporting in 1905 the use of X-rays in 36 cases of breast cancer recorded four in which they were used post-operatively. In each of these recurrence appeared within a few months. Rodman in his monograph on diseases of the breast published in 1908 stated that he had given up the practice, having observed cases in which the outcome appeared to have been adversely affected by radiotherapy.

Nevertheless post-operative radiotherapy continued to have its advocates. Fisher (1915) recommended, for example, a course beginning with a full erythema dose and continuing with treatments at increasing intervals of time over a period of three years. There were of course many modifications of this, varying from a single massive dose, through/

through fractionated doses over a limited period such as Pfhaler's "Saturation method" (Pfhaler, 1926) to extended courses like Fisher's. Improvements in technique, the development of dosimetry into a more exact science and the construction of more reliable and powerful apparatus were accompanied by better results.

Radiotherapy became established in the treatment of advanced and recurrent cases and was even advocated as an alternative to surgery in operable cases. Soiland quoted Lord Moynihan's remarkable statement in 1929 that he had not used surgery for removal of a breast in over a year and doubted if he would ever have to revert to it again (Soiland, 1930). But the doubts as to its value as a supplementary measure to surgery remained. Knox remarked that "many experienced surgeons" held the view that it was of value, but he added "there is urgent need, however, of numerical proof of this fact". This was in 1932.

In the early years treatment by X-rays was directed mainly at the chest wall and the axilla. Later some, in an attempt to cover as many areas of potential tumour spread as possible, extended the irradiated area to include the neck, the opposite chest wall and even the spine (Roberts, 1936). The application of X-rays to the internal mammary nodes seems to have received little attention - partly because of a failure to appreciate the importance of this route of spread/

spread and partly because of the fear of irradiation damage to the underlying lung. Indeed even as late as 1950 this area was not universally irradiated. Pohle (1950) recommended a wide area of irradiation which included the internal mammary nodes as well as the chest wall, the upper abdomen and the supraclavicular region. But Portmann confined his routine irradiation to neck and axilla (Portmann, 1950) while Paterson treated only the chest wall, using glancing fields, and the axilla (Paterson, 1948).

Many years before this, however, two significant advances in the radiotherapy of breast cancer had taken place.

Radium was discovered by the Curies only three years after Roentgen's discovery of X-rays, but, being much less readily obtainable, its entry into the clinical field was a much slower process. When it was developed as a therapeutic agent, however, it was soon realized that it had advantages over X-rays in certain situations. Indeed it remained supreme in these fields for many years. Although today radium has virtually no place in the treatment of breast cancer it played a notable part in the establishment of radiotherapy as a concomitant to surgery.

In 1927 Sampson Handley reported an 80 per cent three-year survival rate in cases treated by radical mastectomy supplemented by the implantation of radium needles into the anterior/

anterior intercostal spaces. His earlier researches into the spread of breast cancer had led him to formulate his permeation theory of lymphatic dissemination (Handley, 1904). He considered that there was no significant lymph drainage from the breast to the internal mammary nodes in normal circumstances but that retrograde spread to these nodes occurred and was seen sufficiently often after radical mastectomy to warrant prophylactic treatment (Handley, 1922). Radium offered the most convenient means of achieving this.

The following year, 1928, Geoffrey Keynes reported the first results of an attempt to carry the use of radium in breast cancer to its logical conclusion. Encouraged by its effectiveness in other regions such as the mouth where it was tending to supersede surgery altogether, Keynes sought to determine whether radium might do likewise in the breast. The severity and mutilating effect of radical mastectomy seems to have played a not insignificant part in this decision.

Keynes' technique, which he gives in full detail in a later paper (Keynes, 1932) consisted of the insertion of radium needles deep to the tumour, in the surrounding breast, and in the lymphatic fields of drainage - axillary, infraclavicular, supraclavicular and internal mammary. Unless the tumour was small and the diagnosis certain he later recommended that a local excision should be carried out/

out or, if it was very bulky, a simple mastectomy (Keynes, 1937). In 1937 Keynes published his long-term results and these compared favourably with those obtained by surgery alone. As a standard of comparison he took Jessop's figures from University College Hospital, London, (Jessop, 1936). This contemporary series had in fact been collected with a view to establishing such a standard. Only one of the 217 cases had been lost sight of and although patients dying of other causes were excluded these were very few in number. The staging was initially clinical but corrected in the light of pathological findings. The staging in Keynes' cases was of course clinical, placing them at a disadvantage in comparisons based on stage.

The results of the two series are compared in Table 1.

Keynes did not advocate that radium ought to supplant surgery altogether but rather that it should be used in conjunction with less extensive surgery. He himself considered that axillary dissection might be a contributing factor in the dissemination of the disease.

Keynes' observations also led him to discard Handley's permeation theory and in this he was undoubtedly influenced by the researches into the lymphatic system carried out by Gray at his own hospital - St. Bartholomew's (Gray, 1936, 1939).

Established/

TABLE 1

	Radium + Minimal Surgery (Keynes, 1937) %	Radical Surgery Alone (Jessop, 1936) %
3-year Survival Rate		
Stage I	83.5	79.2
Stage II	51.2	52.3
Overall	67.0	64.9
5-year Survival Rate		
Stage I	71.4	69.1
Stage II	29.3	30.5
Overall	51.8	48.0

COMPARISON BETWEEN THE RESULTS OBTAINED IN CARCINOMA OF THE BREAST TREATED BY RADICAL SURGERY AND THOSE OBTAINED BY USE OF RADIUM WITH MINIMAL SURGERY

Established by 40 years' experience as the most satisfactory treatment for operable carcinoma of the breast, radical mastectomy was now challenged.

Most were not prepared to go as far as Keynes had gone, but now the possibility remained to be reckoned with that radiotherapy might be as effective as or even more effective than surgery in the treatment of the areas of lymphatic drainage.

In Edinburgh in 1935 dissatisfaction with the results of radical surgery alone led to the use of irradiation following radical mastectomy. The results in the ensuing five years showed an appreciable improvement both in terms of local recurrence rate which fell from 39 per cent to 14 per cent and in the five-year survival rate which in operable cases rose from 36 per cent to 44 per cent (McWhirter, 1948 a).

McWhirter, sharing Keynes' view that radiotherapy could deal effectively with tumour in the lymph nodes draining the breast and that axillary dissection might promote dissemination of tumour cells, now suggested that the combination of simple mastectomy and radiotherapy was a method of treatment worthy of trial.

In 1940 a policy was adopted in which simple mastectomy and radiotherapy replaced radical mastectomy as the/

the mainstay of treatment in carcinoma of the breast. This proved acceptable to the majority of surgeons in the South-east of Scotland and has continued to be followed since that time.

The early results published by McWhirter in 1948 (McWhirter, 1948a) showed a further improvement on those already achieved by radical mastectomy followed by radio-therapy and this was maintained in the large series published in 1955 (McWhirter, 1955).

So far as surgery was concerned the wheel had turned full circle. The early operations long condemned as inadequate, and long superseded by the carefully designed radical mastectomy based on pathological principles, had returned. The radical approach remained, however. Beyond the limits of the breast the knife was replaced by the X-ray and indeed the latter was applied to regions outwith the accepted scope of the knife.

From the beginning the Edinburgh method was the subject of heated controversy. Sir Gordon Gordon-Taylor, for example, said in 1948, "Unfortunately recommendations are nowadays finding their way into the literature which as far as the incompleteness of radical mastectomy is concerned take us back to the procedures of Scultetus and others of the Dark and Middle Ages".

In/

In the late 1930's the concept of the controlled clinical trial had yet to gain general acceptance, and although it was suggested at the time it was not felt to be appropriate to conduct one. For this reason, perhaps more than any other, the controversy has persisted.

SECTION I

MATERIALS AND METHODS

MATERIALS AND METHODS

A few cases of primary carcinoma of the breast are not referred to hospital. A few are referred direct to a radiotherapy department or are seen in medical wards. The great majority are referred primarily to surgical units. The total experience of a group of surgical units over a given period of time therefore approximates closely to the complete spectrum of primary breast carcinoma.

Source of the Case Material

The surgical units chosen for this study were three general surgical units in the Edinburgh Royal Infirmary (the two Professorial Units and one Non-professorial Unit) and the general surgical units at two other Edinburgh hospitals - the Western General Hospital and the Deaconess Hospital. This group of units was selected as representative of those in which carcinoma of the breast is treated according to the Edinburgh policy.

Period covered by Study

The period of time covered was from 1st January 1946 to 31st December 1957, the inclusion of cases being determined by the date of first treatment.

In 1960-61 a smaller, pilot study comprising 496 cases was undertaken and covered the period 1946 to 1955, thus giving/

giving a five-year follow-up for all cases and a ten-year follow-up for those in the first quinquennium. When the present study was commenced it was decided to extend the follow-up period to the end of 1962. As a result it includes a small group of cases with a fifteen-year follow-up.

Case Material

This study is concerned with primary and previously untreated carcinoma of the breast.

During the selected period 1039 cases of breast carcinoma were admitted to the five units.

Of these cases 163 were discarded having been admitted with recurrence of previously treated disease or having had their primary treatment elsewhere. Up to the beginning of 1956 when the Radiotherapy Unit at the Western General Hospital was opened, many of these cases were those admitted for radiotherapy following primary surgical treatment at one of the peripheral hospitals in the region.

Re-admissions either to the original unit or to any one of the five units are not included in the total.

The cases of primary and previously untreated breast carcinoma on which this study is based therefore totals 876.

These/

These were distributed between the different units as follows:

Royal Infirmary, Wards 7 and 8	120 cases
Royal Infirmary, Wards 13 and 14	199 cases
Royal Infirmary, Wards 17 and 18	265 cases
Western General Hospital	154 cases
Deaconess Hospital	138 cases
Total	876 cases

Completeness of Cover

To ensure that the series was as representative as possible considerable efforts were made to ensure coverage of all cases admitted. Wherever possible the sources of information regarding the admission of cases of carcinoma of the breast were double-checked.

In the case of the Royal Infirmary units both a hospital and a unit disease index existed, and in some cases this was supplemented by ward registers. In the Western General Hospital the hospital disease index was checked by a study of the ward registers. In the Deaconess Hospital the admission register was used.

As a result of using these techniques it seems likely that the coverage of patients admitted with carcinoma of the breast must be very close to 100%.

Records/

Records

Forty-six cases in the series (5%) were not referred at any time to the Radiotherapy Department. In the remaining 830 cases, records from both sources were consulted in every instance where such records were available, and this proved to be the case with very few exceptions. After careful search only 28 case records from the surgical units were found to be missing. Two Radiotherapy case records were not found.

There was no case in which no records at all could be found. There were of course many from which certain data were absent, but, taking both records in conjunction, as was usually possible, such gaps in the information obtained were few. These, where relevant, will be specified in the analysis of the data.

The value of data collected in a retrospective study of this type has often been criticized. In most cases this criticism is just. Breast cancer is however almost unique in this respect. Not only is its diagnosis one which tends to be registered and indexed accurately but the clinical features, at least of the primary tumour, are so well defined that they have been found to be recorded with tolerable accuracy and uniformity. The condition indeed tends to be over-recorded so that many case records were examined in which only a simple tumour had been found. These are not of course included in the totals given above.

Abstraction/

Abstraction of Data from Records

The analysis of the data obtained from the pilot study revealed certain deficiencies in classification, and suggested certain other investigations which had not been included originally. The plan of the study was therefore revised and the original case material reviewed afresh.

The data required (with the exception of that relating to histological grading) were abstracted from the case records and recorded on special three-page forms (Plates I-III). Further details are given under the relevant subject headings in the analysis of the data.

Certain additional matter was also recorded on the forms. This was as follows:

1. Age at menopause - in cases at or past the menopause.
2. Explanatory notes - (i) indicating reasons for assigning the given Columbia Stage where this was not apparent from the Manchester Staging.
   (ii) reasons for listing surgical or radiotherapy morbidity as severe.
3. Dates of secondary treatments.
4. Site of first metastasis.
5. Note of cases developing a massive ulcerative chest wall recurrence.

The/

DEPARTMENT OF CLINICAL SURGERY

BREAST CANCER SURVEY

1946 - 1962

UNIT NO. ..... UNIT .....

NAME .....

OPERATING SURGEON .....

		Code
Sex M/F	M	A
Age	under 35	B
	36–40	C
	41–45	D
	46–50	E
	51–55	F
	56–60	G
	61–65	H
	over 65	I
Menopause Before. After. At. Pregnant.	Before	J
	At	K
	Pregnant	L
	Unknown	M
Side R. L. Both.	Right	N
	Both	O
Size (cm)	2 cm or under	P
	Over 2 cm up to 5 cm	Q
	Over 5 cm up to 10 cm	R
	Over 10 cm	S
Site Upper Outer. Upper Inner.	UO	T
Lower Outer. Lower Inner.	UI	UV
Central. Diffuse.	LO	W
	LI	X
	C	YZ
	D	A
	Not stated	E

Stage

Manchester				
Clinician	Radiotherapist	Columbia		
I	I	A	R/T Stage I	I
II	II	B	(If R/T stage not recorded	II 0
III	III	C	ring Clinician's stage.	III U
IVL	IVL	D	Unstaged left unrecorded)	IVL 39
IVD	IVD			IVD 38
			No difference between clinician and R/T	37
			Difference between clinician and R/T	36
			Columbia Stage A	35
			B	34
			C	33
			D	32
Reference to R/T Dept. YES/NO.			Not referred	31

Plate I

First Page of the Abstract Form Used

Treatment Primary Nil R.T.P. Primary Treatment Code
B R.T.R. S 30
S Ho S + RTR 29
S + G Ha ORT 28
S + M Hs
S + M + G O.R.T.
R Other (specify)
Unknown

Secondary Date Date Secondary Treatment 27
EM A
RTM O
Ho ORT
Ha P
Hs Other (specify)

Morbidity Delay Operation to R/T 15 days or over 15 days or over 26
22 days or over (incl. over 22 days)
No. of days if 15 or over 22 days or over 25
Delay due to wound YES/NO Due to wound 24

Surgical Morbidity Nil to moderate Surgical Morbidity
Severe Severe 23
(specify) Relevant but unknown 22

Radiotherapy Morbidity Nil to moderate Radiotherapy Morbidity
Severe Severe 21
(specify) Relevant but unknown 20

Oedema of arm YES/NO/NOT KNOWN Oedema of arm 19
Time of onset after reference date
.....years

Metastases
Axillary Axillary 18
Supraclavicular Supraclavicular 17
Chest wall Chest wall 16
Other (specify)
Date of first evidence of metastasis

Cause of Death (where known to be other than cancer of breast)
Post-operative Cause of death
Intercurrent disease other than 15
Other (specify) breast cancer

Follow-up
Reference date
(Date of operation, 1953 - 1957 cases -
start of R/T etc. 1948 - 1952 cases 14
whichever first.) 1946 - 1947 cases 13

5 year state	10 year state	15 year state			
A	A	A	5 yrs.	A	12
AM	AM	AM		AM	11
D	D	D		untraced	10
Untraced	Untraced (but 10 yr. follow-up possible)	Untraced (but 15 yr. follow-up possible)	10 yrs.	A	9
				AM	8
				untraced (1946-1952 cases only)	7
			15 yrs.	A	6
				AM	5
				untraced (1946-1947 cases only)	4

Date of Death

Survival

Plate II

Second Page of the Abstract Form Used

Pathology **Pathological Diagnosis**

Adenocarcinoma	Ad
Intraduct carcinoma	I
Medullary carcinoma	M
Colloid carcinoma	C
Carcinoma unspecified	U
Spheroidal carcinoma	Sph
Scirrhous carcinoma	Sc
Anaplastic	An
Other	O
Specify -	

Pathological Ref. No.

Histological Grade (Specific group only)

I	Grade II	3
II	III	2
III	Not graded	1

In specific group but not graded - slides unavailable
- slides unsatisfactory
- other (specify)

Gross appearance of section:

	Cut off
circumscribed	circumscribed - Top left corner.
irregular	irregular - Bottom left corner.
borderline	not specified - Bottom right corner.
slide unavailable	
slide unsatisfactory	

Plate III

Third Page of the Abstract Form Used

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DEPARTMENT OF CLINICAL SURGERY

FOLLOW-UP OF BREAST CANCER

NAME [ ] UNIT NO. [ ]

AGE (at diagnosis) [ ] Relation to Menopause before [ ] after [ ]

Clinical Stage of Tumour (Manchester System) [ ] R.T. Stage of Tumour (Manchester System) [ ]

Right or Left [ ] Surgeon [ ]

If not referred to R.T. place X here [ ] Days from operation to start of R.T. [ ]

if more than 14 state reason for delay:-

. . . . . .

Biopsy [ ] Simple [ ] Radical [ ]

Hormone Therapy [ ] Adrenalectomy [ ] Give details

Morbidity from Surgery – nil [ ] slight [ ] severe [ ]

Morbidity from R.T. – nil [ ] slight [ ] severe [ ]

Pathology of Tumour [ ] Path. Ref. No. [ ]

Date of operation or start of R.T., whichever earlier [ ] Site of Metastases – axilla [ ] chest wall [ ] others [ ]

5 year day [ ] Alive [ ] Alive with metastases [ ] Dead [ ]

10 year day [ ] Alive [ ] Alive with metastases [ ] Dead [ ]

Plate IV

Abstract Form Used in the Pilot Study

The data were coded in the right-hand column and transferred to punch cards.

The extent of the revisions suggested by the pilot study can be seen by comparing the abstract form used (Plate IV) with those of the present study.

Follow-up

Out of the 876 cases studied, follow-up to the date of death or to the end of 1962 was obtained in 873. In 839 cases this information was obtained from the case records and in the majority of these from the records of the Radiotherapy Department. Indeed without access to these records kindly granted by Professor R. McWhirter this study would not have been possible.

Follow-up in the remaining 34 cases was through the family doctor, the National Health Service Executive Councils and the Office of the Registrar-General. Precise dates of death or the month and year of death were obtained from these sources in the majority of cases. In two cases, only the year of death was given and previous comparison between such cases and the date given on the death certificate has shown that this may be inaccurate.

Three cases (0.3%) were lost to follow-up. Two of these were lost sight of shortly after their initial treatment. They were aged 62 and 67 respectively. The former was a Stage IV case who received no treatment and the latter/

latter a Stage I case treated by simple mastectomy only.

The remaining case was a 39-year-old woman in Stage IV who was treated by simple mastectomy and radiotherapy. She was alive four years and two months later but moved out of the district thereafter and was lost sight of.

All these cases are assumed to have died of carcinoma of the breast within five years of treatment.

Pathological Material

Histological sections of the primary tumour were made in 774 cases. Forty-one of these were unobtainable but the remainder, provided by the Pathology Departments of the University of Edinburgh, the Royal Infirmary of Edinburgh and the Western General Hospital, were available for grading.

Statistical Methods

Standard tests of statistical significance were applied to the tables in this study. These were carried out by the statistical staff of the Department of Public Health and are given in tabular form in Appendix 1. The use of terms such as "statistically significant" in the text refer to these tests.

Certain tables are given in abbreviated form in the text for the sake of clarity. The full versions are given in the appendices.

Age-corrected rates and rates calculated on an actuarial basis are used in certain cases. Details of these calculations are also to be found in the appendices.

Staging/

Staging

A preliminary note on the staging used is necessary at this point. The subject will however be dealt with at length in a later section.

All cases are staged according to the Manchester System which was in use in Edinburgh at the time although it has since been superseded by the International System. As will be explained later the definitive stage assigned to the case is that given by the radiotherapist. Where this is not known the staging is based on the data in the records.

In reporting cases treated in Edinburgh, McWhirter, to whose publications frequent reference will be made, also classified cases as "Operable", "Locally Advanced" and "Inoperable".

The "Operable" category comprises Manchester Stages I and II. The "Inoperable" category comprises those cases in Stage IV who had distant metastases. The "Locally Advanced" category covers the remainder, that is, Stage III plus those cases in Stage IV with locally advanced disease, including supraclavicular metastases, but without distant metastases. This classification in effect divides Stage IV into two subdivisions - cases with local disease and cases with distant metastases. These subdivisions I have termed Stages IVL and IVD respectively and have classified all cases accordingly. This permits the use of any combination of stages which a particular problem may require.

SECTION II

BASIC FACTORS IN BREAST CANCER

BASIC FACTORS IN BREAST CANCER

Introduction

In the sense that the patients studied represent the total experience of each surgical unit with respect to primary breast carcinoma, this series is unselected.

It is numerically large enough to reflect, at least for the given locality, Edinburgh, the basic pattern of the disease as it presents in surgical practice. The analysis of its attributes and their individual effect on prognosis therefore provides the background against which the more detailed studies are presented and serves to bring out any deviations from the known pattern which might affect the interpretation of these studies. It also provides material, as mentioned earlier, for certain subsidiary studies of interest.

These attributes fall into two groups, those concerned with the patient as a whole and those concerned particularly with the tumour.

The first group is represented by sex, age and menstrual status, the second by side affected, tumour size and site, and clinical stage. A further attribute of the tumour, histological grading, will be dealt with in detail in a separate section.

PATIENT ATTRIBUTES

Sex

Carcinoma of the male breast accounts for about one per cent of all breast cancers, the precise figure varying in different series, for example, Harnett (1948) 1.07%, Nohrman (1949) 0.9%, McWhirter (1955) 0.6% and United Birmingham Hospitals series (1957) 0.7%.

The low incidence is generally regarded as an indication of the lack of hormonal stimulation to which the male breast is subjected, for animal experiments such as those of Lacassagne (1932), have shown that carcinoma can be induced in the male mouse breast by the administration of oestrogens. Nevertheless it has been suggested that if the chance of tumour formation is proportional to the number of epithelial cells at risk the incidence of 1 in 100 is in fact quite high.

Prognosis in male cases of carcinoma of the breast is generally considered to be poorer than in female cases. This has been attributed to a tendency for breast tumours in the male to be overlooked and to the fact that the small size of the male breast results in early infiltration of the surrounding tissue.

Treves and Holleb reporting one of the largest published series in 1955 found an average age of 52 and an overall/

overall five-year survival rate of 29%. The same rate was found by McWhirter (1957) in the operable and locally advanced groups combined (50% in the former and 18% in the latter). The survival rate in the Birmingham series is 48% and in a Mayo Clinic series (Berkson et al., 1957) 41% for cases treated from 1910-41 and 60% for cases treated from 1941-50. The Mayo Clinic figures refer to cases treated by radical mastectomy only.

The variation in results is to some extent associated with the small size of the individual series, but the low level of overall survival rates appears to be due mainly to the high proportion of cases which are advanced when first seen.

There were only four male cases in the present series (0.5%). The important facts of each case are tabulated in Table 2.

The number of cases is of course too small to draw from them any useful conclusions except perhaps to note that all the cases were above the average age found by Treves and Holleb, and that fairly long survival times were achieved in the two early cases. Of particular interest is the survival of Case 1 in whom there were palpable axillary nodes but whose primary treatment was simple mastectomy alone. This patient developed skeletal metastases within a year of primary/

TABLE 2

Case	Age	Clinical Stage	Primary Treatment	Survival
1	55	II	Simple Mastectomy	Alive at 7 yrs. 10 mths. but with metastases.
2	63	IV	Simple Mastectomy + Radiotherapy	1 yr. 2 mths.
3	65	I	Simple Mastectomy + Radiotherapy	7 yrs. 7 mths.
4	88	IV	Simple Mastectomy	4 days

MALE CASES

primary treatment and has had a prolonged remission following bilateral orchidectomy and oestrogen therapy.

Age

Age can be related to the history of the disease in three ways - age at clinical onset, age at time of first treatment (or referral for treatment) and age at death.

Of these, age at clinical onset corresponds most nearly to the age at the actual onset of the disease though the relationship is indeterminate. Defective memory and sometimes subconscious or deliberate falsification make this an inaccurate yardstick.

Both age at the commencement of treatment and age at death have the advantage of being determinable with precision. The latter, the only measure available in mortality statistics, is of little value in determining aetiological or prognostic relationships. The former however is more closely related to the onset and, preceding treatment, can be used as a yardstick to measure its results. It probably represents the best compromise.

Age at the commencement of the first treatment or at the date of decision not to treat is therefore used in this study, as indeed in most studies of the results of treatment, as the definitive age of the patient.

The/

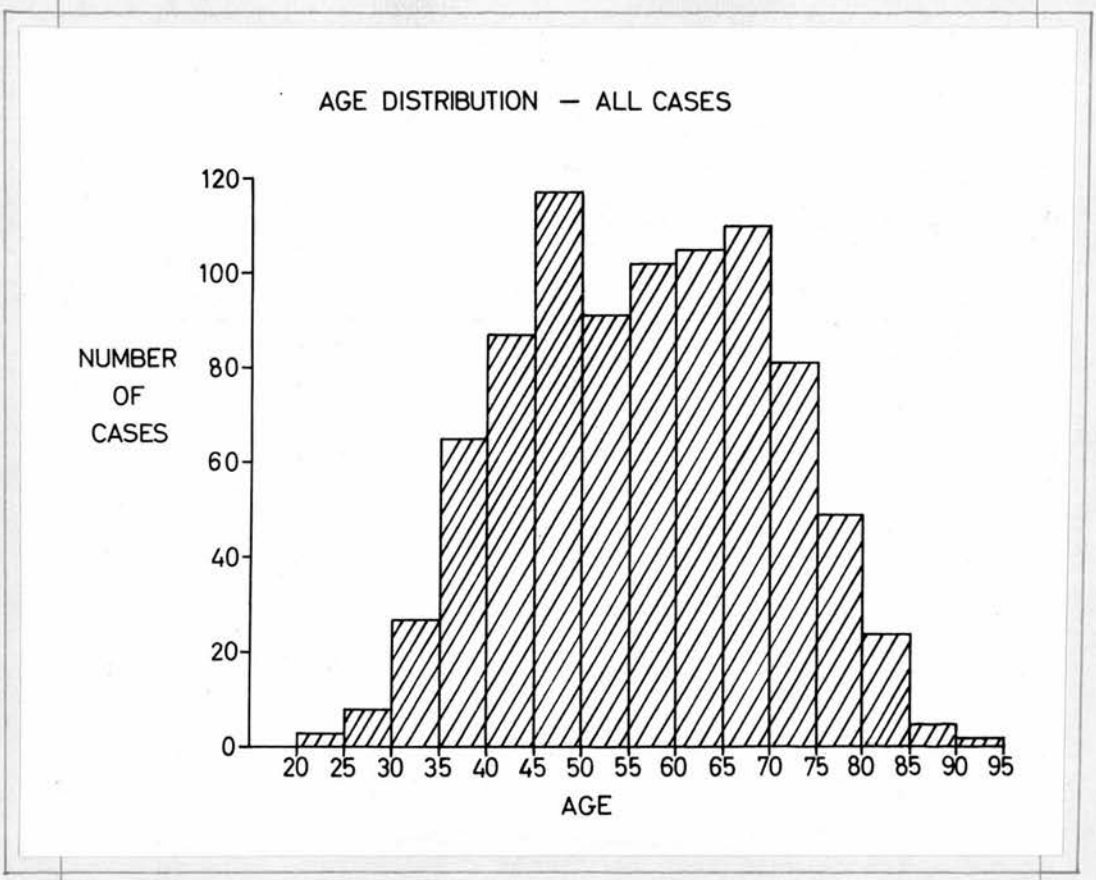
AGE DISTRIBUTION — ALL CASES
NUMBER OF CASES
120
100
80
60
40
20
0
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95
AGE

Figure 1

The patient's age at the time of first treatment was known in all cases. The distribution of the various age groups is shown in Table 3 and Figure 1. The youngest patient was 22 and the oldest 92.

The distribution takes the form of a bimodal curve with peaks at ages 46-50 and 61-70. Bonser et al. (1961) who also observed this type of distribution considered that it could be explained in terms of the relation between carcinoma and cystic disease. The first peak appeared to be due to cases occurring in association with cystic disease and second to those without cystic disease together with a number of cases in whom a long latent period between the development of cystic disease and the tumour was believed to exist. Their peaks were at 40-49 and 60-64 respectively.

Harnett (1948) found two less well-defined peaks at 50-54 and 60-64, while Denoix's series of over 5,000 cases showed bimodal curves only for cases with and without axillary nodes considered separately. The combined figures showed only a single peak (Denoix, 1958). In fact many series including some of considerable size show only a single peak. This occurs at 40-49 in Haagensen's (1956) series, at 45-54 in the series of Williams et al. (1953), at 45-49 in the Mayo Clinic series reported by Berkson et al. (1957) and at 50-54 in Allen and Rigler's (1962) series. The close relation/

TABLE 3

Age	Number of cases	% in age group
21 - 25	3	0.3
26 - 30	8	0.9
31 - 35	27	3.1
36 - 40	65	7.4
41 - 45	87	9.9
46 - 50	117	13.4
51 - 55	91	10.4
56 - 60	102	11.6
61 - 65	105	12.0
66 - 70	110	12.6
71 - 75	81	9.3
76 - 80	49	5.6
81 - 85	24	2.7
86 - 90	5	0.6
91 - 95	2	0.2
	876	

AGE DISTRIBUTION (WHOLE SERIES)

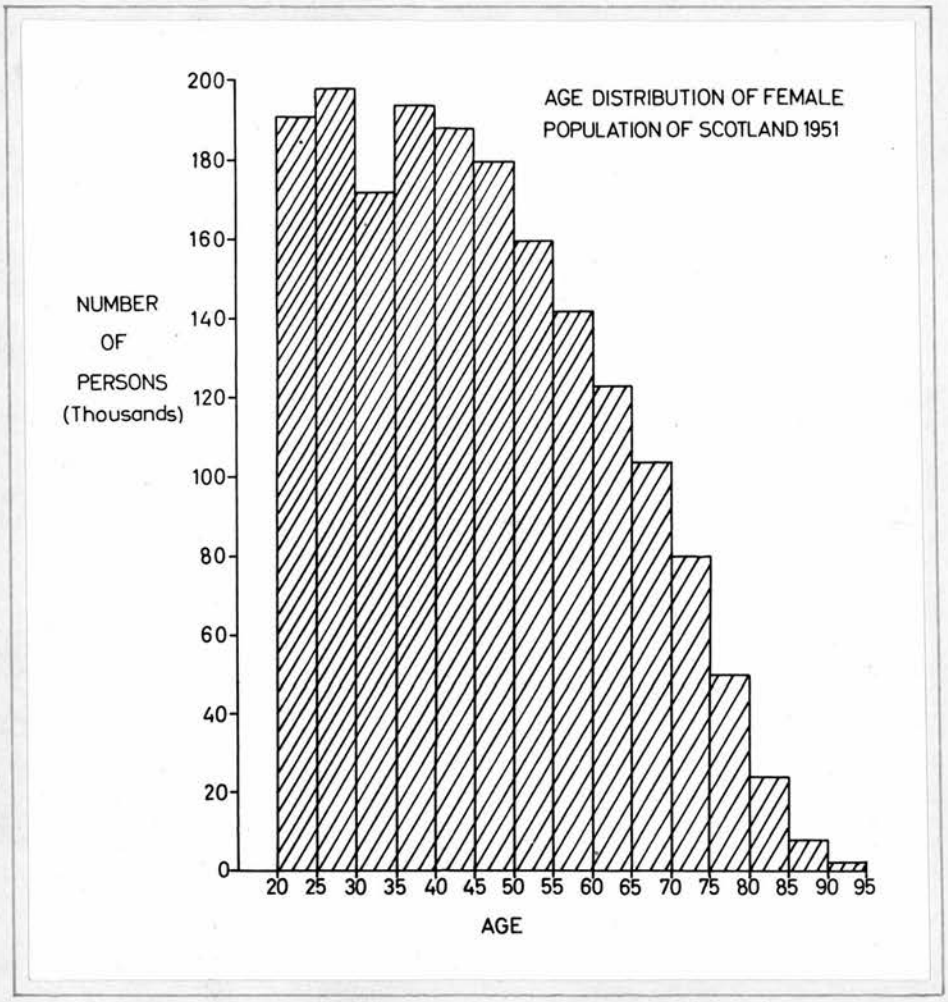
AGE DISTRIBUTION OF FEMALE
POPULATION OF SCOTLAND 1951
NUMBER
OF
PERSONS
(Thousands)
200
180
160
140
120
100
80
60
40
20
0
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95
AGE

Figure 2

relation between these peaks and the menopause is obvious. It may be that the double peak is an artifact.

The peak age of incidence of patients referred to a hospital is not of course necessarily a reflection of the age incidence of the disease in the population, for it takes no account of the number of women alive at each age. This figure can be obtained from the Census Tables and is shown for the 1951 Census (the one appropriate to this study) in histogram form in Figure 2.

By converting the incidence in the present series to a rate (per 100,000 of the population in the specific age group) the age-specific incidence of breast carcinoma as represented by this series is obtained (Figure 3). (For details of the calculations, see Appendix 1, Table 63).

Apart from a fall in the 50-55 age group the incidence rises steadily till the 65-70 quinquennium is reached and thereafter remains approximately constant till after the age of 85. As there were only seven cases between 85 and 95 the estimation becomes very unreliable at this point.

It is thus evident that the true incidence of breast carcinoma is not maximal at the menopause but at a much later age.

There is however a well marked irregularity in the curve between 45 and 55 years of age. This may be seen either/

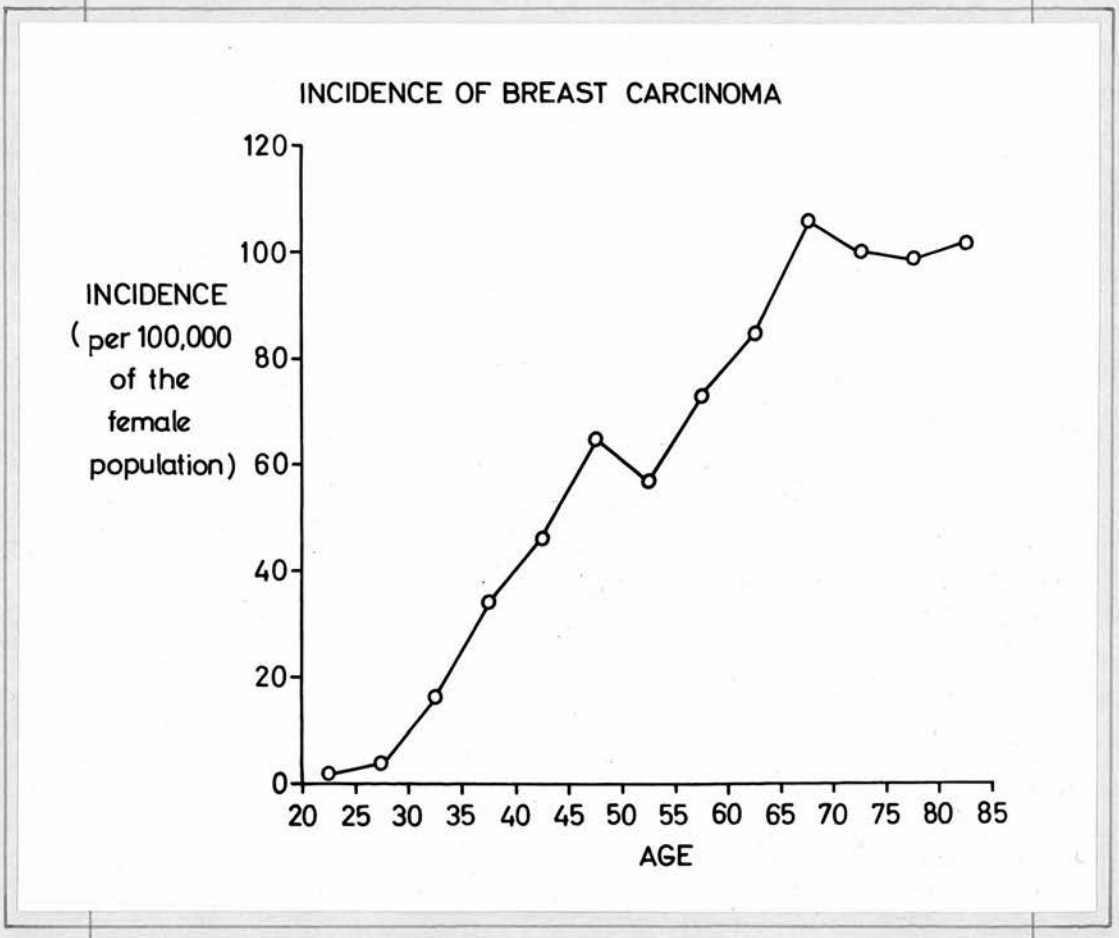
INCIDENCE OF BREAST CARCINOMA
INCIDENCE
(per 100,000
of the
female
population)
120
100
80
60
40
20
0
20 25 30 35 40 45 50 55 60 65 70 75 80 85
AGE

Figure 3

either as a relative increase in the incidence in 45-50 quinquennium or a relative decrease between 50 and 55. The general shape of the curve favours the latter interpretation.

This feature, which is the counterpart of the bimodal curve already mentioned, is a well-known feature of the incidence of breast carcinoma. Clemmesen (1948) who demonstrated it in a large series obtained from the Danish Cancer Registry found it to be statistically significant, although MacMahon (1957) considers it to be an artifact. Smithers (1952) sees in it evidence of a protective effect of the natural menopause.

Age and Prognosis

Conflicting views have been put forward with regard to age as a prognostic factor in carcinoma of the breast. Nohrman (1949) found prognosis to be relatively poor in patients under the age of 30, relatively good from 31 to 40 and poor again over 70. The intervening period 41-70, during which it was steady, was taken as the reference point. Smithers et al. (1952) found a maximal survival rate in the age group 41-50. Moore et al. (1958) in their series from Middletown, U.S.A. showed a similar peak but also found a higher rate of survival in the 60-70 age group. Taylor and Wallace (1947) found a rising survival rate with increasing/

increasing age, while McWhirter (1957) found a falling rate. Kaae (1952) concluded that such differences as his series showed were not significant.

Amongst the factors contributing to this confused picture are small numbers in the specified age groups, differences in stage distribution in the different age groups and of course the decreased life-expectancy of the older age groups.

Brinkley and Haybittle (1959) showed that in their series a correction for decreased life-expectancy eliminated the decrease in survival rate with age which was shown by their crude survival rates.

In the younger age groups the apparent fall in survival rate reported by some has been attributed by Smithers et al. (1952) and Cutler (1961) to the inclusion of cases of carcinoma arising in association with pregnancy and lactation. Smithers has also demonstrated that if correction is made for differences in stage distribution the prognosis in the 35-50 age group is in fact better than average.

The age-specific crude five-year survival rate for the present series is given in Table 4, larger numbers being obtained by combining certain of the age groups used in Table 3.

The/

TABLE 4

Age	No. of cases	5-year survivors	% 5-year survivors
40 or under	103	47	46
41 - 50	204	97	48
51 - 60	193	94	49
61 - 70	215	90	42
Over 70	161	43	27

CRUDE 5-YEAR SURVIVAL RATES

WHOLE SERIES - BY AGES

The crude five-year survival rate is thus almost constant up to the age of 60 and then declines.

The effect of eliminating cases associated with pregnancy and lactation (19 cases in all) is shown for the first two age groups in Table 5. Comparison with Table 4 shows that the survival rate of the pregnant cases does not affect that of the group as a whole.

Correction for Life Expectancy

Table 6 gives the corrected age-specific survival rates when allowance is made for differing life expectancies in the different age groups. These are based on the 1951 Life Tables published by the Registrar-General. (For details of the calculations, see Appendix 1, Table 64).

Allowance being thus made for natural mortality, age is seen to affect survival in this series less unevenly than was apparent from the crude survival rates.

The two main points of interest in these figures are the lower rates seen in the youngest and oldest age groups. Before the significance of these can be considered it is necessary to see to what extent differences in stage distribution affect the prognosis in the different age groups.

Age, Stage and Prognosis

The simplest way to allow for the effect of differing stage distribution in the different age groups is to calculate the age-specific survival rates separately for each/

TABLE 5

Age	Number of cases not associated with pregnancy	5-year survivors	% 5-year survivors
40 or under	90	42	47
41 - 50	198	95	48

EFFECT OF PREGNANCY ON SURVIVAL RATES

TABLE 6

Age	Crude 5-year survival rate %	Corrected 5-year survival rate %
40 or under	46	46
41 - 50	48	49
51 - 60	48	51
61 - 70	42	48
Over 70	27	43

CORRECTED 5-YEAR SURVIVAL RATES

WHOLE SERIES - BY AGES

each stage. This, however, results in the subdivision of the case material into groups which are quite small numerically. In the case of Stage III the numbers are too small for the calculation of meaningful results.

It is also necessary to make allowance in each case for differences in life expectancy and to express the survival rates for each age and stage as corrected rates. The results are given in Table 7, Stage III being omitted. The full version is given in Appendix 1 (Table 66).

From Table 7 it can be seen that the trend shown by the overall corrected survival rates (Table 6) is one that is largely independent of the clinical stage. In each stage the survival rate is relatively low in the youngest age group and, in Stages I and II though not in Stage IV, in the oldest age group. The remaining cases occupy an intermediate position with regard to prognosis.

Both these trends - a higher mortality in the youngest and in the oldest cases - have been noted in previous reports. The failure of some to observe them may be due to several factors of which the commonest appear to be a failure to take into account either differences in stage distribution or in life expectancy or both. It is obvious too that only in large series can such allowances be made and still leave groups of cases large enough to give valid results.

Of the two trends, that in the youngest age group is probably the more significant. In the oldest age group the correction/

TABLE 7

AGE	5 YEAR CORRECTED SURVIVAL RATES (%)		
	STAGE		
	I	II	IV
40 or under	71	50	5
41-50	73	55	8
51-60	77	61	10
61-70	75	64	11
over 70	65	44	14

AGE AND PROGNOSIS
CORRECTED AGE SPECIFIC 5 YEAR SURVIVAL RATES BY STAGE
(for full version see Table 66, Appendix 1)

correction for life expectancy is relatively large and the validity of the comparison leans heavily upon it.

Apart from these two groups the present results suggest that age is not a factor which greatly affects prognosis.

MENSTRUAL STATUS

It was usually possible to determine the menstrual status of the patients from the information in the case records. However to reduce the number excluded from consideration because this fact was not recorded, it was decided to assume that all patients aged 61 and over were post-menopausal. In fact in no case where the age at the menopause was recorded was it over 60. It was felt that this procedure introduced no appreciable error.

No such arbitrary rule could be usefully applied to the lower limit of the age of the menopause but the menstrual status in patients under 61 was unknown in only 38 cases. There were 834 cases in the series in whom the menstrual status was known or definable. These are specified in Table 8.

Age at Menopause

In 469 of the post-menopausal women in the series (including those at the menopause) the age of the menopause was known. The mean age of the menopause in this group was/

TABLE 8

	No. of cases	% of total number of females
Pre-menopausal	226	26
- of whom pregnant	19	2
At menopause	42	5
Post-menopausal	566	65
Total known	834	
Unknown	38	4
TOTAL	872	100

MENSTRUAL STATUS

(4 male cases excluded)

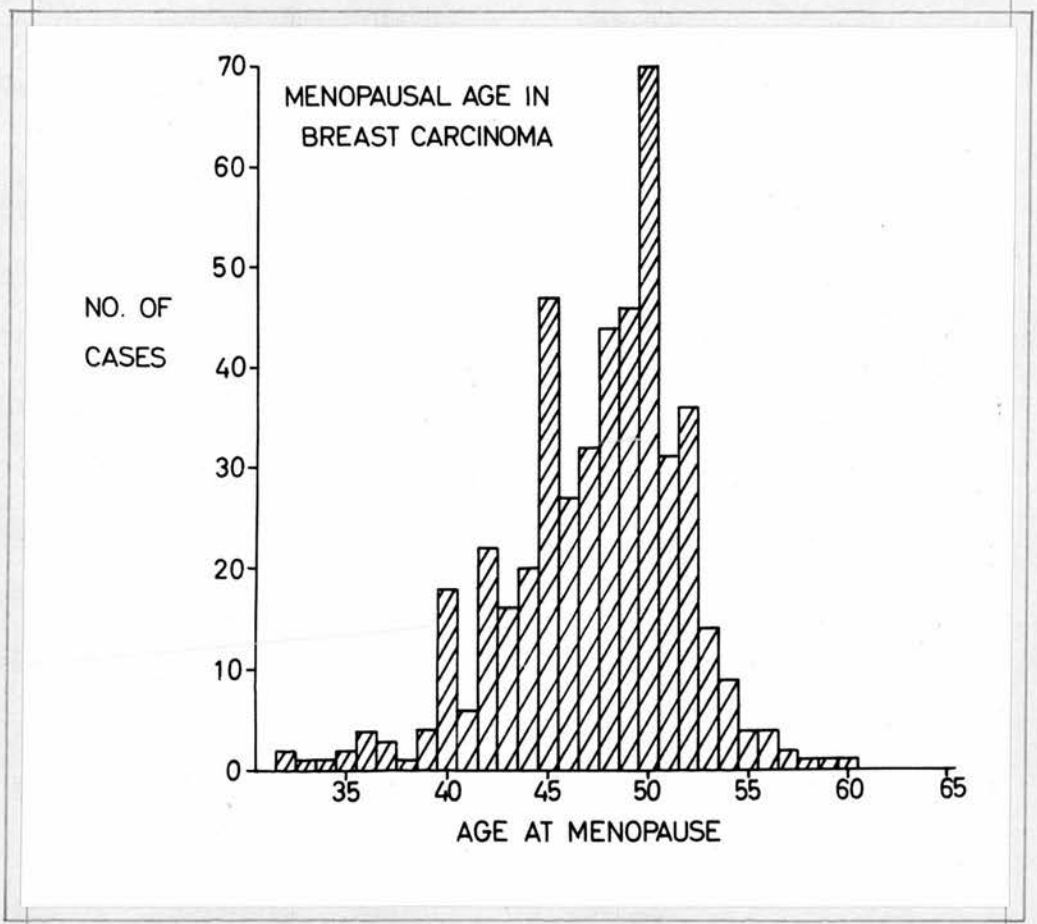
MENOPAUSAL AGE IN
BREAST CARCINOMA
NO. OF
CASES
70
60
50
40
30
20
10
0
35
40
45
50
55
60
65
AGE AT MENOPAUSE

Figure 4

was 47.4 (standard deviation 4.3). The earliest menopause was at 31, the latest at 60. The distribution is shown graphically in Figure 4.

The sharp peaks at the round-number ages of 45 and 50 suggest that there is a tendency for patients to give an approximate age when asked about their menopause. It is a common experience to find that patients have difficulty in remembering even the year of the menopause with accuracy. This was pointed out in the report of the subcommittee of the Women's Medical Federation (1933) set up to study the duration of menstrual life, and they in fact noted that the age of the menarche in spite of the greater time interval was much more accurately recollected. Lane-Claypon's (1926) figures show similar peaks although she makes no comment on their significance.

In this series there were 112 cases who were either at or within the five years following the year of the menopause. While other factors, such as the effect of the menopause itself on the incidence of breast cancer, may influence the distribution in such a group, these patients would be more likely to recall time of onset of the menopause accurately. The spread in this group was smaller, the earliest menopause being at 41 and the latest at 57 while the mean age 48.8 (S.D. = 3.1) was slightly older. The distribution curve as illustrated in Figure 5 is somewhat smoother and supports the/

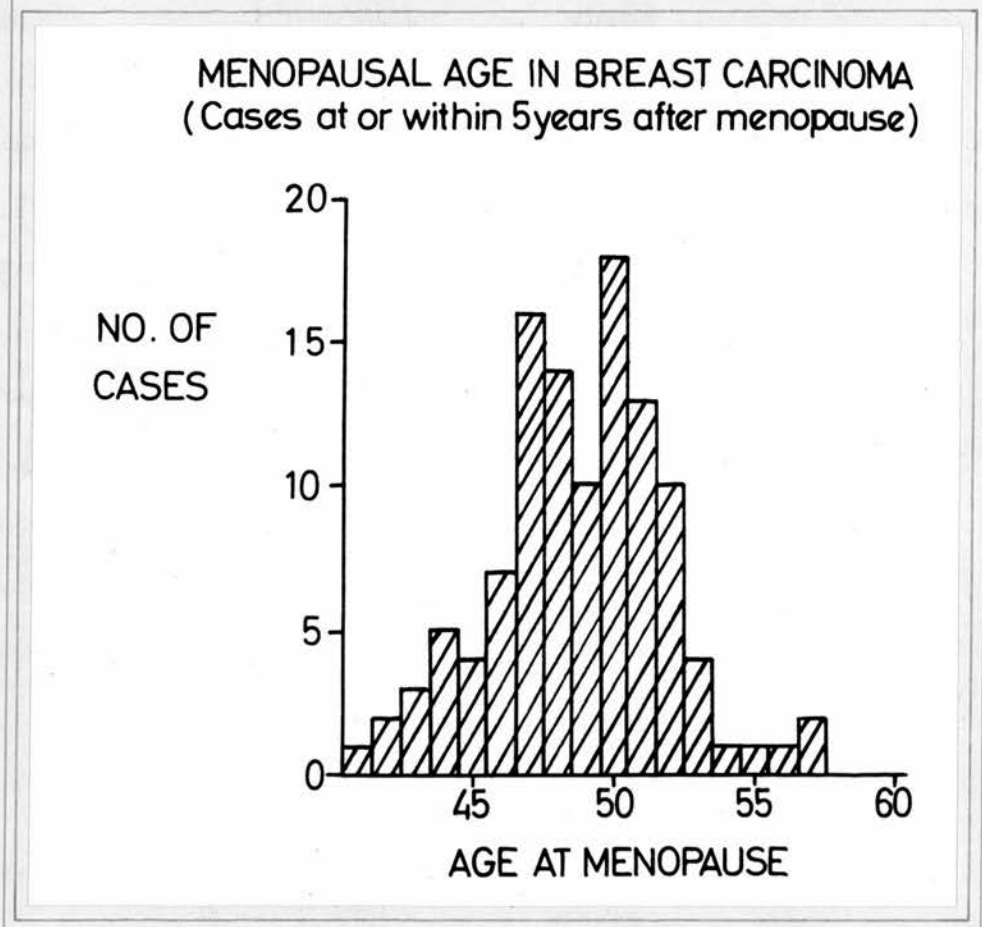
MENOPAUSAL AGE IN BREAST CARCINOMA
(Cases at or within 5years after menopause)
NO. OF CASES
20
15
10
5
0
45
50
55
60
AGE AT MENOPAUSE

Figure 5

the contention that some of the irregularities in Figure 4 are due to inaccuracies in determining the age of the menopause.

The age at which normal women reach the menopause has a wide range but the commonest lies between 46 and 48 (Israel, 1959). Bachman reviewing a large number of such observations agrees with this figure but makes the further observation that in the last hundred years it has increased from 46 to 48.

Although it is true that breast cancer most commonly presents in the age group associated with the onset of the menopause in normal women, it has been suggested by some that the menopause itself tends to occur later in patients with breast cancer. There is however no unanimity in literature on this point.

To a certain extent this view has been based on erroneous calculations. Olch (1937) and Heiberg and Heiberg (1940) both estimated the incidence of the menopause in patients who were over 50 at the time of onset of carcinoma of the breast. They found 55% and 61% respectively of their cases reached the menopause after 50 as compared with a normal incidence of about 30%.

If one considers only cases over the age of 50 at the time of the onset of the disease then one excludes a group of cases in whom, if the menopause had been reached, it must have/

have occurred under the age of 50. In these circumstances the average age of the menopause is bound to be elevated.

This can be demonstrated in the present series although the differences are not as great. Thirty-seven per cent of the cases reached the menopause at 50 or over. If only those cases who were 50 or over when first treated are included this figure rises to 42%.

The average age of the menopause in several series of cases of breast cancer where the observations have not been restricted to a specific age group is given in Table 9.

In conclusion, it appears that there is little evidence to support the contention that breast cancer patients differ from normal women in the time of onset of the menopause.

PROGNOSIS IN RELATION TO THE MENOPAUSE

Changes in survival rates for the age groups related to the onset of the menopause have been attributed to the effect of the menopause on the prognosis of the tumour. Evans and Leucutia (1939) found that the 50-59 age group had the poorest survival rate in their series and associated this with the post-menopausal state. McKenzie (1955) basing his conclusions on the cancer registration data from England and Wales held a similar opinion.

Bonser/

TABLE 9

Author	Mean age at menopause (yrs.)
Adair (1947)	46.5
Lane Claypon (1926)	48.3
Nohrman (1949)	49.5
Present series	47.4

MEAN AGE AT MENOPAUSE IN CASES OF BREAST CANCER

Bonser et al. (1961) point out however that while irregularities in the middle age groups may be related to the menopause, the wide range of the date of the menopause renders such conclusions dubious.

Even where the actual menstrual status of the patient has been taken into consideration the results have not been consistent. Richards (1948) found that the ten-year survival rate was poorer in the group of cases presenting with breast cancer at or within the five years following the menopause than in either the pre-menopausal group or in those presenting more than five years after the menopause. Smithers (1952) came to a similar conclusion but considered the observed fall in survival rate to be relative to an increase in survival rate in the preceding group. He believed that the natural menopause exerted a beneficial effect on the cases who already had breast cancer when it occurred. This effect would not be seen in those developing the disease after the menopause.

Nohrman on the other hand found in his Radium-hemmet series (1949) no difference in survival rates in relation to menstrual status when correction was made for deaths from intercurrent disease. Similarly Goldenberg et al. (1961) could find no significant difference in a study of cases between the ages of 45 and 54.

As/

As has already been mentioned there were 112 cases in this series who were first treated either at the menopause or within the succeeding five years. The five-year survival rate in this group is 40% as compared with 48% for all cases between 41 and 60 (see Table 6). The stage distribution also shows a shift from Stage I and II to Stages III and IV as compared with all cases in the same age range (Table 10). This however is not statistically significant nor does it account for the difference in prognosis, for in each stage (Table 10a) except Stage IV the prognosis is worse in the cases at or shortly after the menopause than that of all cases in the same age range. This confirms the view of the majority of authors.

Summary

The data relating to menstrual status in this series fail to confirm the view that the age at which the menopause occurs in patients with breast cancer is different from that of normal women.

The prognosis in cases occurring at or just after the menopause is poorer than the average for the same age group. This appears to be a genuine difference not accounted for by differences in stage distribution.

TABLE 10

	STAGE (% of cases in each stage)			
	I	II	III	IV
All cases 41 - 50	36	30	7	26
All cases 51 - 60	35	30	9	26
Cases at or within 5 yrs. of the menopause	34	24	11	31

STAGE DISTRIBUTION IN RELATION TO MENOPAUSE
(For full version see Table 67, Appendix 1)

TABLE 10a

	STAGE (% 5 year survivors in each stage)			
	I	II	III	IV
All cases 41 - 60	72	55	47	9
Cases at or within 5 yrs. of the menopause	66	41	33	11

5 YEAR SURVIVAL RATE IN RELATION TO MENOPAUSE

Breast Cancer and Pregnancy

Breast cancer occurring in association with pregnancy or lactation has long been considered to have a bad prognosis. In recent years however this view has been challenged.

In 1937 Harrington reported the results in 92 cases of breast carcinoma associated with pregnancy and lactation. These formed part of a series of 4,628 cases seen at the Mayo Clinic and like the majority of the reports on breast cancer which have come from this centre this report dealt with treated cases only.

The overall 5-year survival rate of the 92 cases was poor - 14.5%. However the cases without axillary metastasis had almost as high a survival rate (61.5%) as the comparable group in the whole series (72.1%). Of considerable significance was the finding that 84.8% of the pregnant cases had axillary metastasis compared with 63.8% in the whole series. Furthermore the histological grade of the majority of these tumours was high.

Three important points therefore emerged from this study. First that cases of carcinoma of the breast associated with pregnancy tended to be more advanced when first seen, secondly that for a given degree of advancement the prognosis differed little from that of breast cancer unrelated to pregnancy and thirdly that the histological grade tended to be high.

Subsequent/

Subsequent studies have generally confirmed these observations. Richards (1948) found that 71% of his cases fell into Stage III while Haagensen (1956) found lymph node involvement in 80% of such cases undergoing radical mastectomy. McWhirter (1957) reports a 48% five-year survival rate in the operable group, although in his earlier series (1955) only a 40% five-year survival was achieved. Treves and Holleb (1958) on the other hand found a survival rate of only 27.6% in operable cases.

There were only 19 cases in the present series associated with pregnancy or lactation. Seven of these (37%) survived five years, a survival rate quite close to that of the whole series. It is pointless to calculate the percentages in the different stages in such a small group or to determine the survival rates by stages. The cases are therefore listed serially with a note of other certain points of interest such as method of treatment (Table 11).

The tendency for the disease to be relatively advanced is apparent from these cases. The histological grading shows a striking preponderance of Grade III though there is no obvious correlation between this and survival. Bloom (1958) also found a high incidence of Grade III tumours in his pregnant cases.

Rapid progression of the disease was a feature of those cases who survived less than five years. There were 11 such cases; 6 of them died with 7 months of treatment.

TABLE 11

Case	Age	Stage	Grade	Treatment*	Result
1	43	I	-	Standard	Alive and well at 10 years
2	35	I	III	Standard	Alive and well at 10 years
3	40	II	-	Standard + O.R.	Died 2 years 2 months
4	34	II	-	Standard	Died 9 years 6 months
5	34	II	I	Standard	Died 4 years 8 months
6	34	II	III	Standard + O.R.	Alive and well at 10 years
7	33	II	III	Standard	Died 1 year 5 months
8	38	II	III	Standard	Died 5 years 5 months
9	38	II	III	Standard	Alive and well at 10 years
10	45	II	III	Standard	Died 1 year
11	42	III	-	Standard + O.R.	Alive and well at 5 years
12	33	III	II	Standard	Died 5 months
13	46	III	II	Standard	Died 2 years 6 months
14	47	III	II	Standard	Died 5 months
15	29	IV	-	Radiotherapy only	Died 7 months
16	28	IV	-	Radiotherapy + O.R.	Died 5 months
17	36	IV	-	Standard + O.R.	Died 1 year 4 months
18	42	IV	III	Standard + O.R.	Died 5 months
19	33	IV	III	Simple mastectomy, palliative radiotherapy and O.R.	Died 7 months

CARCINOMA OF THE BREAST ASSOCIATED WITH

PREGNANCY AND LACTATION

* Standard = simple mastectomy + radical radiotherapy.
O.R. = ovarian irradiation.

TUMOUR ATTRIBUTES

Side

It is a peculiar fact that breast carcinoma occurs rather more frequently in the left breast than in the right.

The ratio of left to right can vary considerably as the collected series of Garfinkel et al. (1959) show. Indeed some of their series showed a reversal of the ratio. The preponderance of tumours of the left breast is accepted however and although not great it is statistically highly significant (Busk and Clemmesen, 1947).

The reasons given for this are various and none are universally accepted. Smithers et al. (1952) put forward the commonest of these, that the left breast is more exposed to trauma than the right. They find support for this view in their own series where antecedent trauma was commoner in the case of the left breast than in the right. However there is very little evidence in favour of trauma as an aetiological factor in breast carcinoma. Garfinkel et al. suggest that the difference may be due to lactation anomalies or differences in the distribution of aberrant breast tissue. McWhirter (1957) has put forward the suggestion that the left breast is more readily palpated by right-handed women and that tumours of the right breast are more easily missed. In his own series he found that small tumours/

tumours were commoner on the left, evidence which supports his contention. This theory however implies that a number of right-sided tumours are overlooked, either not giving rise to any symptoms during the patient's lifetime or causing symptoms which are not diagnosed as being due to carcinoma of the breast.

In the present series the only interest in laterality is to determine whether it conforms to the usual pattern. This is found to be the case. There were 9 cases in whom the tumour was bilateral when first seen. Of the remaining 867 cases, 418 had tumours of the right breast and 449 had tumours of the left breast - a ratio of 100:107.

Some of the ratios reported in the literature are shown in Table 12 for comparison.

Bilateral Breast Cancer

Nine cases in this series (1%) presented with bilateral breast cancer. Forty-five cases (5%) subsequently developed cancer of the opposite breast.

The incidence of simultaneous bilateral breast cancer given by different authors varies considerably. Guiss (1954) gives an incidence of 0.3%, Herrmann (1955) and Haagensen (1956) an incidence of 0.4% while at the other extreme is Allen and Rigler's (1962) figure of 6%.

Part/

TABLE 12

Series	Ratio R : L
Garfinkel et al. (1959) (Ratio for U.S. series)	100 : 105
Nohrman (1949)	100 : 109
Haagensen (1956)	100 : 109
Busk and Clemmesen (1947)	100 : 111
Harnett (1948)	100 : 111
Smithers (1952a)	100 : 114
Present series	100 : 107

SIDE AFFECTED IN BREAST CANCER

PUBLISHED RATIOS

Part of this variation is due to attempts to eliminate metastatic cases by adopting certain criteria to define a second primary tumour (Reese, 1953; Guiss, 1954). The differences also stem in some series from the consideration of treated cases only.

Such differences are even more marked in estimates of the incidence of breast cancer developing at a later date in the second breast. Guiss gives an incidence of 0.7% while in Allen and Rigler's cases the incidence is 9%. An attempt has been made to divide the cases of consecutive bilateral breast cancer in the present series into those assumed to be metastatic and those assumed to be new primary tumours. There is a considerable possibility of error in such assumptions, but good evidence was found for assuming that 5 of these cases represented independent primary tumours (see p. 168).

Site

The site of tumours in the breast has become a subject of considerable interest, for site has been shown to determine the distribution of metastases to the internal mammary and axillary nodes. This in turn has been found to affect prognosis and has given rise to much thought in the planning of treatment.

The relation of site to prognosis and the results of treatment will be dealt with in a later section in relation to/

to cases treated by the standard method. At this point only the relative frequencies of tumours in the different parts of the breast in the series as a whole will be considered.

For this purpose the location of the tumour was recorded as being in one of the four quadrants of the breast, or central or diffuse. When the tumour lay largely in one quadrant but extended into another it was recorded as lying in the quadrant in which its greater part lay. When this was indeterminate the site was recorded as unknown. This latter category also of course included those tumours whose site was not given in the case records. When the tumour filled the whole or the greater part of the breast it was recorded as diffuse. If it was small and centrally placed it was recorded as central. The findings were as shown in Table 13.

The order of frequency in the various sites is similar to that given in other series reported in the literature. The ratio of inner half tumours to outer half tumours is however rather higher in this series than the average.

Size

The size of the tumour is related to its duration but since the rate of growth varies in different cases, and possibly at different times in the same case, the relationship/

TABLE 13

	No. of cases		% of total	
Upper outer quadrant	342		39	
Lower outer quadrant	78		9	
Outer Half		420		48
Upper inner quadrant	214		25	
Lower inner quadrant	50		6	
Inner Half		264		25
Central	92		11	
Diffuse	54		6	
Unknown	37		4	
TOTAL	867			

SITE OF THE TUMOUR (BILATERAL CASES EXCLUDED)

relationship is not a precise one. One would expect however that size would bear the same sort of relationship to prognosis as is the case with stage and for the same reason. Although Sutherland (1960) reviewing the literature concluded that the decrease in survival rate with increasing size applied only to tumours of intermediate size, many have found that the relationship holds for the whole range. Goldenberg et al. (1961) noted that small tumours have a better prognosis irrespective of age; Adair (1949) found a progressive decrease in prognosis with size irrespective of involvement of axillary nodes; Taylor and Wallace (1947), McWhirter (1960) and Allen and Rigler (1962) also found a steady decrease in survival rate and in the last series the relationship was almost linear.

The tumours in the present series were grouped into four categories according to size. The proportion in each group is shown in Table 14 and the relationship between size and prognosis in Table 15. The latter table shows a very clear-cut correlation.

CLINICAL STAGE

The close relationship between the extent of the disease and ultimate survival of the patient has given clinical/

TABLE 14

Diameter of tumour	No. of cases	% of total
2 cm. or under	97	11
over 2 cm. up to 5 cm.	475	55
over 5 cm. up to 10 cm.	205	24
over 10 cm.	29	3
unknown	61	7
TOTAL	867	

SIZE OF TUMOUR

(Bilateral cases excluded)

TABLE 15

Diameter of tumour	No. of cases	No. of 5-year survival	5-year survival rate (%)
2 cm. or under	97	73	75
over 2 cm. up to 5 cm.	475	227	48
over 5 cm. up to 10 cm.	205	46	22
over 10 cm.	29	2	7

PROGNOSIS AND SIZE

clinical stage pride of place amongst the factors used to assess prognosis.

Not only is staging of value in assessing the prognosis in the individual case, it is also of the greatest importance in the classification of clinical material. If groups of cases are to be compared it becomes essential to know that they are comparable in respect of the moiety studied. In the case of breast cancer this moiety is usually survival. Staging is the best method available to determine whether the groups under comparison are equivalent in their prospects of survival.

The great importance of staging should not however result in its limitations being overlooked. These are studied in detail later. At this point however it is worth noting that staging is essentially a measure of the position reached by the tumour in its natural history at a given point in time. Only when taken in conjunction with the time factor, e.g. the duration of symptoms, will it yield information about the rate of growth of the tumour. Unfortunately, such estimates of time are often unreliable.

Of the other prognostic factors reviewed so far sex and pregnancy may well influence the natural history of the tumour but such cases are too few in number to provide reliable figures. Age and menstrual status do appear to influence/

influence the behaviour of the tumour but, as has been shown, do not appear to do so to a very great extent. Size and site are related to stage rather than separate attributes of the tumour.

Histological grading on the other hand appears to reflect a fundamental attribute of the tumour and to measure its potential malignancy. But, as will be shown later, it lacks the sensitivity that clinical staging possesses as a prognostic index.

Clinical staging therefore remains the basic instrument of classification in breast cancer and, although it is also of value in assessing the prognosis in the individual case, this is perhaps its most important function. It is not primarily, as Riddell (1954) believes, a means of determining the method of treatment.

The Evolution of Staging

The relationship between the extent of the disease and prognosis has been recognised, although not always understood, for centuries. Steinthal in 1905 was probably the first to base a formal classification of breast cancer on the extent of the disease. He defined three groups as follows (the following is a loose translation):

"Group I Cases where the growth came on very slowly, where the tumour measured up to 1 cm. across and/

and lay entirely within the breast. The tumour showed no fixation to the skin. One or more axillary nodes might be present but these were usually first found at operation.

Group II Cases with definite tumours stationary a long time and then starting to enlarge. Skin beginning to be adherent. Nodes easily found.

Group III Where the breast itself is enlarged by the tumour and the tumour adherent to skin and deep tissues. Supraclavicular nodes involved in addition to axillary nodes."

Portmann (1937) modified this by excluding nodal metastasis from the first group and limiting it to "few" in the second. Distant metastasis, not mentioned in Steinthal's classification was added to the third group. Portmann later subdivided his classification into four groups, the fourth consisting of cases with extensive local disease as well as those with distant metastases. This in modified form was recommended for general use by the International Congress on Radiology (Lewison, 1955). The Manchester System used in this country is very similar.

The separation of cases with distant metastases from all others led to the suggestion of five-stage systems (Richards, 1948; Smithers et al., 1952) and ultimately to the four-stage International System devised by the International/

International Union against Cancer in 1956. Separation of this group is also achieved by McWhirter's modification of the Manchester System.

With the common use of radical mastectomy in the treatment of breast carcinoma and the tendency to report the results of treated cases only, there has been a frequent disregard of clinical staging altogether. Cases in many series are classified only according to the presence or absence of histologically involved axillary nodes and are accordingly valueless for purposes of comparison with cases in which this information is not obtainable.

Until the introduction of the International System of Staging there was no general agreement on the use of systems of clinical staging. In consequence many different systems, such as those mentioned above, were used to classify the series reported in the literature. This too has added, in spite of the broad similarity between the different systems, to the difficulties of comparing such series. Even the International System has yet to gain universal acceptance, and indeed is regarded by some such as Haagensen (1963) as too cumbersome for general use. Nevertheless it appears to be in no way more difficult than that recommended by Haagensen himself (Haagensen et al., 1963).

The/

The Manchester System

The Manchester System of clinical staging was in use in Edinburgh during the whole period covered by this study although it has since been superseded by the International System. It was therefore the obvious system to use.

A brief note on the use of the Manchester Staging system in this study has already been given (p. 25). The full specifications of the system as given in the 2nd Statistical Report of the Holt Radium Institute (1946) are as follows:

"Stage I Growth confined to the breast.
Involvement of skin directly over and in continuity with the tumour does not affect staging if area small in relation to the size of the breast.

Stage II As Stage I with palpable mobile axillary nodes.

Stage III Growth extending beyond the corpus mammae.
a) Skin fixed over a large area) $\pm$ mobile
b) Fixation to underlying muscle) $\mp$ axillary nodes

Stage IV Growth extending beyond the breast area.
a) Fixation of nodes.
b) Complete fixation of tumour to chest wall.
c) Supraclavicular nodes.
d) Secondary deposits in skin wide of tumour.
e) Secondary deposits in opposite breast.
f) Distant metastases."

McWhirter/

McWhirter (1955) has elaborated his interpretation of the Manchester System as used in Edinburgh and in relation to his categories of operable, locally advanced and inoperable, as follows:-

Ulceration of skin does not affect staging but patients placed in Stage III if skin involvement so gross that a graft would have been required if operation had been performed.

Fixation to pectoral fascia. Stage III only if fixation complete.

Fixation of nodes to one another - taken as evidence of extracapsular spread, therefore Stage IV even if mass as a whole still retains some degree of mobility.

Distant metastases - not assumed unless clear clinical or radiological evidence of presence.

Locally advanced Stage IV. Complete fixation to chest wall; fixed axillary nodes; supraclavicular nodes; widespread involvement of cutaneous lymphatics including skin nodules.

Inoperable Stage IV. Secondary deposits in opposite breast. Distant metastasis in bone, lung, etc.

The use of the abbreviations IVL and IVD for the last two categories has already been explained.

Determination/

Determination of Stage

The stage assigned to the case in the records of the Radiotherapy Department has been taken as the definitive stage for the purposes of this study. Where this was not available the staging was based on the clinical information in the surgical case records.

The division of Stage IV into the subsections IVL and IVD is not specified in the Radiotherapy records. It has therefore been made, where possible, from the clinical information available in these records.

In addition each case was assigned a stage based on the surgical case records whether or not that case was staged by the Radiotherapy Department. In a few cases there was insufficient information available to do this.

In surgical case records it is uncommon for a numerical stage to be recorded. Adequate information on which to assess staging was however nearly always found.

The data recorded in the surgical case records are of course usually based on the examination carried out by the house-surgeon. The findings of more senior members of the staff tend to be recorded in the briefer fashion customary in out-patient records. This is often unsuitable for staging purposes, though where possible facts so recorded were used to give a more accurate picture. Where an actual stage was assigned by a senior member of the staff this was generally taken as the surgical opinion of the stage.

Two/

Two separate estimates of the stage were in fact available in 731 cases. These were used to investigate the accuracy of clinical staging. The radiotherapists' estimate, where available, was taken as the definitive stage for the purpose of further studies, since it was considered to be on the whole more uniform. Standardisation of examination methods in the Radiotherapy Department and the habitual recording of the stage make it likely that this is so.

The Reliability of Clinical Staging

The relationship between stage and prognosis depends on the following four factors:

1. The degree to which the subsequent progress of the disease depends on its extent at a given point in time.
2. The degree to which treatment affects prognosis independently of stage.
3. The design of the staging system.
4. The accuracy of the staging itself.

It has already been said that staging estimates the state of progress of the disease at a given point in time. The natural history of breast cancer is, however, very variable and the relationship between the stage and the ultimate/

ultimate prognosis even if uninfluenced by treatment cannot be one of great precision.

It is well established that the effect of treatment is dependent on stage but it is not necessarily wholly dependent. It is probable that at all stages treatment may exercise an effect on the natural history of the disease which is determined by factors other than stage itself. Again the relationship is a broad and not a precise one.

Within these limitations which are inherent in the nature of the process of staging, its usefulness depends on the design of the staging system and the accuracy with which it can be carried out.

The main purpose of staging is to separate from each other groups of cases in which the prognosis is different. A system of staging can do this only if the factors chosen to define the stages are in fact of prognostic importance. If for example the involvement of axillary nodes had no effect on prognosis the separation of the groups commonly called Stage I and Stage II would be of no value. In fact in most accepted systems each subdivision does have a clearly differing prognosis. The relative merits of different systems depend on whether the differences are greater or smaller, and also on the ease with which they can be clinically defined.

In/

In the last analysis the value of a system depends on the accuracy with which the process of staging can be carried out.

Accuracy in Staging

In the 731 cases in which two separate stagings were available in this series there were differences in 203 (27.8%). Stages IVL and IVD were considered as separate stages for this purpose in view of their importance in the classification (Operable, Locally Advanced, etc.) used in reporting the Edinburgh series. In fact differences between these two stages occurred in only 11 cases.

While, as has been mentioned, these differences may be due in part to the inexperience of housemen, it is by no means certain that in all series of cases reported in the literature staging has been recorded numerically by an experienced observer when the patient is first seen. The figure of 27.8% is probably about the lower limit of the reliability of staging.

It is of interest to note however that a higher stage was recorded with almost equal frequency in the two groups. 14.5% of the stages recorded from the Radiotherapy records were higher than the corresponding stages derived from the unit records, while in 13.3% the reverse was the case. These differences would therefore tend to cancel each other out and also serve to demonstrate that there is no suggestion of a bias in staging in one or other direction.

The/

The main differences found are listed in Table 16; the full list is given in Appendix 2 (Tables 80 and 81).

The well-known difficulty of determining the presence of palpable nodes in the axilla is thus seen to be the commonest source of discrepancy. The differences between Stage IVL on the one hand and Stages II and III on the other are also related to this problem. These differences are mainly due to disagreement regarding the fixation or matting of axillary nodes.

There have been many attempts to determine the accuracy of clinical palpation of the axilla by comparing the pathological findings after radical mastectomy with the original clinical findings. The estimates vary widely. Gylstorff-Petersen (1944) found the nodes to be involved at operation in 67% of cases who had none palpable clinically. Zippin and Kohn (1960) in an evaluation of the International Staging System found the incidence to be 40%. Nohrman's (1949) figure was 28%. It seems likely that Gylstorff-Petersen's figure is excessively high and may merely reflect very casual palpation or recording of axillary nodes. In support of this is the fact that of the cases in which nodes were recorded as palpable only 12% were found to be uninvolved at operation. Zippin and Kohn found 38% histologically negative axillae in such cases and Nohrman 15%.

Even/

TABLE 16

Differences between stages	No. of cases		% of total differences
I and II	82		40
I and III	29	50	25
II and III	21		
II and IVL	25		12
III and IVL	18		9
Others	28		14
	203		

THE ACCURACY OF CLINICAL STAGING

DIFFERENCES FOUND BETWEEN SURGICAL AND RADIOTHERAPY RECORDS

Even these estimates are not entirely reliable for it has also been shown by Saphir and Amromin (1948) and by Pickren (1961) that pathological examination of the axilla can itself be subject to appreciable error. These authors found that if more sections are taken more nodes are found. They concluded that routine examination may underestimate the number of involved nodes by 20-30%.

The results obtained in the present series throw light on a different aspect of the problem. Not only does clinical examination give an erroneous estimate of the actual involvement of axillary nodes, but the findings may vary from one observer to the next.

McNair and Dudley drew attention to this problem in 1960 when they reported the results of an experiment in which a number of experienced surgeons and a radiotherapist compared their findings on the random examination of the axillae in patients with and without breast pathology. They found disagreement between the examiners in 40% of the examinations of patients without breast pathology and in 35% of those with pathology. Even more remarkable was the fact that the axilla was recorded as positive on as many occasions in patients without pathology as in those with pathology. This confirmed a further study in which positive findings had been recorded in the axillae in 50% of 62 normal women examined by the two authors. In this latter study differences between the observers occurred in 27%.

The/

The figures in the present series show that in practice there is a considerably smaller difference as far as Stages I and II are concerned, because such differences while representing 40% of all the observed differences amounted to only 11% of the whole series of 731 cases. These figures do not in fact support McNair and Dudley's conclusion that the use of axillary nodes for clinical staging is valueless and misleading. There is of course no evidence herein to dispute their other contention that palpable axillary nodes are a normal finding in 50% of women. It may however be significant that palpable nodes in the opposite axilla were seldom noted.

There are other grounds on which these conclusions can be criticized however. The first of these relates to the function of staging, which has been elaborated above (p. 60). If clinical staging is a form of scientific measurement and it is intended to evaluate it as such, then it is essential to do so with observers experienced in its use. The majority of surgeons, however experienced in clinical examination, may not be equally experienced in the formal procedure of clinical staging. Comparisons between their estimates of stage have therefore less validity. It is of course a corollary of this that where conclusions are to be based on staging, this must be carried out by those experienced in the procedure.

The/

The second criticism, though based on a post hoc, ergo propter hoc argument, is perhaps of equal importance. Clinical staging has in fact been found to distinguish between groups of patients with a very definite difference in prognosis, where the distinction depends solely on the presence or absence of palpable axillary nodes. The difference in prognosis between Clinical Stage I and Clinical Stage II is undisputed. This is the proper function of staging and therefore the justification of its method. That the distinction lacks a high degree of precision no one would dispute; that it is valueless or even misleading has by no means been proven.

More unexpected than the differences in the estimation of axillary nodes are those related to Stage III. This is all the more striking when it is considered that this is numerically the smallest of all the stages.

The great majority of those differences between Stages I and II on the one hand and Stage III on the other (which form 25% of the total) are due to differences of opinion regarding fixation to the pectoral fascia or muscles. It has not been generally realized that this is an important source of inaccuracy in clinical staging. It has indeed been rendered more so in the Manchester System by the distinction between complete and incomplete fixation to fascia - only the former, in McWhirter's interpretation (McWhirter, 1955), being included in Stage III. This subsidiary/

subsidiary distinction does not determine stage in the International Classification where both complete and incomplete fixation place the patient in Stage III.

The most serious errors in staging are however those which are by their very nature undetectable - those due to the presence of small metastatic deposits. No method of examination yet devised, even the detection of circulating tumour cells in the peripheral blood, is able to demonstrate the existence of such foci. It is probably such foci that account for most of the discrepancies between expected and achieved results in early cases.

All these factors have led to a distrust of clinical staging. But as has been said much of this stems from a misunderstanding of its purpose.

Staging plays an important part in this study as indeed it does in all such studies of breast carcinoma. Its limits of error have now been defined in relation to the present series. It is however assumed that by using the stage allocated by the radiotherapist in all relevant cases, the actual error will fall well within these limits.

Stage Distribution in the Present Series

In comparisons with other series of cases, a knowledge of the relative stage distributions is of paramount importance. Unfortunately this is all too often unavailable/

unavailable. Differences in stage distribution in various reported series are in fact common. They are due mainly to selection of cases, differences between regions and differences between different periods of time.

It is however important in view of the object of this study to establish its relationship to the larger group of cases published by McWhirter in 1955. It is on the results obtained in these cases that the policy adopted by McWhirter has been judged, and it would be specious indeed to attempt a critique based on a series of cases which differed radically from what might be termed the parent series. Some of the earlier cases in the present series are in fact included in McWhirter's 1955 series, and only 5% of the whole series did not pass through the Radiotherapy Department.

The data published in 1955 allow two sets of comparisons to be made - stage distribution and survival rates. These are set out in Tables 17-19. (For full versions of these Tables see Appendix 1, Tables 68-70).

The basic similarity of the two series is readily seen. There are however certain differences which are worthy of comment.

The present series has a higher proportion of cases in the operable group which is just statistically significant (p lies between 0.02 and 0.05). This increase is/

TABLE 17

Stage	McWhirter's 1955 series %	Present series %
I	31	36
II	26	26
III	13	9
IV	30	29

STAGE DISTRIBUTION

MANCHESTER CLASSIFICATION

TABLE 18

Classification	McWhirter's 1955 series %	Present series %
Operable	56	62
Locally advanced	29	28
Distant metastases present	15	11

STAGE DISTRIBUTION

McWHIRTER'S MODIFICATION OF

MANCHESTER CLASSIFICATION

TABLE 19

	McWhirter's 1955 series %	Present series %
All cases		
5 yr. survival rate	42	42
10 yr. survival rate	25	31
Operable		
5 yr. survival rate	58	58
10 yr. survival rate	39	45
Locally advanced		
5 yr. survival rate	30	22
10 yr. survival rate	15	10
Distant metastases present		
5 yr. survival rate	4	3
10 yr. survival rate	0	0

SURVIVAL RATES

COMPARISON WITH McWHIRTER'S 1955 SERIES

is, as Table 17 shows, in the Stage I cases in this group. The overall five-year survival rate for the two series is however identical and it can be seen from Table 19 that the effect of the increase in cases in the operable group, whose five-year survival rate is also identical with the McWhirter series, is offset by the lower survival rate in the locally advanced group. As the detailed analyses in the later parts of this study will be largely concerned with the operable group, this difference in survival rate in the locally advanced group is unimportant. It is interesting to note however that these two changes are not reflected in the overall survival rate as they cancel each other out.

SECTION III

OVERALL RESULTS

OVERALL RESULTS

General Considerations

The results of a particular method of treatment in carcinoma of the breast depend almost entirely on the selection of cases for that treatment. The more precise the selection the better the results. Such results cannot of themselves be used to measure the effectiveness of the method.

The overall results achieved in an unselected group of cases does, on the other hand, provide information about the effectiveness of the treatment policy applied to the whole group. The accuracy of the measure depends in turn on the degree to which the pattern of the disease in the group surveyed reflects the pattern found in the population as a whole.

In practical terms this is best achieved when the group embraces all cases occurring in a geographical area - a situation attained, or nearly attained in McWhirter's Edinburgh series and Watson's Saskatchewan series (Watson, 1959).

Even when such ideal conditions are fulfilled the measure so obtained is of no value unless it can be compared with the results of a different treatment policy determined under similar conditions. In practice this circumstance is rare/

rare and where it does obtain further difficulties arise if comparisons are made between different geographical areas or between cases treated during different periods of time.

The comparison between the two series quoted above illustrates this problem. McWhirter's treatment policy was based on simple mastectomy and radiotherapy, Watson's on radical mastectomy with radiotherapy in selected cases. The overall five-year survival rate in the former series was 42%, in the latter 52%. At first sight the latter policy seems to have achieved a clear advantage.

The published data however provide no means of establishing with any confidence that the case material of the two series is comparable, however representative each may be of its own area. Staging in the two series is by different methods and indeed in Watson's series by a mixture of clinical and pathological staging. Age distribution is not given and there is no information to enable one to determine whether the members of the one community tended to present themselves at an earlier stage of the disease than those of the other.

But of even less value are those series founded on a narrower basis such as the statistics of a single hospital. It seems all the more remarkable therefore that reviewing 11 such series Rosahn (1957) found an overall five-year survival rate lying between 40.2% and 42.8% in six of them. The lowest level however was 34.6% (Smithers et al., 1952), and the highest 47.2% (Haagensen, 1956) a range of nearly 13%.

Among/

Among more recent series quoting overall survival rates, and including all cases regardless of treatment, are those of Brinkley and Haybittle covering an approximate geographical area (Cambridge and district), Moore et al. again covering a geographical area (Muncie, Indiana -"Middletown, U.S.A."- and its surrounding county), Cutler et al. - all cases registered in the State of Connecticut, Allen and Rigler - a series of consecutive admissions to a teaching hospital, and Devitt based on cases referred to a cancer clinic. The five-year survival rates are listed in Table 20.

Again the wide spread is apparent. To what extent if any the differences are due to differences in treatment it is not possible to say for variations in staging, treatment policy and even in the information available are so great.

Many important series reported in the literature including the very large Mayo Clinic series (Berkson et al., 1957) are concerned entirely with treated cases, and some with cases treated by one method only. From these little help can be obtained. Haagensen has attempted to circumvent this difficulty by applying a uniform staging system to the cases reported from a number of different centres (Haagensen et al., 1963). In this International Co-operative Study, results within each stage or group of stages are compared. It is apparent however that in some of/

TABLE 20

Author	Years covered	Overall 5-year survival rate
Moore et al. 1958	1935 - 1951	54
Brinkley and Haybittle 1959	1948 - 1952	41
Cutler et al. 1959	1935 - 1944	44
Allen and Rigler 1962	1946 - 1951	56
Devitt 1962	1946 - 1956	51

OVERALL 5-YEAR SURVIVAL RATES IN BREAST CANCER

of the contributing series the staging has been retrospective and the comparability of the groups thus becomes suspect.

It is therefore obvious that unless the differences between different methods of treatment are quite gross they cannot be established by such comparisons as have been considered. It is also apparent that groups of cases can be compared only if they are drawn from the same area, at the same time and staged by the same observers. Such conditions are fulfilled only in a random clinical trial.

The Edinburgh method of simple mastectomy and radiotherapy has in fact been submitted to such a trial in Denmark (Dahl-Iversen, 1963) and a similar trial has been started in Cambridge (Brinkley and Haybittle, 1959). In the former trial comparison was with extended radical mastectomy and no significant difference in the results was found. The results of the latter have not yet been published.

OVERALL RESULTS - PRESENT SERIES

Some of the overall results particularly the five-year survival rates have already been mentioned. The complete figures for the whole series are presented here, and are analysed in relation to stage and histological grade.

In calculating these results the three cases lost to follow-up are, as already explained, assumed to have died within five years of treatment.

The/

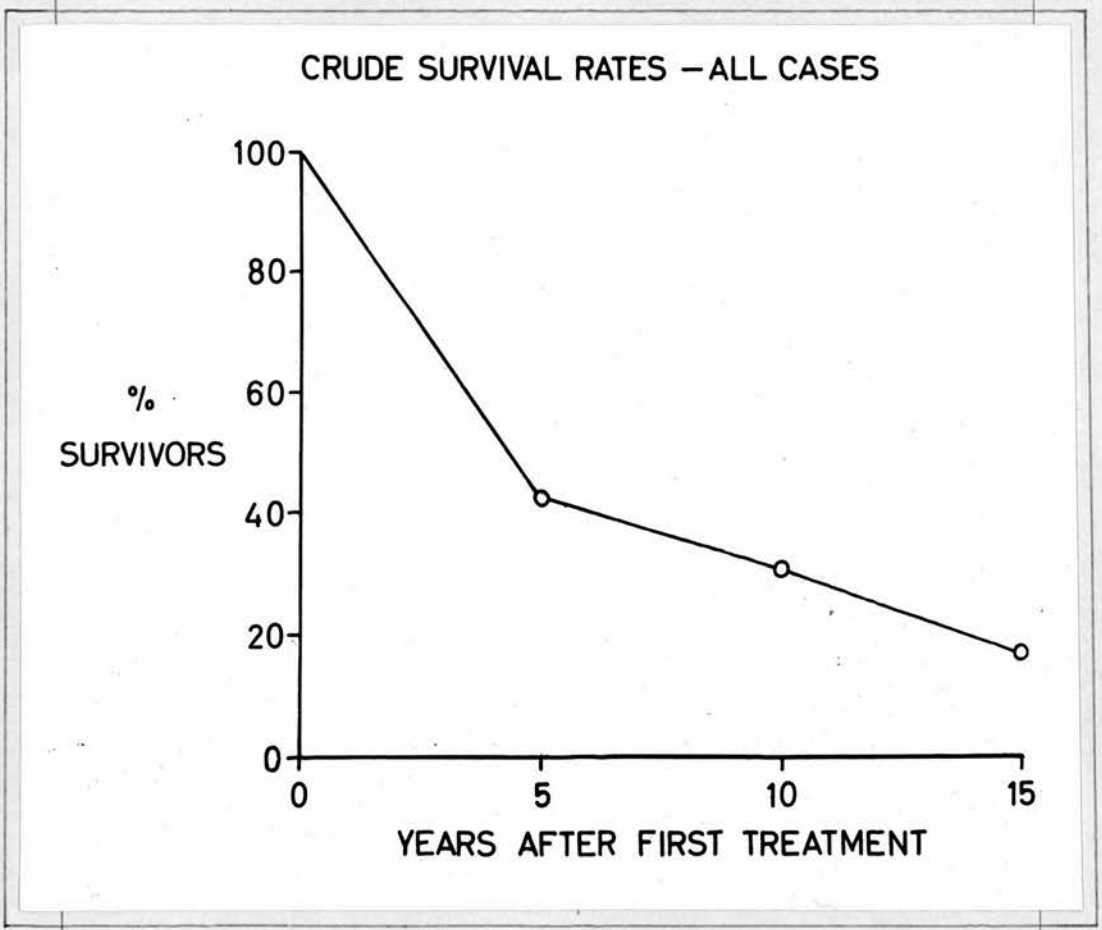
CRUDE SURVIVAL RATES – ALL CASES
100
80
60
40
20
0
%
SURVIVORS
0
5
10
15
YEARS AFTER FIRST TREATMENT

Figure 6

The whole series of 876 cases is available for the calculation of five-year survival rates. Four hundred and eighty-seven cases treated between 1946 and 1952 inclusive are available for the calculation of ten-year rates. The fifteen-year rates are based on the 109 cases treated in the years 1946 and 1947.

The overall rates are summarized in Table 21, and illustrated graphically in Figure 6.

A number of cases reaching each quinquennium were known to have recurrent or metastatic disease (Table 22) and this is true even of cases surviving 15 years. Consequently the percentage of cases surviving free of disease at each quinquennium (the so-called clinical cure rate) is lower than the corresponding overall survival - at least as far as the third quinquennium (Table 23). But as Figure 7 shows, the corresponding curves approach each other more closely with each successive quinquennium, although this is in part due to the decreased total number of cases.

If the survival rates are plotted on a logarithmic scale the slope of the curve at any point corresponds to the death rate at that point (Berkson et al., 1957; Cutler et al., 1959). If such a curve is compared with a similar curve based on the normal survival rate for a similar population, the relationship between the death rates can be seen by comparing the slope at identical points in the two curves.

A/

TABLE 21

Length of follow-up	No. of cases in series	No. of cases surviving	% surviving
5 years	876	371	42.4
10 years	487	151	31.0
15 years	109	18	16.5

CRUDE SURVIVAL RATES -
ALL CASES

TABLE 22

State at:	No. alive	No. alive but with recurrence	$\frac{\text{Cases with recurrence}}{\text{Total survivors}} \times 100$
5 years	371	70	19%
10 years	151	16	11%
15 years	18	2	11%

INCIDENCE OF CASES AT EACH QUINQUENNIUM WITH RECURRENT OR METASTATIC DISEASE

TABLE 23

Length of follow-up	No. of survivors without evident disease	% of total cases
5 years	301	34.4
10 years	135	27.7
15 years	16	14.7

SURVIVORS WITHOUT EVIDENT DISEASE AT EACH QUINQUENNIUM

("CLINICAL CURE RATE")

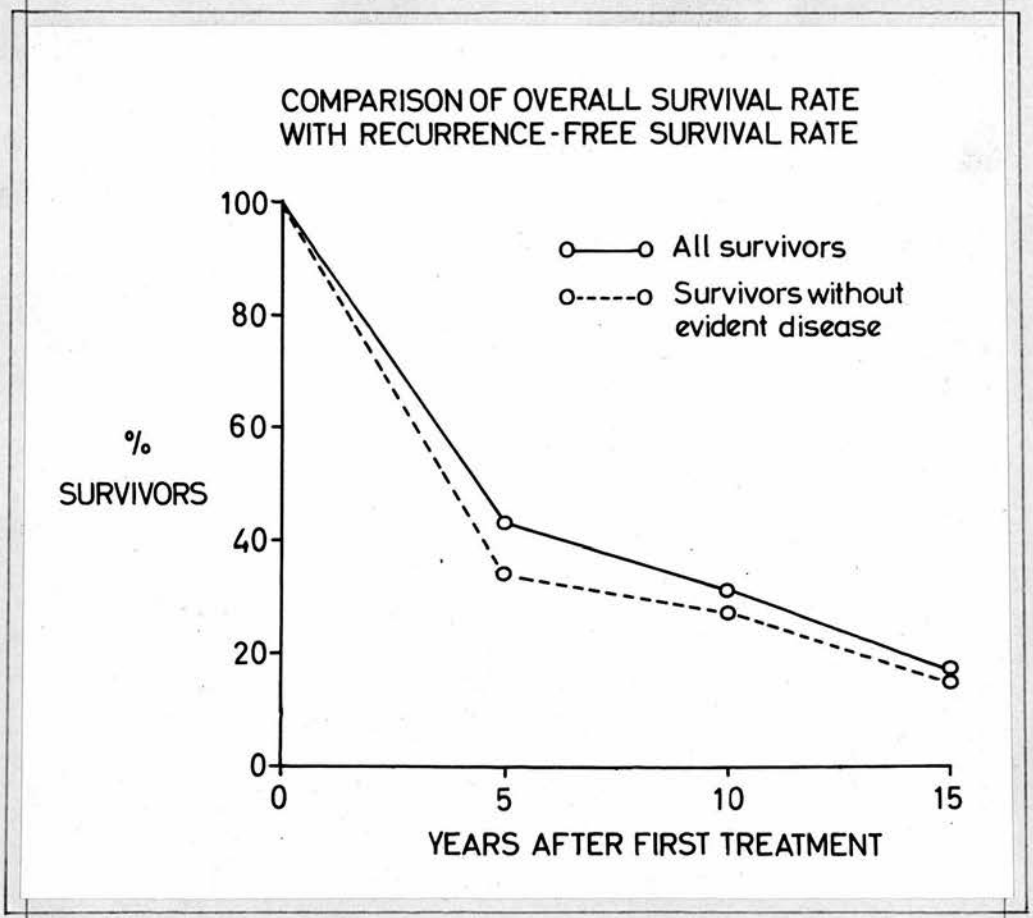
COMPARISON OF OVERALL SURVIVAL RATE
WITH RECURRENCE-FREE SURVIVAL RATE
100
80
60
40
20
0
%
SURVIVORS
All survivors
Survivors without evident disease
0
5
10
15
YEARS AFTER FIRST TREATMENT

Figure 7

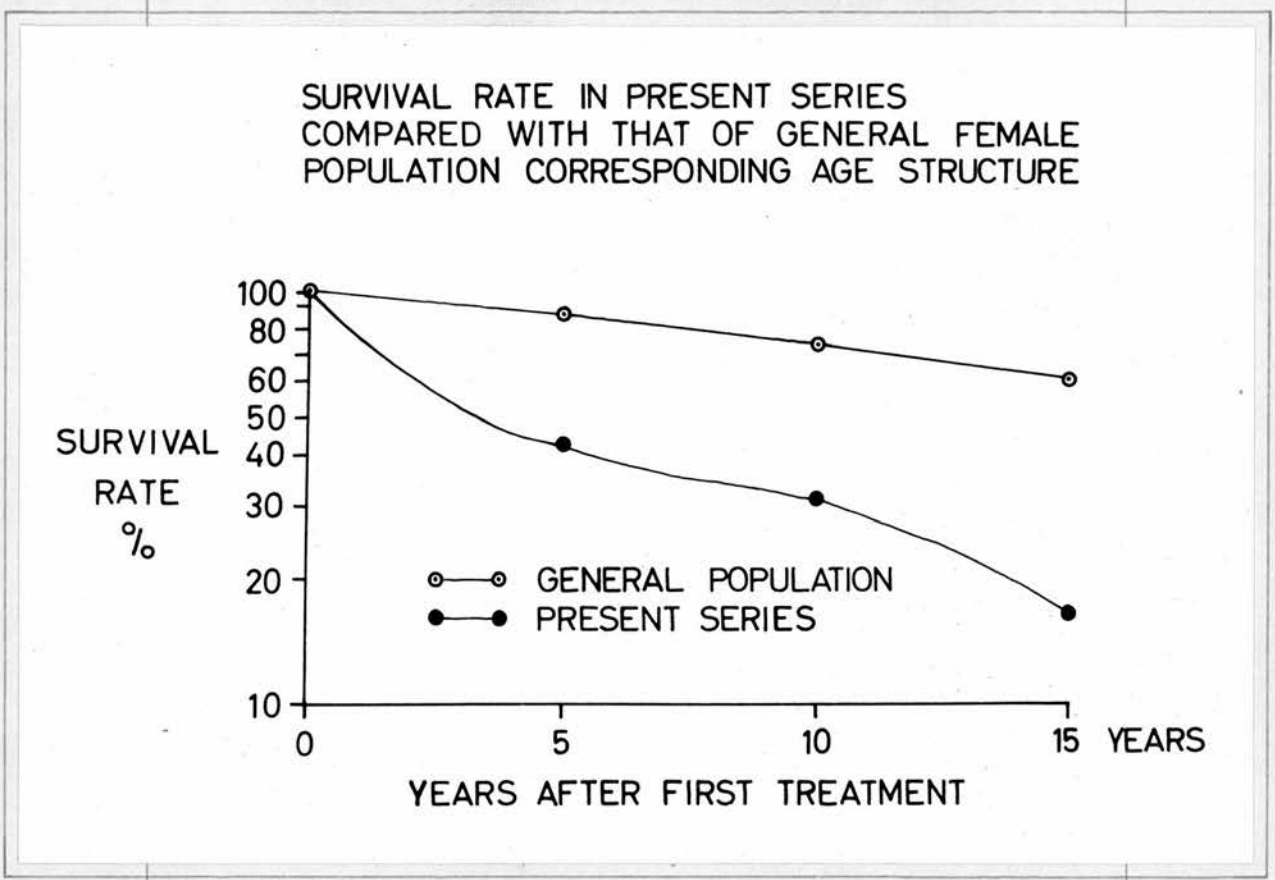
SURVIVAL RATE IN PRESENT SERIES
COMPARED WITH THAT OF GENERAL FEMALE
POPULATION CORRESPONDING AGE STRUCTURE
SURVIVAL
RATE
%
100
80
60
50
40
30
20
10
GENERAL POPULATION
PRESENT SERIES
0
5
10
15
YEARS
YEARS AFTER FIRST TREATMENT

Figure 8

A curve of the latter type can be calculated from the 1951 Life Tables to correspond to the age distribution of the present series (see Appendix 1). This curve and that of the corrected survival rates in the present series are shown plotted logarithmically in Figure 8.

The curves are parallel for a short distance at about seven and a half years, but thereafter diverge again. It is therefore clear that the death rate of breast cancer patients as a whole continues to be greater than that of the general population at least until after 15 years. Cutler et al. in fact found that parallelism did not occur until the period 15-20 years.

Both Figures 7 and 8 therefore demonstrate the error of equating survival with cure even after 15 years.

Deaths from Other Causes

Corrections for life expectancy and comparison with the natural mortality of a comparable population imply that a proportion of deaths in cases of carcinoma of the breast are due to other causes. The natural mortality of course includes deaths from breast cancer but the error thus introduced is a very small one.

Recently Ederer et al. (1963) in a study of a large series based on cancer registration statistics in Connecticut have shown that the proportion of deaths from intercurrent disease to those due to carcinoma increases as each quinquennium is passed.

The/

The deaths from other causes recorded in this series fall into three main groups - post-operative deaths, deaths from intercurrent disease where breast cancer is known to be present and deaths from intercurrent disease where the patient is apparently free of recurrent or metastatic disease. Only the last group is relevant in this connection for both post-operative deaths (many of which followed secondary procedures such as adrenalectomy for metastatic disease) and deaths where tumour was known to be present are directly or indirectly associated with the primary disease.

There are of course many fallacies in the estimation of death from intercurrent disease. The intercurrent disease may not be recorded and the death therefore assumed to be due to breast cancer; recurrence or metastasis may be overlooked or undetectable; and, as McWhirter (1948b) has pointed out, even where an autopsy is performed it is possible to overlook tumour deposits. Ederer et al. comment that in death certification there is a tendency to underestimate breast cancer as a cause of death. In the present series where the information regarding the patient's death is frequently based on a form returned by the family doctor the reverse probably holds true. One has assumed that death is due to breast cancer unless intercurrent disease is specifically stated to be the cause of death and there is no suggestion that recurrent or metastatic disease

was/

was also present. In consequence, as Table 24 shows, the incidence of death from intercurrent disease (thus defined) is low and shows no appreciable change from quinquennium to quinquennium. It is probable therefore that information regarding deaths from intercurrent disease in this series is inadequate for use as a correction factor.

OVERALL RESULTS IN RELATION TO STAGE AND GRADE

The overall results in the present series in relation to stage and histological grade are shown in Tables 25 and 26 and in the corresponding graphs - Figures 9 and 10.

As already mentioned the staging is in all cases in accordance with the Manchester System with the modification described which divides Stage IV into two subgroups. The histological grading is based on Scarff's method (see Section IV - Histological Grading).

In both tables the numbers in each of the fifteen-year categories are seen to be very small. It is clear that one cannot subdivide this group to such an extent and obtain meaningful results. It is in this group too that age distribution calls for the largest corrections and in which the crude figures in consequence have least meaning.

Two/

TABLE 24

Period	Total number of deaths	Deaths from intercurrent disease	Proportion of deaths due to intercurrent disease
0 - 5 years	505	26	5%
5 - 10 years	336	18	5%
10 - 15 years	91	3	3%

DEATHS FROM INTERCURRENT DISEASE

TABLE 25

Follow-up	STAGE														
	I			II			III			IVL			IVD		
	Total cases	Survivors	Survival rate (%)	Total cases	Survivors	Survival rate (%)	Total cases	Survivors	Survival rate (%)	Total cases	Survivors	Survival rate (%)	Total cases	Survivors	Survival rate (%)
5 yr.	315	202	64	224	113	50	80	34	43	161	19	12	96	3	3
10 yr.	187	84	45	120	54	45	45	9	20	85	4	5	50	0	0
15 yr.	31	4	13	28	9	32	16	5	31	21	0	0	13	0	0

SURVIVAL RATES BY STAGES (ALL CASES)

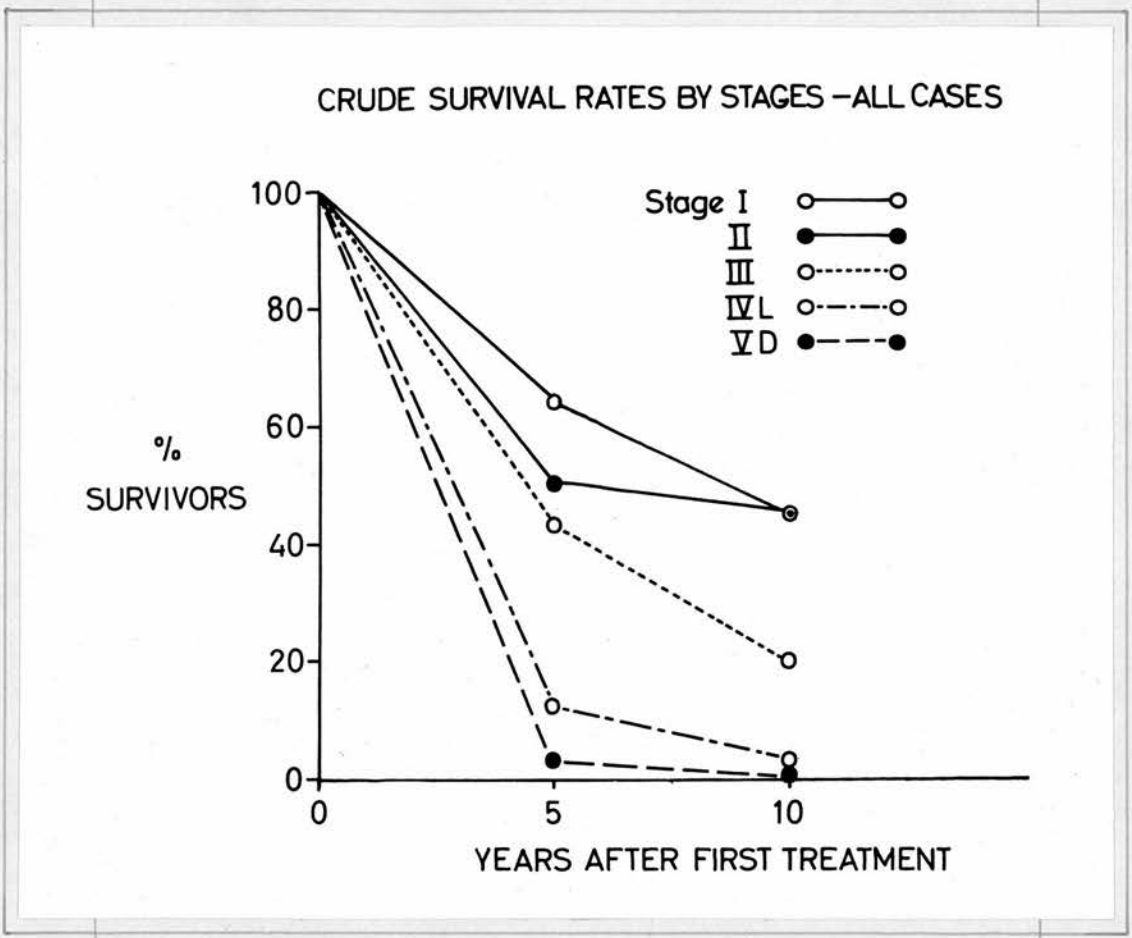
CRUDE SURVIVAL RATES BY STAGES – ALL CASES
Stage I
II
III
IVL
VD
100
80
60
40
20
0
%
SURVIVORS
0
5
10
YEARS AFTER FIRST TREATMENT

Figure 9

TABLE 26

Follow-up	HISTOLOGICAL GRADE								
	I			II			III		
	Total cases	Survivors	Survival rate (%)	Total cases	Survivors	Survival rate (%)	Total cases	Survivors	Survival rate (%)
5 years	74	55	74	355	168	47	258	90	35
10 years	45	19	42	208	64	31	129	41	32
15 years	9	3	33	54	7	13	19	4	21

SURVIVAL RATES BY HISTOLOGICAL GRADES (ALL CASES)

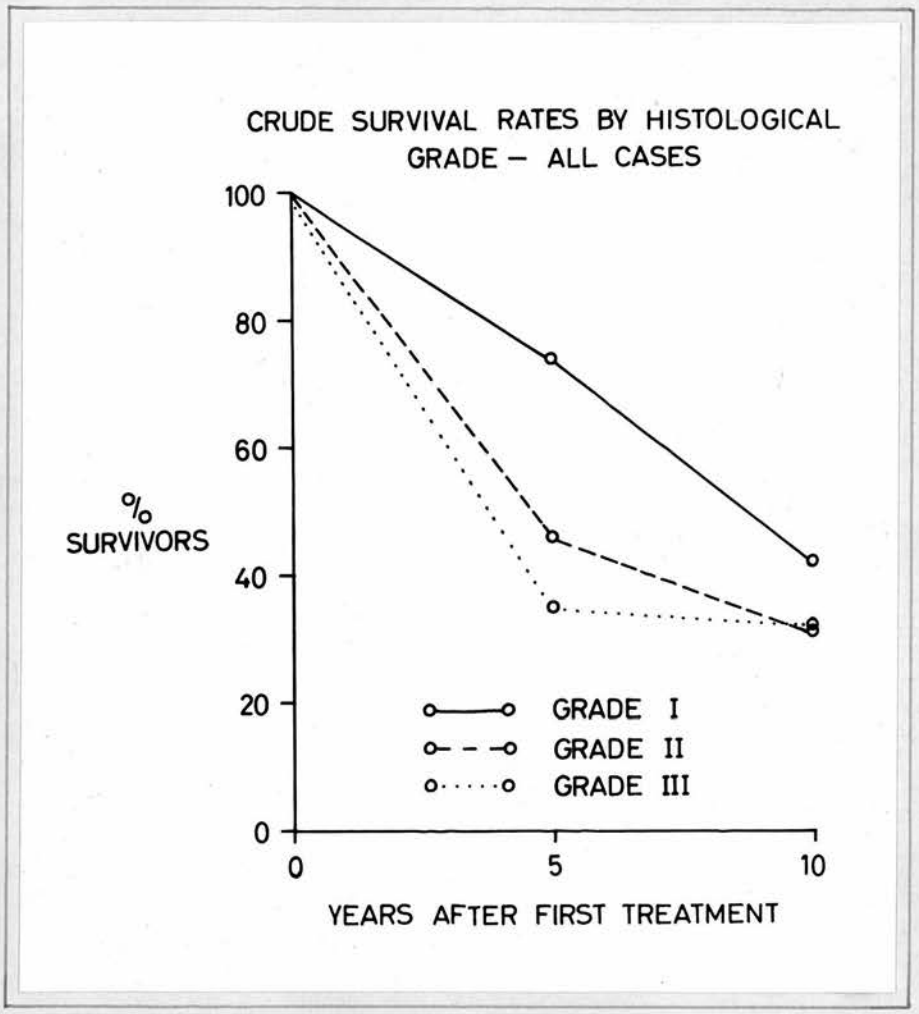
CRUDE SURVIVAL RATES BY HISTOLOGICAL GRADE – ALL CASES
100
80
60
40
20
0
% SURVIVORS
GRADE I
GRADE II
GRADE III
0
5
10
YEARS AFTER FIRST TREATMENT

Figure 10

Two features of these tables are however of considerable interest - the similar survival rates at 10 years for Stages I and II and for Grades II and III.

Since these features are found in the ten-year survival rates but not in the five-year survival rates the possibility of artifact due to differing life expectancies exists. This must be excluded before any other conclusions can be drawn.

Since the proportion of patients alive diminishes with increasing time it is also obvious that the curves representing parts of the total (e.g. separate stages or grades) must approach each other. The use of corrected survival rates while eliminating age distribution as a source of error does not affect this trend.

On the basis of the known age distributions in the different stages and grades, age-corrected survival rates have been calculated (Tables 27 and 27a). The method of calculation is given in Tables 71-74 (Appendix 1).

It is apparent that variations in age distribution have tended to obscure the different prognosis between Stages I and II at 10 years, but this is not so in relation to Grades II and III and it would therefore appear that the distinctions between Grades II and III are not sufficient to demonstrate a difference in prognosis at 10 years. The differences in five-year survival rates are little affected by corrections for age distribution.

Conclusions/

TABLE 27

Stage	5-year survival rates		10-year survival rates	
	Crude	Corrected	Crude	Corrected
I	64	73	45	60
II	50	56	45	56
III	43	49	20	27
IVL	12	14	5	7
IVD	3	4	0	0

AGE-CORRECTED SURVIVAL RATES BY STAGES

TABLE 27a

Grade	5-year survival rates		10-year survival rates	
	Crude	Corrected	Crude	Corrected
I	74	83	42	54
II	47	54	31	42
III	35	40	32	41

AGE-CORRECTED SURVIVAL RATES BY GRADES

CONCLUSIONS

The correspondence between the present series and that published by McWhirter in 1955 was established in the previous section.

Further analysis of the overall figures in relation to stage and grade shows a reliable degree of correlation between these and prognosis up to 10 years - with the exception of Grades II and III where there is no difference at 10 years. At 15 years the figures are too small to give reliable results.

In common with other reported series these cases show a continuing mortality from breast cancer itself up to 15 years after treatment.

SECTION IV

HISTOLOGICAL GRADING

HISTOLOGICAL GRADING

Introduction

Histological grading is a means of determining the malignancy of a tumour from a histological study of its cells.

This simple definition however rests on other concepts less easy to define. In the first place it depends on the meaning of malignancy. In this context the term malignancy is used in the relative sense of degree of malignancy rather than in the absolute sense in which malignant tumours as a whole are separated from benign. One starts from the point at which the diagnosis of malignancy has been made. The borderline between benign and malignant tumours which indeed renders the use of the term absolute of doubtful validity is not the concern of histological grading.

Accepting this meaning of malignancy as a term of degree, and therefore by implication measurable, one is led to define the terms or units in which it is to be measured. There are a number of possibilities from local invasiveness to death of the host. The latter is the most convenient measure albeit a rather crude one, for it enables one to formulate the mathematical statement that malignancy is inversely proportional to the time of survival of the host from the onset of the malignant process.

In/

In practice, as has already been discussed, the time of onset of the malignant process cannot be determined and one must consequently take an arbitrary point in time, such as the time of first treatment, to represent it. Clearly this introduces the possibility of considerable error.

Survival, furthermore, is determined by other factors unrelated to this intrinsic property of the tumour termed malignancy. These factors include:

1. Chance.

2. Intercurrent disease, often related to age.

3. Host response.

4. Treatment.

Chance may determine the site of the tumour and its relation to the pathways of spread. The early invasion of a lymph vessel or a blood vessel may be determined in part by chance. The sites of metastatic spread may likewise be chance effects and survival after metastasis depends to some extent on this factor. This problem is connected with the relationship between stage and survival which has already been dealt with at some length (p.60). The possibility remains however that the degree of malignancy and the clinical stage at the time of presentation are interrelated.

Intercurrent disease, commoner in the aged, may well determine the survival time rather than the malignancy of the tumour and in most cases is independent of the tumour.

Host/

Host response however closely related to or even determined by the tumour is not strictly speaking an intrinsic property of the tumour. Little is known with certainty of the nature or existence of a host response in cancer and it is possible the malignancy and host response are overlapping fields. This problem will be discussed again when the different grading systems are reviewed.

While it seems obvious that treatment, or at least the more radical forms of treatment, influence the course of the disease it is by no means easy to prove this conclusively. There is also some justification for the belief that the response to treatment is determined by the biological properties of the tumour (Macdonald, 1951) with which the term malignancy as used here is virtually synonymous.

In order therefore to use survival as a measure of malignancy certain allowances or corrections must be made. Of these the stage of the disease is the most important and can be allowed for by comparing survival rates of different tumours within the same stage. Allowance can be made for intercurrent disease by using an estimate of normal life expectancy obtained from the appropriate life tables. The part played by host response is largely indeterminate. The effect of treatment can be annulled at least in part by considering/

considering cases treated in the same way. With regard to survival time itself, the usual measure is of course the proportion of patients surviving for a given period.

The Object of Histological Grading

Histological grading although it may be clothed in mathematical terms is not a method of great accuracy. Even if it were, the other factors affecting prognosis would blur its usefulness as a prognostic index. At best it can indicate in broad terms the prognosis of a group, never of the individual. It has therefore only two possible uses. The first and most acceptable of these is to define groups of cases sharing a common biological characteristic. The value of this is considerable for it helps to increase the validity of comparisons between groups of cases. This is of course of particular importance in any study of the results of treatment. To ignore the relative distribution of histological grades within such groups may not introduce an error of the magnitude which would appear if the distribution of stages was ignored, but it would nevertheless introduce an error of some importance.

The second and more controversial use of histological grading is in the selection of treatment. Here its validity depends on the relation between grading and the response to different methods of treatment.

The/

The Development of Histological Grading

Von Hansemann is usually thought to have been the first to suggest, as he did in 1893, that the prognosis of a tumour bore some relationship to its histological structure (Haagensen, 1933). Dennis in the United States had observed this independently in 1891 but his work seems to have escaped notice. In the opinion of Dennis "the histological character of the tumour itself influences more than any other cause the recurrence of carcinoma of the breast".

It was not however until 1920 that an attempt was made to classify tumours according to the degree of anaplasia. Broders working under MacCarty at the Mayo Clinic devised a system for grading squamous epitheliomas. He based this on the ground that differentiated cells have no power of regeneration and that cancer cells are "regenerative" to the extent that they are undifferentiated.. The grades were allocated simply on the numerical proportion of differentiated cells in the section. There were four such grades, Grade I having 75 per cent or more differentiated cells, Grade IV being completely undifferentiated.

Comparing the grading with the survival of his cases Broders found a good correlation between the degree of differentiation and the prognosis.

Following/

Following Broders' lead Greenough in 1925 applied similar criteria to the grading of breast tumours. The factors by which he assessed differentiation have remained the basis of most systems used for breast carcinoma. These included adenomatous formation, cell size and variability, nuclear size and variability, hyperchromatism and mitotic figures. Each of these he attempted to evaluate separately in relation to prognosis. His figures were however small and at times of doubtful validity, but in a number of instances the correlation seemed clear, particularly when the assessment of malignancy was based on a combination of these factors.

Meanwhile Sistrunk and MacCarty (1922) and MacCarty (1922) were exploring the significance of other histological features in relation to prognosis. Broders' interest had been confined to the tumour cells. Sistrunk and MacCarty turned to the stroma in search of evidence of a defence mechanism. Fibrosis, hyalinization and lymphocytic infiltration were each tested and the first two shown to be associated with a good prognosis.

White in 1927 found Greenough's criteria related to the five-year survival rate in breast cancer but could find no such correlation with the stromal factors studied by Sistrunk and MacCarty.

Thus/

Thus at an early stage in the evolution of grading systems two main streams are apparent. Each is still evident. Common to all systems are the characteristics of the tumour cells. The two streams are represented on the one hand by those systems which confine themselves to such characteristics, and on the other by those which consider, in addition, certain stromal features.

In England the development of systems of the first type was carried a stage further by Patey and Scarff in 1928. Greenough's criteria were simplified, each factor was considered separately and the tumour classified accordingly into one of three groups. These groups were as follows: Group 1 - slight degree of malignancy; Group 2 - moderate malignancy; Group 3 - marked malignancy. In a small series of cases of breast cancer these groupings were found to correlate quite well with survival. In 1938 Scarff and Handley reported a larger series of breast cancer cases confirming the value of the method as a prognostic index.

Bloom (1950) adopted Scarff's method which by this time had become both simpler and more precise. Only three features were assessed - tubule formation, nuclear irregularity and mitosis (including hyperchromatism). Each of these was given a numerical score and the tumour placed in one of three grades according to the total score.

Bloom/

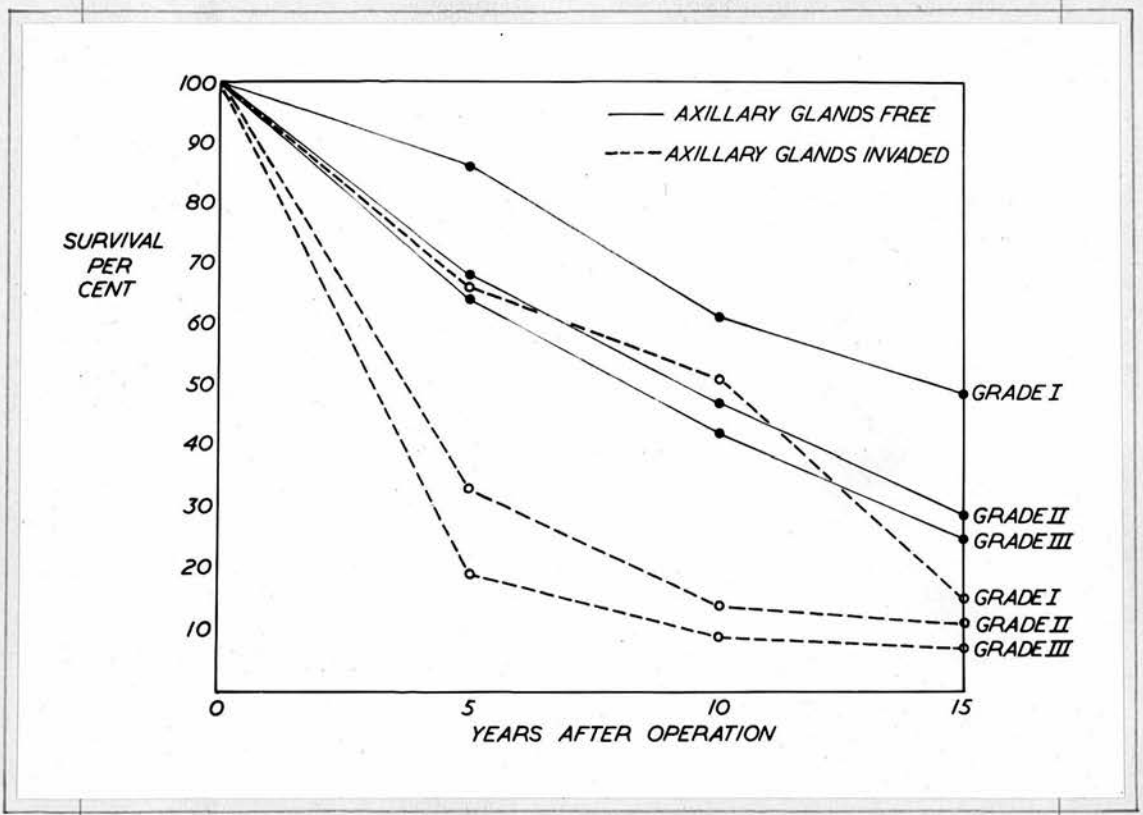

Figure 11

Histological Grade and Prognosis in Relation to Axillary Node Involvement (after Bloom and Richardson, 1957).

Bloom reported a series of 470 cases and with Richardson in 1957 a series of 1,400 cases both confirming the correlation between histological grade and prognosis. This correlation was also found to be independent of the stage of disease as judged by histological examination of the axillary nodes (Fig. 11). A similar observation had been made by Greenough and also by Haagensen (1933).

Haagensen's system though rather more complex than Scarff's is of the same type. It was derived from a study of numerous factors both cellular and stromal and includes only those found to be of prognostic significance. By this means he arrived at similar criteria to those adopted by Scarff. All stromal factors except the rather uncommon feature of gelatinous degeneration were eliminated (Haagensen, 1933).

In the United States, however, Broders' original system, adapted for use in breast tumours, still holds sway. Probably the largest series of cases in which the results of histological grading are reported is that of Berkson and his colleagues from the Mayo Clinic (Berkson et al., 1957). In this series of some 8,700 cases Broders' method was used. Here too correlation with survival and independence of stage are clearly demonstrated (Fig. 12).

In/

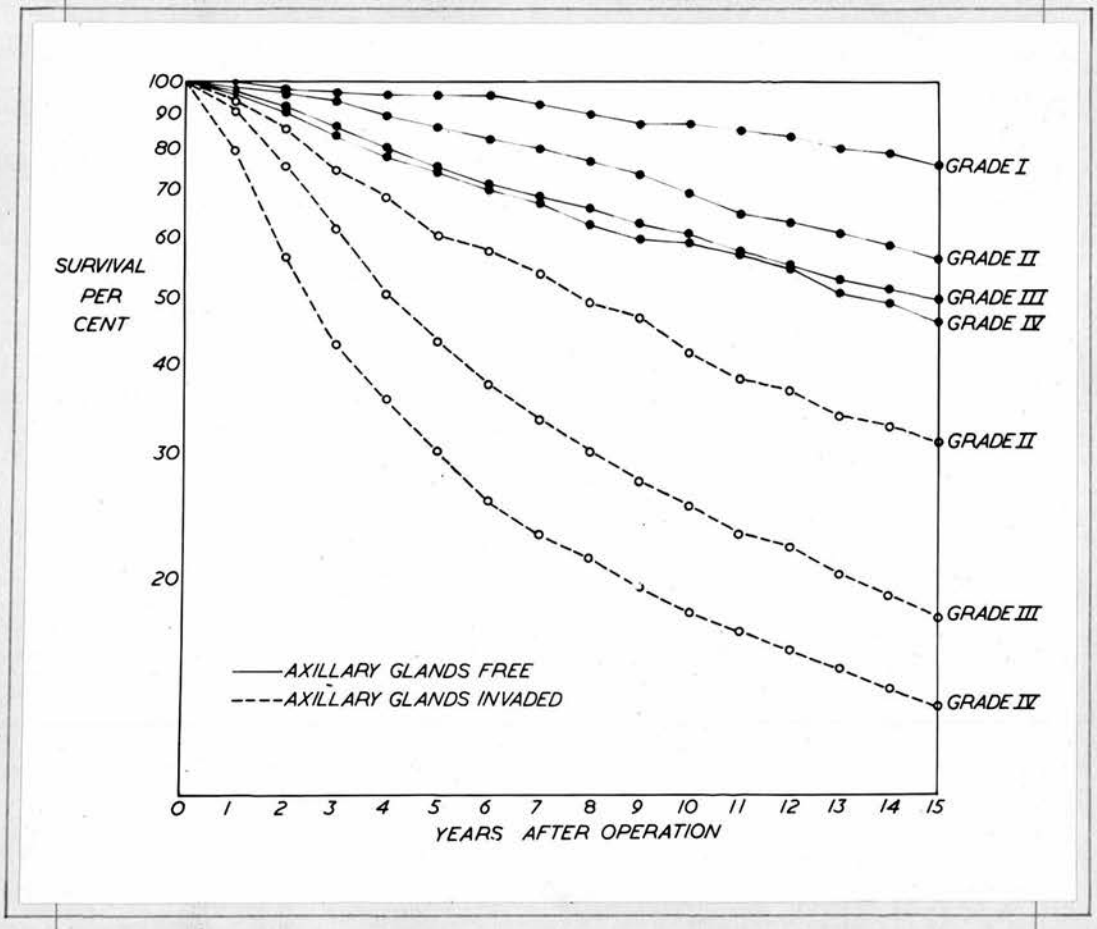

Figure 12

Histological Grade and Prognosis in Relation to Axillary Node Involvement (after Berkson et al., 1957).

HUEPER (1930)

"The Histological Malignogram"

- I. Special cell and structural characteristics
  - 1. Special type
  - 2. Nucleo-cytoplasmic ratio
  - 3. Number of pencil cells
  - 4. Infiltrative growth
  - 5. Parenchyma-stromal relationship
- II. Cytoplasm
  - 6. Irregularity of size
  - 7. Irregularity of shape
  - 8. Distinctness of outline
  - 9. Chromatism
  - 10. Functional activity
- III. Nuclei
  - 11. Irregularity of size
  - 12. Irregularity of shape
  - 13. Chromatism
  - 14. Hyperchromation
  - 15. Number of mitoses
  - 16. Irregularity of mitoses
- IV. Stroma
  - 17. Character
  - 18. Vascularity
  - 19. Type of cellular infiltration
  - 20. Amount of cellular infiltration

Each of the 20 sub groups divided into four degrees scoring 1 - 4 points giving a possible total of 80 points. Grading based on total score.

Figure 13

In spite of doubts as to their value, the stromal factors introduced by Sistrunk and MacCarty continued to enjoy popularity in the construction of grading systems. Flothow (1928) found evidence particularly in favour of fibrosis and hyalinization, regarding lymphocytic infiltration as an early, but relatively ineffective defence mechanism. The grading systems used by Smith and Bartlett (1929), Evans (1933) and Sophian (1935) all took stromal factors into account.

The acme and at the same time the reductio ad absurdum of such systems was that devised by Schmitz and his colleagues in 1926 and later modified for use in breast tumours (Schmitz and Hueper, 1930) (Fig. 13). Each of the factors shown was subdivided into four degrees and given a corresponding number of points. The final grading was based on the total points scored. Many of the estimates required could hardly be achieved on the average histological section or would require a most laborious examination, and the doubtful validity of certain factors in determining prognosis would tend to obscure the effect of those which were valid. In fact the correlation between grade and prognosis is not very striking.

More recently Hultborn and Törnberg (1960) in Stockholm have used lymphocytic infiltration and an assessment of invasiveness/

invasiveness at the periphery of the tumour in addition to the usual cellular factors. While the correlation between grade and prognosis is clear it is difficult to determine whether this is influenced more by the cellular characteristics or by the stromal features.

A further histological factor, sinus histiocytosis in the draining lymph nodes, has been advocated by Black and his colleagues (1955). The presence of histiocytes in the sinuses of axillary nodes not involved by tumour is rated on a scale from 0 to 4 according to the degree of the cellular reaction. This rating is combined with those based on features of the tumour cells to determine the grade of the tumour. The grade showed a correlation with prognosis but a similar correlation was found when cases were classified by the degree of sinus histiocytosis alone. Berg (1959) and Moore et al. (1960) failed to confirm this latter finding. Black's most recent report however (Cutler, Black and Goldenberg, 1963) reiterates the claim and bases it on a series of 597 cases. The method is of course applicable only to cases where the axillary nodes are available for histological examination. Furthermore if all available nodes are extensively involved by tumour no assessment of sinus histiocytosis can be made.

The/

The appearance of the tumour margin was used by Hultborn and Törnberg to assess invasiveness. This feature alone has been made the basis of a classification of breast tumours by Lane and his colleagues (1961). Since this is based largely on a naked-eye or low-power inspection of the slide or of the fresh tumour it is not strictly speaking a form of histological grading. It does however seek to establish a relationship between a feature of the tumour and prognosis. Lane's results show that cases with "well-delimited" tumours had a 10-year survival rate twice that of cases whose tumours showed an irregular margin. All the cases were classed as operable according to the rather strict criteria of Haagensen from whose unit the series was taken. A higher proportion of partially-differentiated tumours was found in the irregular tumour group but the numbers are small and probably not significant. Likewise there was an impression not tested numerically that pleomorphism was commoner in the well-delimited tumour group.

Criticisms of Histological Grading

From its inception grading has not lacked critics. The criticisms that can be levelled against it fall into two groups - those concerned with the concepts on which grading depends, and those concerned with the reliability of the process.

The/

The relationship between anaplasia and malignancy is generally accepted. Cowdry (1955) points out that the fully differentiated mature cell loses its power of multiplication. Growth potential resides in the undifferentiated cell. Conversely rapid growth restricts the ability of the cell to differentiate (Lauren, 1961) and, as Scarff (1948) has pointed out, this introduces a potential source of error. If the histological features reflect rapidity of growth then they will reflect malignancy only in so far as malignancy and growth rate are related. This is commonly but not invariably the case.

The concept of a defence mechanism or host reaction is more nebulous. Apart from sinus histiocytosis two phenomena have been put forward as evidence of this - fibrosis and lymphocytic infiltration.

Fibrosis is a common feature of a carcinoma of the breast. Approximately 75 per cent are classified as scirrhous (Anderson, 1957). The expression "scirrhous reaction" is an accepted part of the pathologist's terminology. Evidence that this represents a defence mechanism is, however, lacking. There is even doubt that it represents a reaction at all (Dawson and Tod, 1934). The breast or at least that part of it in which the glandular tissue lies and from which tumours arise, is a fibrous organ. The fibrous tissue seen in relation to a carcinoma is commonly/

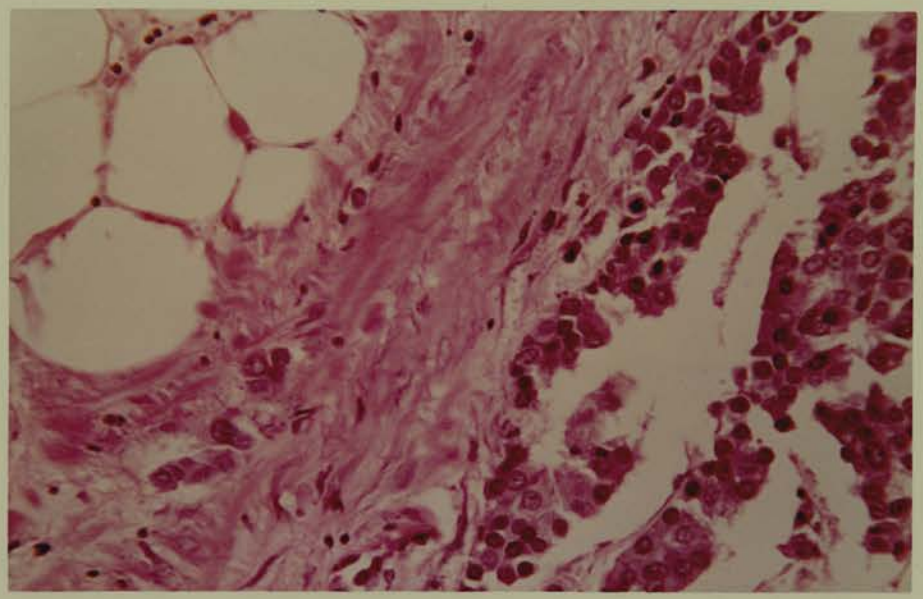

Plate 5

The Edge of a Scirrhous Carcinoma of the Breast

Note the dense acellular nature of the fibrous tissue. (x 300).

commonly mature and relatively acellular. This is true even at the periphery of the tumour (Plate 5) whereas here, where active growth is presumably occurring, one would expect to find evidence of fibroblastic activity. Furthermore where groups of cells are penetrating the fatty tissue of the breast and extending beyond the main body of the tumour one often finds no evidence of fibrosis (Plate 6).

It is true that in some cases marked fibroblastic activity is seen in relation to breast carcinoma but this is uncommon and does not constitute fibrosis in the sense used in histological grading.

In the light of present knowledge of the immunological function of lymphocytes and the possibility that certain tumours may have antigenic properties, it is not difficult to accept lymphocytic infiltration as evidence of a host reaction. Dawson and Tod (1934) however suggested that such infiltration may be due to necrosis of the tumour and Larmi and Saxen (1963) have demonstrated that necrosis and lymphocytic infiltration tend to occur together. The latter series nevertheless showed a slight trend in favour of a better prognosis in the cases showing this association.

The evidence that lymphocytic infiltration is a significant factor in determining prognosis is however conflicting. This may be due in part to the difficulty in assessing it, for wide variations in different parts of the tumour/

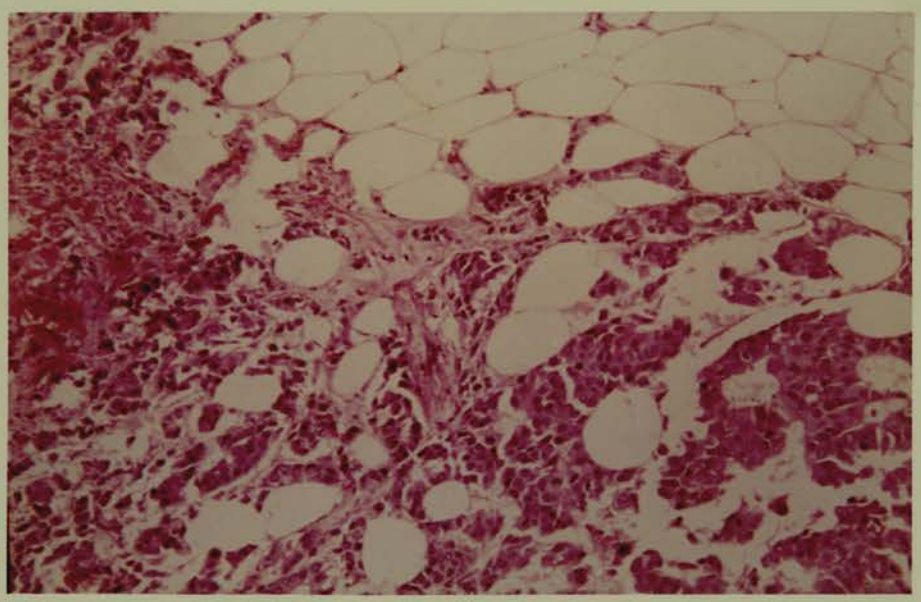

Plate 6

The Edge of a Scirrhous Carcinoma of the Breast

The tumour cells extending out into the fatty tissue of the breast in the lower right hand part of the field show no associated fibrosis, whereas those in the centre of the field are embedded in dense fibrous tissue. (x 150).

tumour occur. To include it as a factor in grading is to prejudge an issue which is as yet unsettled.

Regardless of the validity of such stromal factors in assessing prognosis, their inclusion in grading systems implies some confusion of thought. The basic concept of histological grading is the assessment of malignancy from the histological characteristics of the tumour itself. Host reactions, if any, may or may not be related to these characteristics but, in any event, represent a different aspect of the tumour-host relationship. As such there is much to be said for giving them separate consideration.

While accepting that certain histological features do bear some relationship to the degree of malignancy, many have doubted whether they can be assessed quantitatively.

Like most biological phenomena these features show an infinite gradation. Any attempt to break them down into degrees, such as slight, moderate and marked, involves arbitrary distinctions which are almost certain to be difficult to define with precision. A histological section 5 microns in thickness is also a very small sample of the entire tumour. Are estimates, themselves subject to inaccuracy, based on such sample, valid for the whole tumour?

These are the main criticisms of grading. A rather more hypothetical objection is that metastatic deposits, in the axillary nodes for example, may show an alteration in the/

the degree of malignancy and this may possibly affect the outcome more than the grade of the primary tumour.

Where arbitrary distinctions have been drawn, an important test of their value is the extent to which the results based upon them are reproducible. This fundamental point has received surprisingly little attention. Greenough (1925) had his grading checked by a separate observer and found a difference of opinion in 10 per cent of cases. His whole series amounted to only about 70 cases. Schmitz and Hueper (1926) whose complex grading system has already been described, claim that the average variation in the total score was three points, but they give no indication of the range of this variation. No other authors appear to have applied such tests. Willis' undocumented statement that "it is not surprising to learn that different graders reach different conclusions on the same material", therefore remains unchallenged (Willis, 1948). Apart from the labour involved, it is difficult to see why this problem has not been tackled.

The probability that one or more sections provide an adequate sample of the whole tumour can be determined by observing the variations seen within one section or in separate sections. Some of the confusion regarding this seems to arise from observed variations in the general pattern of a tumour. It is commonly found, for example, that/

that tumour cells may form large clumps in one area and be separated by fibrous tissue into thin strands in another. This however is not relevant, and as Evans (1933) has pointed out, attempts to relate prognosis to the overall histological pattern, e.g. scirrhous or medullary, have indeed proved very unsatisfactory. The problem is whether tubule formation, pleomorphism, the incidence of mitotic figures and similar features vary in a similar way.

Patey and Scarff (1928) considered that provided a fairly large portion of the tumour was included in the section such variations were not significant. Smith and Bartlett (1929) on the other hand found that a lack of homogeneity in the tumour added considerably to the problems of grading. Haagensen (1933) estimated that variations of a degree sufficient to make grading difficult occurred in only 10 per cent of cases. He concluded that the study of three or four sections was adequate in "the great majority of instances". Bloom (1950) agreed with Patey and Scarff, whose system he used, and found by grading different parts of the same tumour that the result was unaffected.

Differences in grade between the primary tumour and lymph node metastases have been studied by Patey and Scarff (1929) who found agreement in 90 per cent of cases, the/

the remainder showing a lower grade in the nodes in most instances. Bloom and Richardson (1957) found the same grade in 82 per cent and Haagensen (1933) in 70 per cent. In Haagensen's series 20 per cent of the nodal metastases had a higher grade and 10 per cent a lower grade than the primary tumour. Such differences even if significant in the determination of prognosis do not therefore seem to be common.

More general criticisms of grading have been advanced on a number of occasions. To Reimann (1929) the multiplicity of histological features seemed to make any attempt at grading futile. He pointed out that many of these features could be determined by factors unrelated to malignancy. Broders' series was criticized by Plaut (1927) who considered that differences in tumour size alone could have accounted for the results attributed to differences in grade. He drew attention to the frequency of amitotic division in cancer cells and felt that this detracted from the value of mitotic counts in the determination of grade.

Bonser and her colleagues (1961) whilst supporting the use of a simple system, such as Scarff's, in breast cancer, point out that many pathologists regard grading as impossible or useless. In fact the subject receives little or no mention in most textbooks of pathology. Willis (1948), however/

however, is outspoken in his condemnation of grading. He regards the use of numerical grades as fallacious, conferring a spurious precision on a process which is "largely guesswork". At the same time he accepts that a competent pathologist's opinion as to the degree of malignancy is of value.

The dilemma seems to lie in the interpretation of grading. Numerical grades do indeed suggest a mathematical precision which is quite spurious, but this would mislead only those who are unsure of the nature and limitations of grading. Numerical grades in fact merely codify the pathologist's opinion. If this opinion is of value in the study of tumours it can be used only in numerical form. Grading is a substitute for such terms as "moderately differentiated", "fairly frequent mitoses", "a tendency to anaplasia".

GRADING TECHNIQUE

The method first described by Patey and Scarff in 1928 and detailed in its later simplified form by Bloom and Richardson (1957) has the merits of simplicity and acceptable criteria. It seems to be the most satisfactory of those currently used in grading carcinoma of the breast and for this reason has been adopted in the present study.

Through/

Through the kindness of Professor Scarff a period was spent studying this technique in his Department at the Middlesex Hospital.

Technique

The grading is carried out on routine histological sections of the primary tumour. All sections are stained in the standard way with haematoxylin and eosin. The grading is based on the average findings after studying the different areas of tumour in all the available sections.

In this series the average number of sections per case was probably between two and three, though not all of them were of the primary tumour. Those of the tumour itself probably averaged between one and two per case.

Three characteristics of the tumour are separately assessed. These are tubule formation, hyperchromatism and mitosis, and nuclear irregularity or pleomorphism. Each of these characteristics is allotted a score of one to three. The sum of the three scores determines the grade according to the following scheme.

	Total score
Grade I	3 - 5
Grade II	6 - 7
Grade III	8 - 9

Each slide is first examined with a standard low-power (16 mm.) objective, preferably after a preliminary survey with/

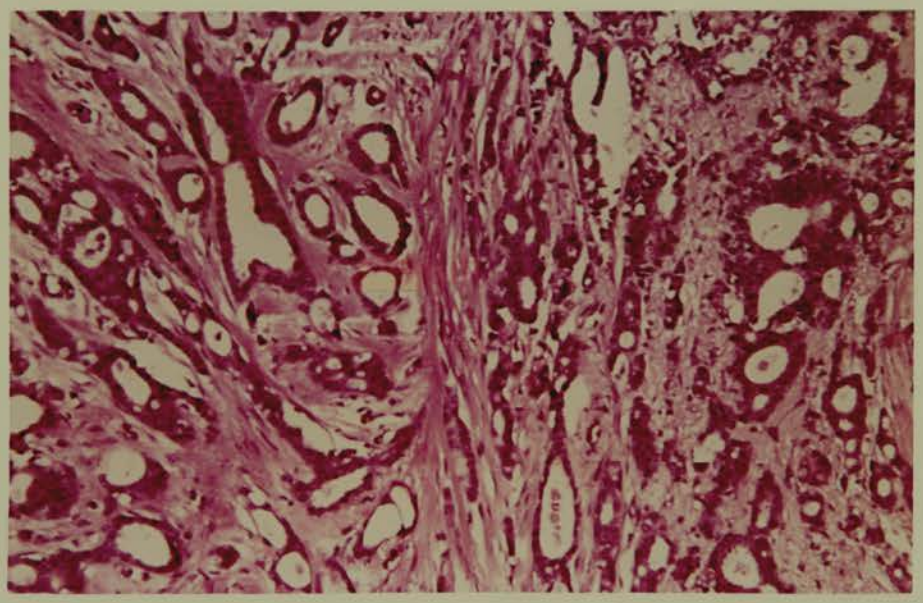

Plate 7

Tubule Formation

Widespread tubule formation of this type is given a score of 1. (x 130).

with a scanning (40 mm.) objective. A x6 eyepiece is used throughout. This is of particular importance in fixing a standard size for the high power field.

With low-power magnification the degree of tubule formation is readily seen in most cases and the appropriate score provisionally allocated. The section is then examined under high-power magnification using a 4 mm. objective. In the first few fields examined an estimate of the extent of hyperchromatism and mitosis and of pleomorphism is made, and a provisional score allocated.

Numerous other fields are then examined and the score adjusted if necessary to conform to the overall picture. It is usually easier to consider one feature at a time at this stage. It may also be necessary to use high power magnification to confirm doubtful appearances of tubule formation observed during the low-power examination.

Tubule Formation

Where tubule formation is widespread and to be found in practically every field a score of 1 is given (Plate 7). Where there is no evidence of tubule formation the score is 3. A score of 2 is given where some evidence of tubule formation is present, up to a moderate degree which does not extend to all parts of the tumour (Plate 8). The range covered by the score of 2 is quite extensive.

Hyperchromatism/

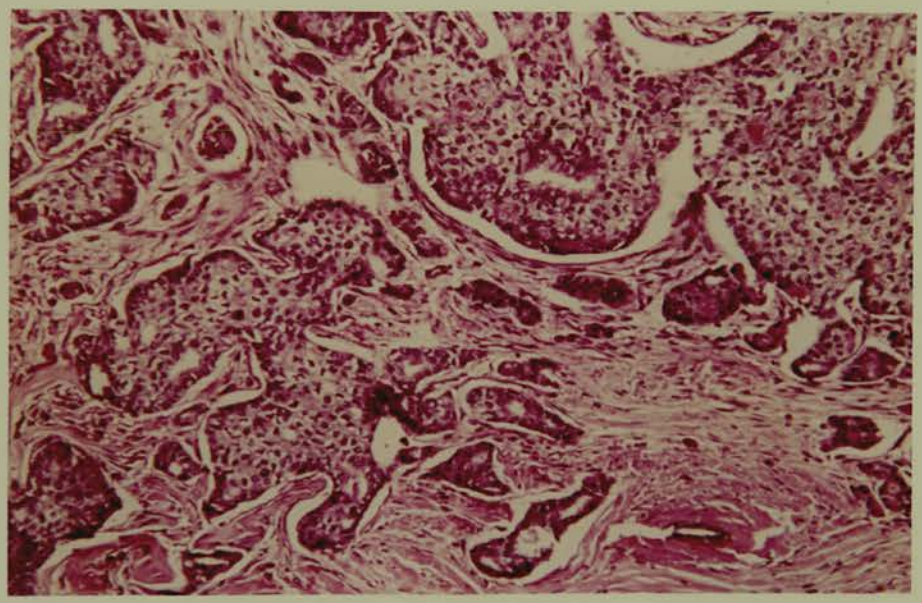

Plate 8

Tubule Formation

The tubules in this tumour are less well-formed and fewer in number than those illustrated in Plate 7. The score allocated to this factor was 2. (x 130).

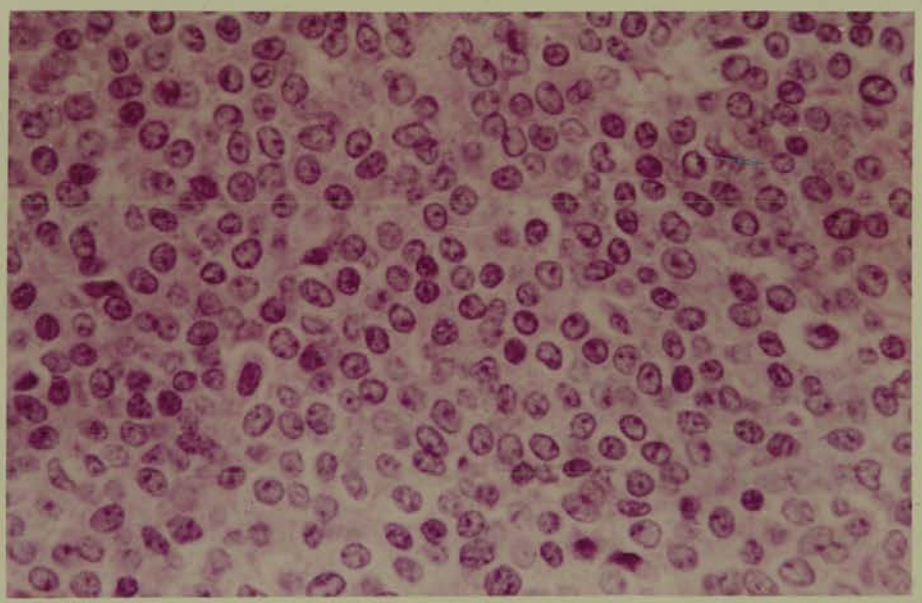

Plate 9

Nuclear Characteristics

Note the uniformity of the nuclei, the infrequency of hyperchromatism and the absence of mitotic figures. Such a tumour is rated a score of 1 both in respect of nuclear pleomorphism and of hyperchromatism and mitosis. (x 540).

Hyperchromatism and Mitosis

If the cells show little or no nuclear hyperchromatism and no more than an occasional mitosis the score for this characteristic is 1 (Plate 9). A tumour with numerous mitoses, that is mitoses occurring in almost every high-power field and multiple mitoses in some, is rated as 3 (Plate 10). The score of 2 is allotted to tumours in which hyperchromatism is common and mitosis more than occasional.

In assessing the frequency of mitosis an attempt is made to allow for the number of cells in the field examined. This of course may vary widely, being many in solid masses of cells in medullary tumours but comparatively few in the scattered groups of some scirrhous tumours.

Nuclear Pleomorphism

Uniformity of nuclear size and shape throughout the section is scored as 1 (Plate 9). Wide variability of nuclei or the presence of giant cells determines a score of 3 (Plates 10 and 11). The intermediate stages are scored 2 (Plate 12).

From the above it can be seen that a degree of subjectivity is implicit in the method and is indeed unavoidable. It can be minimized by training and practice, but it is also important to grade tumours without any knowledge of the case and this was carefully adhered to in the present series.

It/

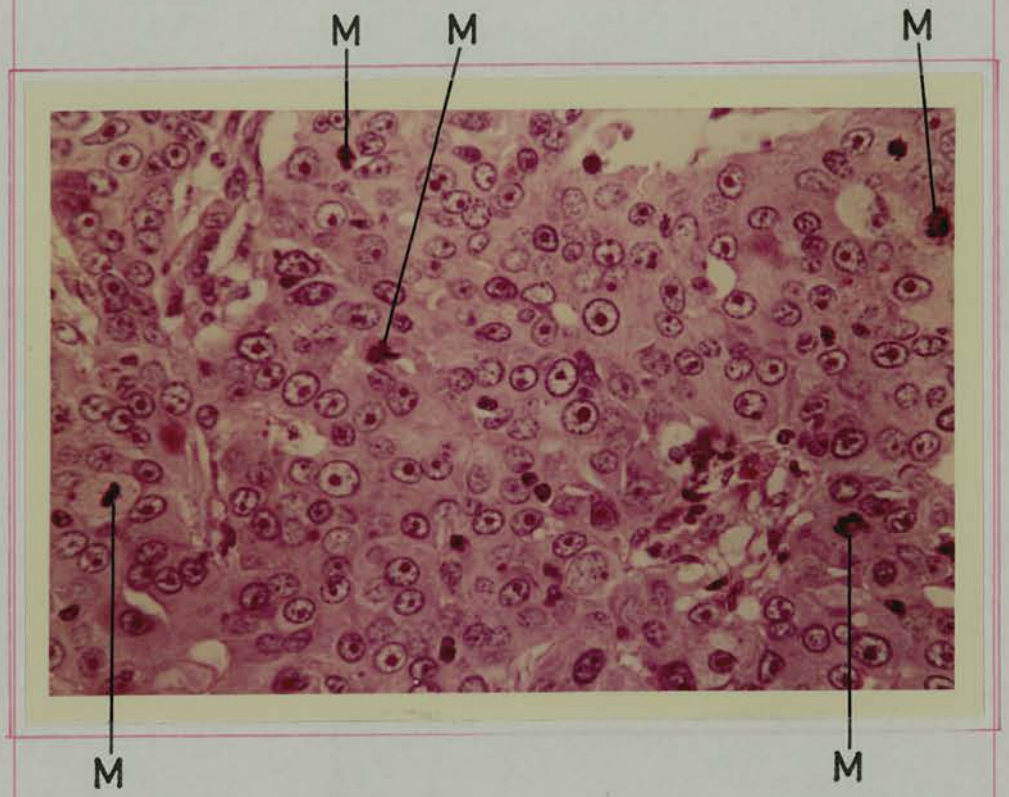

Plate 10

Nuclear Characteristics

In this tumour the nuclei showed considerable variation in size and numerous mitotic figures several of which are present in this field (M). Both these characteristics were allotted a score of 3. (x 450).

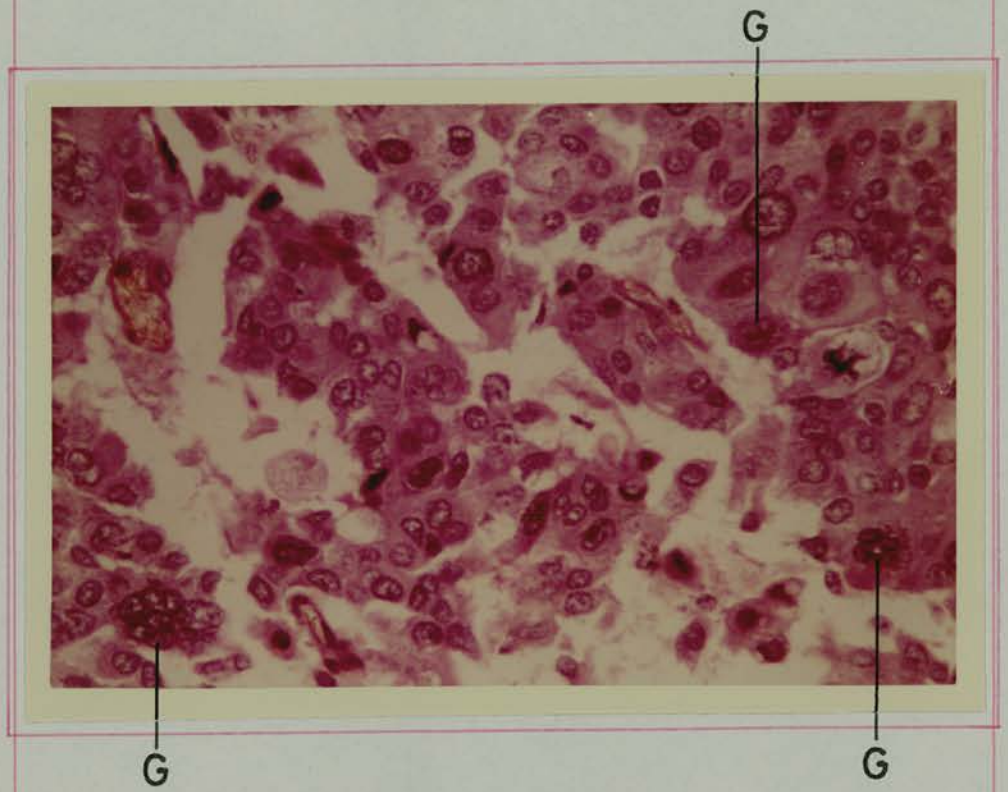

Plate 11

Nuclear Characteristics

Note the wide range of nuclear size and shape and the presence of a number of multinucleate giant cells (G). A score of 3 was allotted to nuclear pleomorphism in this tumour. (x 450).

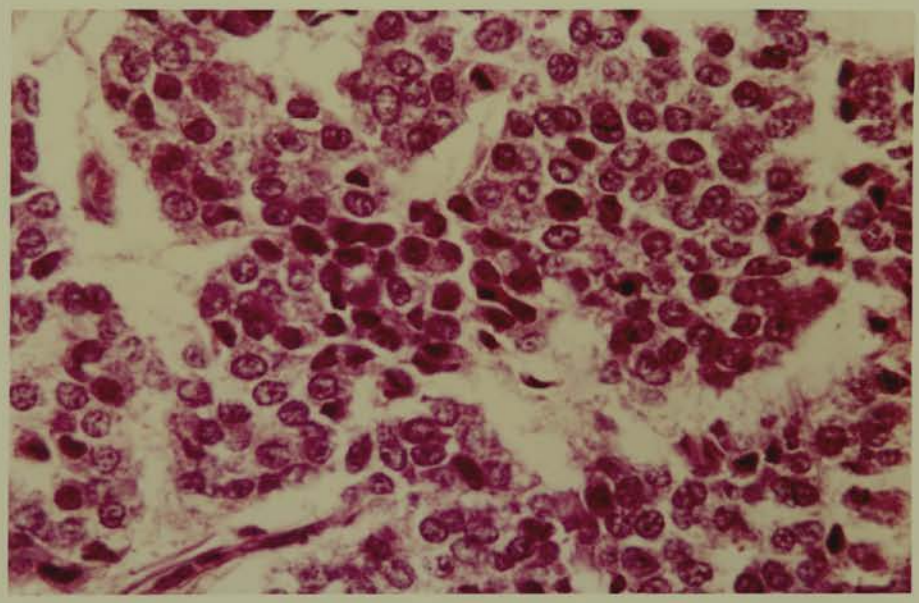

Plate 12

Nuclear Characteristics

Pleomorphism in this tumour is of an intermediate degree, c.f. Plates 9 and 10. There is also a moderate degree of hyperchromatism. Both these characteristics were allocated a score of 2. (x 600).

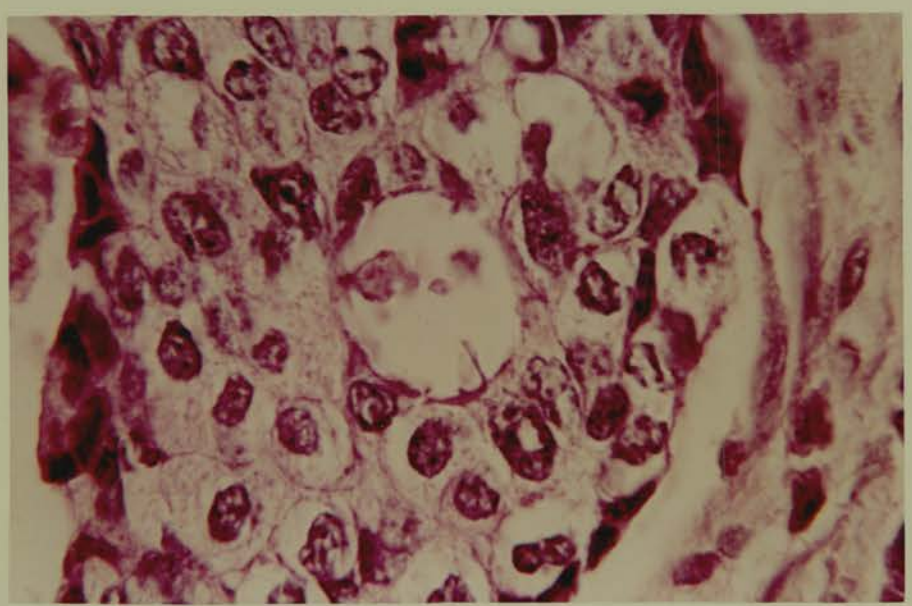

Plate 13

False Tubule Formation

The appearance of a tubule produced by loss of a cell or cells from a solid mass. Note how under high magnification it is apparent from the arrangement of the surrounding cells that this is not a true tubule. (x 900).

It is obvious that in effect the system separates two extremes - Grades I and III - from a less well defined middle group - Grade II. The allocation of three scores to Grade I, i.e. 3 - 5, reduces the effect of this to some extent.

Finally a consideration of the criteria used to determine score makes it clear that there is a borderline between scores which must be ill-defined. This introduces a certain error into the allocation of scores and, though to a lesser extent, of grades.

Difficulties in Evaluation of Histological Appearances

There are a number of circumstances in which tubule formation is imitated by the arrangement of cells in the tumour. These include the necrosis of individual cells in the centre of a group (Plate 13), growth of the tumour around fat globules (Plate 14), the fortuitous arrangement cells in rosette formation and clefts due to shrinkage. Most of these are easily resolved on high-power examination, and of particular assistance in this respect is the polarity of the cells with respect to the space enclosed.

Some tumour sections show dense staining of the majority of nuclei making the estimation of hyperchromatism and mitosis difficult. A heavy infiltration with chronic inflammatory cells also adds to the difficulty of this particular assessment.

Nuclear/

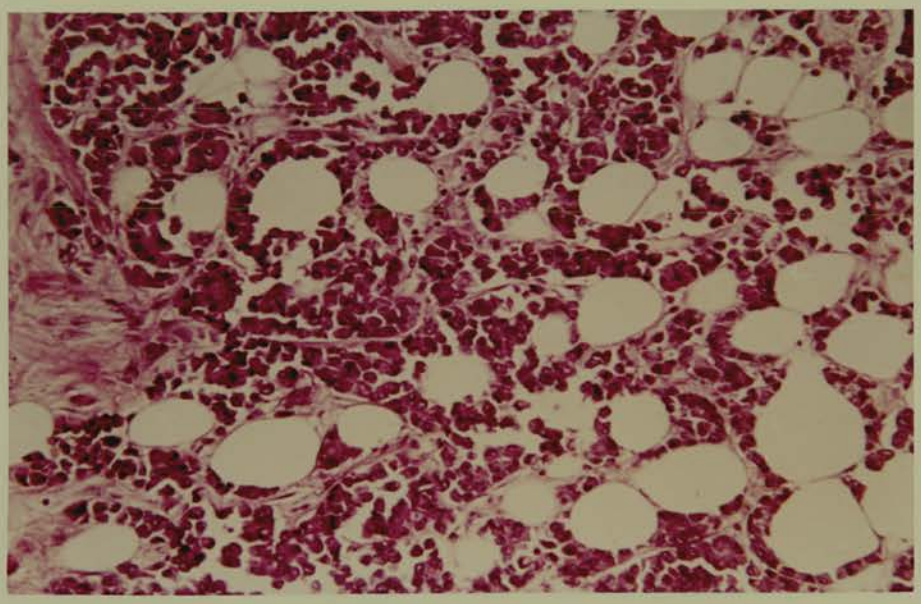

Plate 14

False Tubule Formation

An appearance resembling tubule formation is produced by the growth of tumour cells round the margins of fat cells at the periphery of the tumour. (x 170).

Nuclear pleomorphism is seldom difficult to assess but the identification of giant cells sometimes presents problems, particularly where the allotment of a score of 3 hinges on this. All doubtful aggregations of cells are ignored.

THE RELIABILITY OF GRADING

Sections of axillary node metastases were not of course often available in this series and no attempt was therefore made to grade them. However it was observed that where such sections could be compared with the primary tumour the features were generally similar.

It was also confirmed that the characteristics on which grading of the primary tumour was based differed little from one part of the tumour to another. In fact in only six cases (0.8 per cent of all cases for whom sections were available) was the variation so great as to make grading impossible.

It was decided to attempt to determine the reproducibility of the results by taking and regrading a sample of the whole material. For this purpose every 10th case was taken, allowing for those in whom no pathological examination was made and those in whom the slides were not readily available a second time. In all, the/

the sample covered 67 cases (total cases graded in the series = 687). Differences in grade were found in 34 per cent but these never exceeded one grade and the majority of differences were between Grades II and III. There appeared to be a trend towards smaller differences in the cases graded later in the series.

The range of variation in allocation of grade therefore appears to be similar to that found in clinical staging. There is some evidence that grading like staging improves with experience but it seems unlikely that the error inherent in standard methods can be less than about 20%. From the nature of the process already described and from the frequency with which cases on the borderline between Grades II and III were encountered it is difficult to see how one could expect otherwise.

Although the approximate nature of grading has not always been emphasized it is nevertheless true that correlation with prognosis is well established. The results reported in this series confirm this.

RESULTS

Material

Of the 876 cases in this series no microscopical examination of the primary tumour was made in 102 cases. This latter figure includes two cases in whom the primary tumour was removed and examined some considerable time after the initial treatment.

Six hundred and eighty-seven of the remaining cases were graded. The reasons for not grading the other 87 are listed in Table 28.

Distribution of Grades

The overall distribution of grades in the 687 cases is as shown in Table 29 and Figure 14.

Age and Grade

The effect of age on the distribution of grade is indicated in Table 30.

Comparison with Table 29 shows that the pattern of grade distribution over the age of 45 is similar to the overall pattern. In younger patients however the relative proportions of Grades II and III are reversed so that Grade III becomes the predominant grade. Although the figures are combined to give a larger number the trend is apparent in each subdivision of the 45 or under group. (See Appendix 1 for full version of this and subsequent tables.)

TABLE 28

Reasons for not grading	Cases
Slides unavailable	41
Extensive necrosis, poor fixation etc.	23
Insufficient tumour in sections	17
Variation in histological pattern	6
	87

HISTOLOGICAL MATERIAL NOT GRADED

TABLE 29

Grade	No. of cases	% of cases in grade
I	74	11
II	355	52
III	258	37
	687	100

DISTRIBUTION OF GRADES

(ALL CASES)

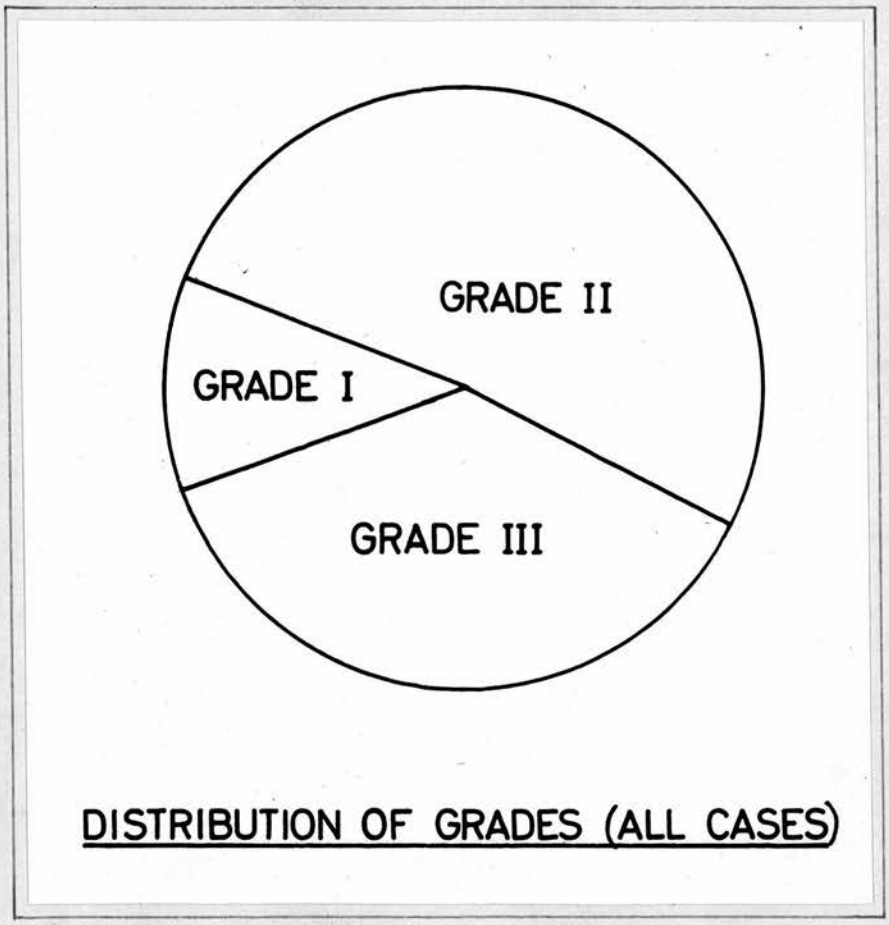

Figure 14

TABLE 30

Age	% of cases in each grade		
	I	II	III
45 or under	11	40	49
46 - 60	11	53	36
over 60	11	56	33

AGE AND GRADE

Stage and Grade

Because of the dominant effect of stage on prognosis the relationship between grade and stage is of considerable importance. If the two are closely linked it would be difficult to establish whether grade has an independent effect on prognosis.

This relationship is set out in Table 31.

Although there are some variations in proportions, the general distribution of grades is seen to be approximately the same for all stages except Stage IVD (cases presenting with distant metastases). In this stage there is a striking difference in the relative proportions of Grades II and III. There is also a noticeable increase in the proportion of Grade I in Stage I. This suggests that Grade I tumours are relatively slow growing and therefore remain in Stage I for a longer period.

Broadly speaking, however, clinical stage at the time of presentation does not appear to be determined by the grade of the tumour. Nor are the histological features used to assess grade apparently determined by the clinical stage of the disease. It seems reasonable to assume from these observations that the histological grade of a tumour is a relatively fixed property and does not change as the tumour becomes more advanced.

It/

TABLE 31

Stage	% of cases in each grade		
	I	II	III
I	15	54	31
II	10	48	42
III	11	59	30
IVL	3	53	43
IVD	7	34	59

STAGE AND GRADE

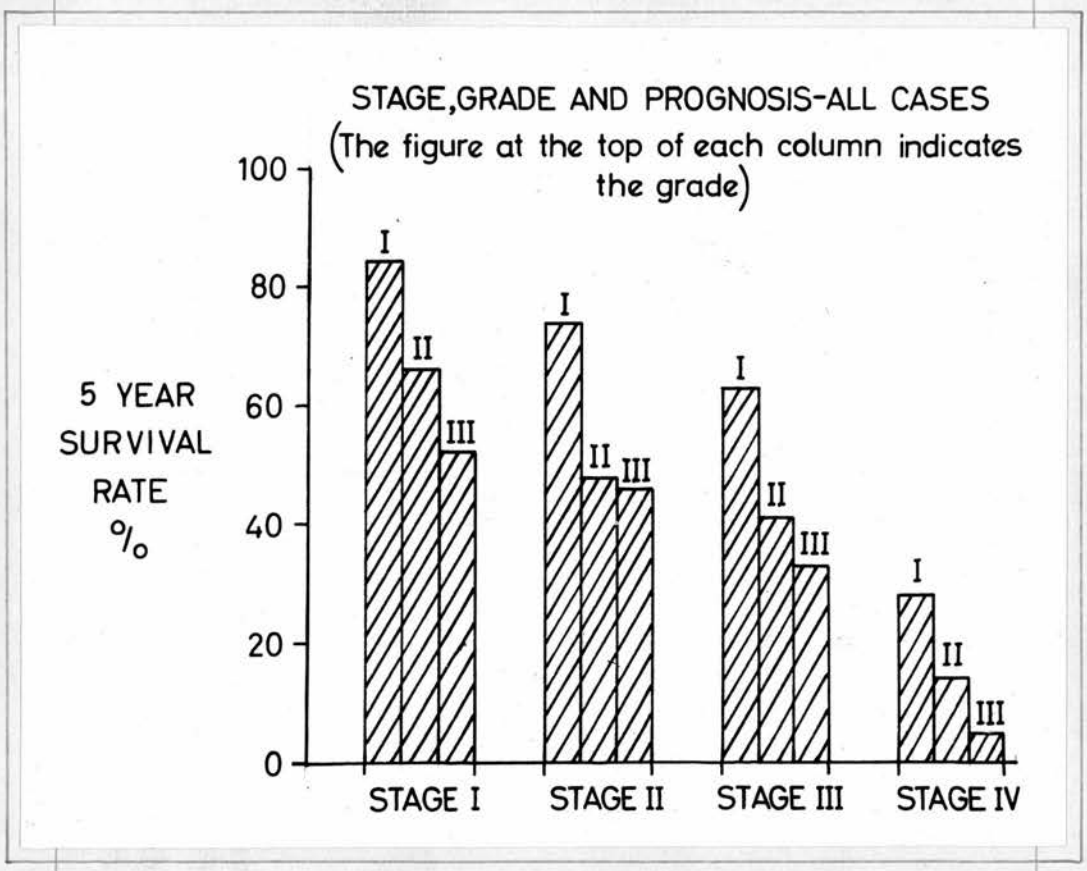
STAGE,GRADE AND PROGNOSIS-ALL CASES
(The figure at the top of each column indicates the grade)
5 YEAR SURVIVAL RATE %
100
80
60
40
20
0
I
II
III
STAGE I
STAGE II
STAGE III
STAGE IV

Figure 15

It has already been demonstrated for the series as a whole that prognosis is related to grade (Table 26 and Fig. 10). It is necessary to show that this is independent of the clinical stage before it can be concluded that the grade itself influences prognosis.

The survival rates for each grade in the different stages are shown in Table 32 and illustrated graphically in Figure 15.

In each separate stage the five-year survival rates show a similar variation in relation to the histological grade. In all the prognosis is markedly better in Grade I cases than in Grade III cases, Grade II showing an intermediate position.

It seems clear therefore that the prognostic factor determined by histological grade is independent of the clinical stage of the disease.

Grade and Prognosis in Relation to Treatment

In order to investigate the possible effect of grade on the result of treatment those cases treated by simple mastectomy and radiotherapy were considered separately. There were 573 such cases. Grading was carried out in 502. The distribution of grades was similar to that in the series as a whole (Grade I 11 per cent, Grade II 51 per cent, Grade III 38 per cent).

The/

TABLE 32

Stage	5-year survival rates in each grade (%)		
	I	II	III
I	85	66	51
II	75	48	47
III	63	41	33
IV	28	14	5

STAGE, GRADE AND PROGNOSIS (ALL CASES)

The survival rates, overall and by stages are set out in Tables 33 and 34 and illustrated in Figures 16 and 17.

DISCUSSION

The distribution of cases between the different grades varies to some extent from series to series and depends in part on the grading system used. But as can be seen from Table 35 the general pattern is similar. Grade I is invariably the smallest group. The largest is more commonly Grade III but in some series, as in the present one, Grade II predominates. This latter may well be a reflection of the difficulty already noted of defining a sharp borderline between these two grades.

The younger age groups according to Cade (1950) show a greater proportion of the higher grades of malignancy. With this, the findings in the present series agree. Bloom (1950) failed to demonstrate any such relationship. His figures for the youngest age group were however rather small.

The principal interest in grading lies in its relationship to prognosis. The evidence presented here confirms that of many authors that the histological grade shows a well-defined correlation with prognosis.

Were the higher grades associated mainly with the more advanced stages then the correlation shown between grade and prognosis could well be a reflection of the greater effect of the stage of the disease. However, the/

TABLE 33

Follow-up period	Survival rate in each grade (%)		
	I	II	III
5 years	81	56	42
10 years	47	40	38
15 years	42	20	20

GRADE AND PROGNOSIS IN TREATED GROUP

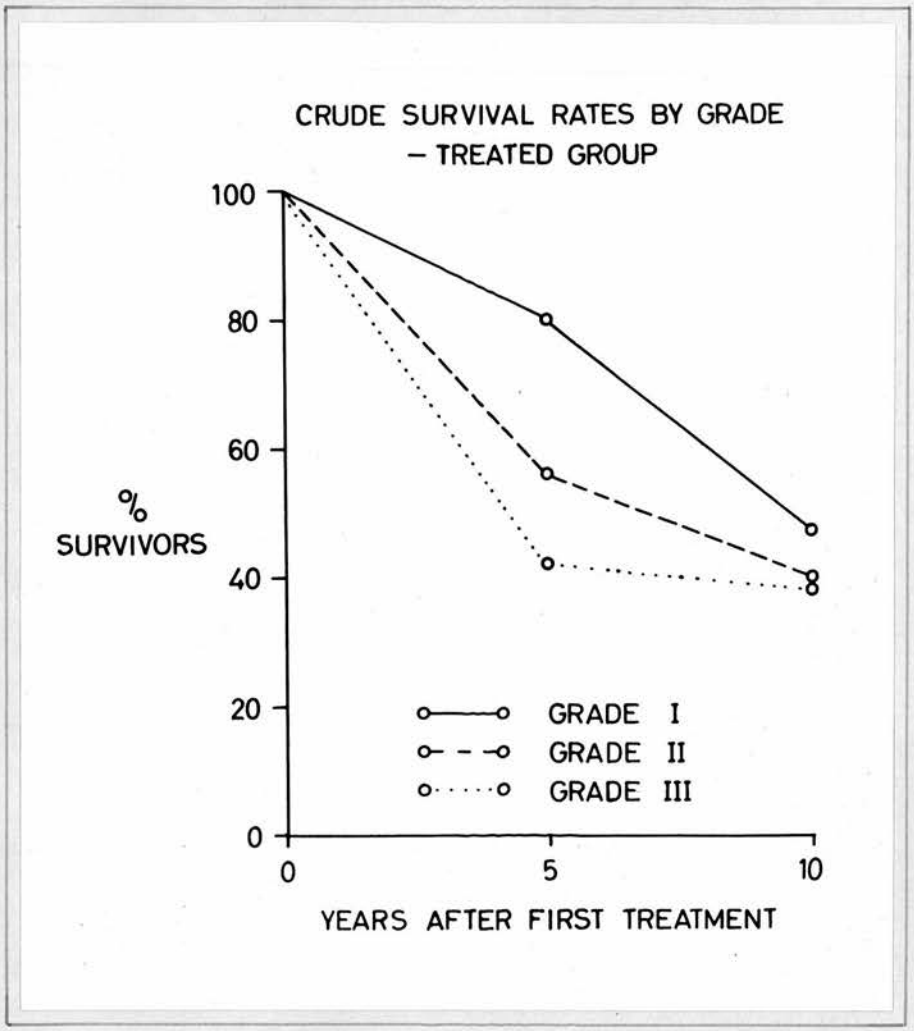
CRUDE SURVIVAL RATES BY GRADE
– TREATED GROUP
100
80
60
40
20
0
% SURVIVORS
GRADE I
GRADE II
GRADE III
0
5
10
YEARS AFTER FIRST TREATMENT

Figure 16

TABLE 34

Stage	5-year survival rates in each grade (%)		
	I	II	III
I	86	71	57
II	83	57	48
III	75	54	38
IV	33	16	9

GRADE, STAGE AND PROGNOSIS IN TREATED GROUP

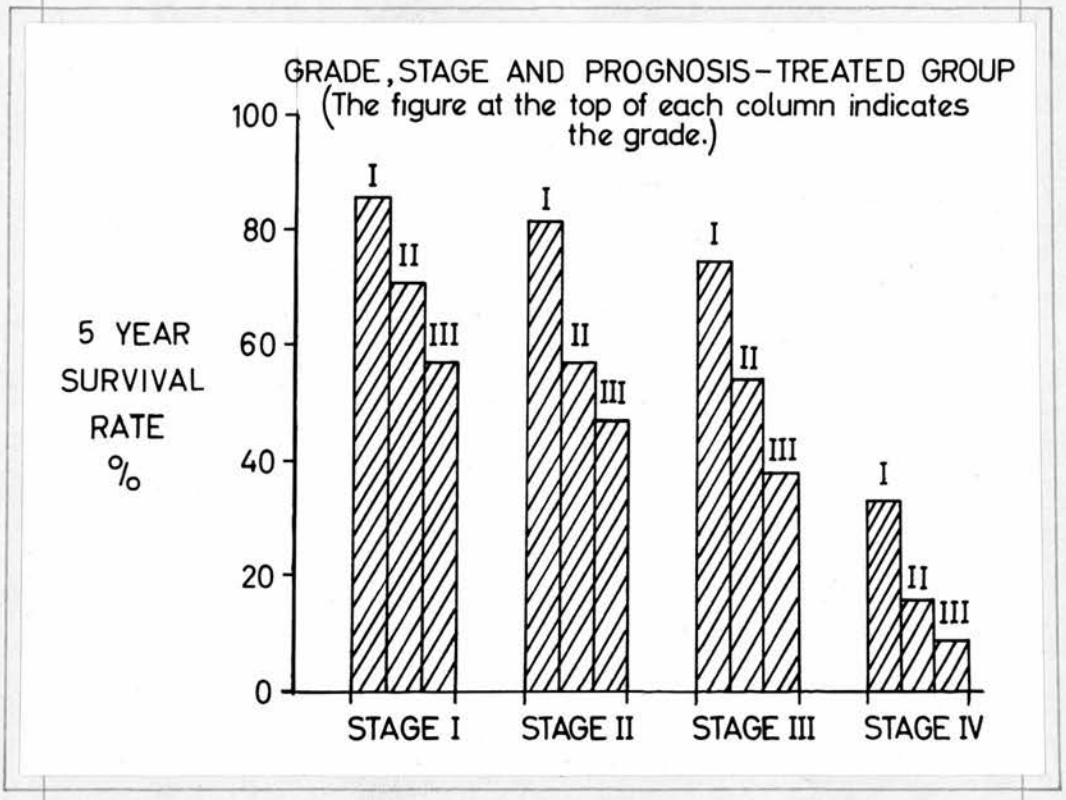
GRADE, STAGE AND PROGNOSIS - TREATED GROUP
(The figure at the top of each column indicates the grade.)
5 YEAR SURVIVAL RATE %
100
80
60
40
20
0
I
II
III
STAGE I
STAGE II
STAGE III
STAGE IV

Figure 17

TABLE 35

Series	% of cases in each grade		
	I	II	III
Taylor and Wallace (1950)	2	47	51
Kaae (1952)*	4	39	57
Bloom and Richardson (1957)	26	45	29
Haagensen (1956)	8	38	54
Black and Speer (1957)	20	30	49
Berkson et al. (1957)*	1.4	47	51
Hultborn and Törnberg (1960)	11	51	37
Present series	11	52	37

* Broders' System used. Grade II taken as equivalent to Broders' Grades II and III, Grade III as equivalent to Broders' Grade IV.

DISTRIBUTION OF GRADES

the results given above show that this is not the case. It has also been demonstrated that if each stage is considered separately the correlation between grade and prognosis still holds. It is of interest to note that in the treated group (Table 34) the prognosis, as expressed by the five-year survival rate, shows little difference in the first three stages in Grade I cases. This may well reflect the radiocurability of such cases (see below) or the relatively slow rate of growth of these tumours.

The latter finding is in agreement with Bloom and Richardson (1956) who have also explored the effect of grade on prognosis in relation to clinical stage. Most authors, for example Berkson and his colleagues (1956) and Hultborn and Törnberg (1960), have confined themselves to the broader groups of cases defined by the presence or absence of histologically involved axillary nodes. Within these groups too, the same correlation is found.

The present series is unique in two respects. It contains a large proportion of cases treated by simple mastectomy and radiotherapy and it provides histological material for a considerable number of advanced cases. The latter circumstance is due to the applicability of the standard method to such cases.

Little is known about radiosensitivity in relation to histological grade in carcinoma of the breast (Bonser et al., 1961). As Cade (1948) remarks there is a general tendency/

tendency for the more anaplastic tumours to be more radiosensitive. Scarff and Andrews (1956) however emphasize that radiosensitivity and radiocurability are not synonymous, and Glücksmann's studies in relation to the treatment of carcinoma of the cervix (Glücksmann, 1948) have shown that in fact radiosensitivity and radiocurability are inversely related to each other. The more anaplastic tumours are indeed more radiosensitive, but radiocurability is related to the degree of differentiation.

Kaae in 1952 reported a series of cases of breast carcinoma treated by pre-operative radiotherapy followed by radical mastectomy. He found on examination of the irradiated breast removed at operation that the higher grades of malignancy (determined on the pre-treatment biopsy specimen) were associated with the greater histological response to therapy. On the other hand the results of treatment were best in the cases with well-differentiated tumours.

In the treatment of carcinoma of the breast by simple mastectomy and radiotherapy as practised in Edinburgh, radiotherapy must play an important part in the control of the disease. This is particularly true in Stages II and III where in the majority of cases surgical removal of tumour tissue will be incomplete. In so far as the results depend on the treatment they will reflect to some degree the radiocurability of the tumour. The relationship between grade and prognosis in this particular/

particular group of cases (Fig. 17) should therefore reflect the relationship between grade and radiocurability.

One can consequently postulate that in breast carcinoma as in carcinoma of the cervix the well-differentiated tumour responds more effectively in terms of survival to radiotherapy.

Since such tumours are presumably the least radiosensitive it is obvious that there is a possible alternative hypothesis - that radiotherapy plays little part in the control of the disease and that the proportion of patients surviving five or more years is determined by the natural history of their particular tumours. Indeed Bloom and his colleagues (1962) have shown in a series consisting mainly of advanced cases that survival in untreated breast carcinoma is also influenced by histological grade.

It is also true, since the staging in the present series is clinical, that a proportion of cases in Stages II and III would not in fact have tumour beyond the breast itself and would therefore be curable by surgery alone.

In this group (Stages II and III) the five-year survival rate is however 54% (calculated from Table 44, p. 174). It seems unlikely that this could be accounted for either by the natural history of the disease or by the errors introduced by clinical staging.

One may therefore conclude that radiotherapy as such plays a significant part in the control of the disease in Stage/

Stage II and Stage III cases treated by simple mastectomy and radiotherapy, and that histological grade is probably one of the factors determining its effect.

Finally one might remark in passing on the high proportion of Grade III tumours in cases presenting with distant metastases. It is well known that the presence of distant metastases is not always associated with advanced local disease. Nor, as is commonly the case with the latter, is it always related to the known duration of the tumour. It will be seen in Table 31 that in Stages III and IVL which represent the locally advanced cases, the ratio of Grade II to Grade III tumours is very similar to the overall pattern - and is quite different from that found in Grade IVD. This would seem to be strong evidence of the superior metastasizing potential of the Grade III tumour, and further evidence that grade reflects the intrinsic malignancy of the tumour.

The thesis that the histological grade of a tumour is a prognostic index determined by the biological properties of the tumour is thus strongly supported by the facts ascertained from this series.

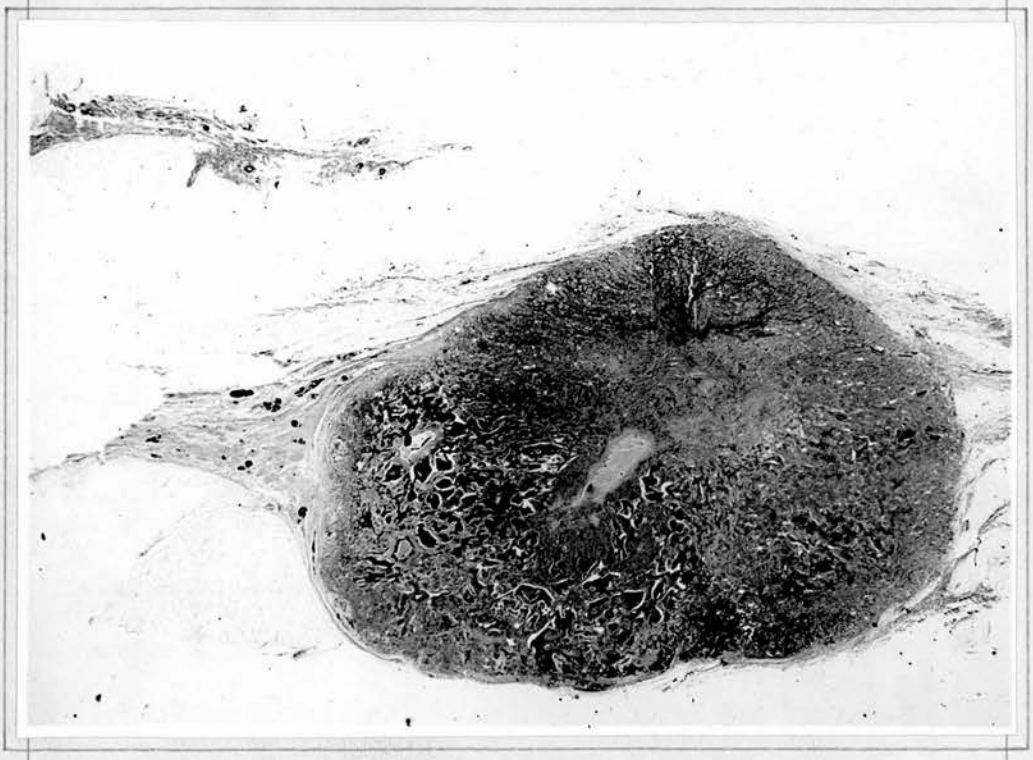

Plate 15

Tumour Contour

Well-delimited tumour. (x 6).

TUMOUR CONTOUR

The study of tumour contour published in 1961 by Lane and his colleagues from C.D. Haagensen's unit has stimulated interest in this subject. The contour as assessed by naked-eye inspection of the histological sections appears to be a significant yet very simple attribute of the tumour (Plates 15 and 16).

Accordingly this factor was assessed in all cases in whom grading had been carried out. It soon became apparent that assessment was less easily made than one would imagine. In certain cases such as those which were predominantly intraductal the tumour was present in discrete areas and no overall contour was discernible. Most of these cases were excluded as "special types" in Lane's study and constituted 15 per cent of the total cases. In other instances however the cutting of the section left only a small part of the contour visible or again the contour itself did not fall clearly into either category. All these constituted an indeterminate group which amounted to 21 per cent in the present study.

This left 540 cases in which the contour of tumour was assessed as either well-delimited or irregular (Table 36). The corresponding proportions in Lane's series were 23 per cent and 77 per cent.

Contour/

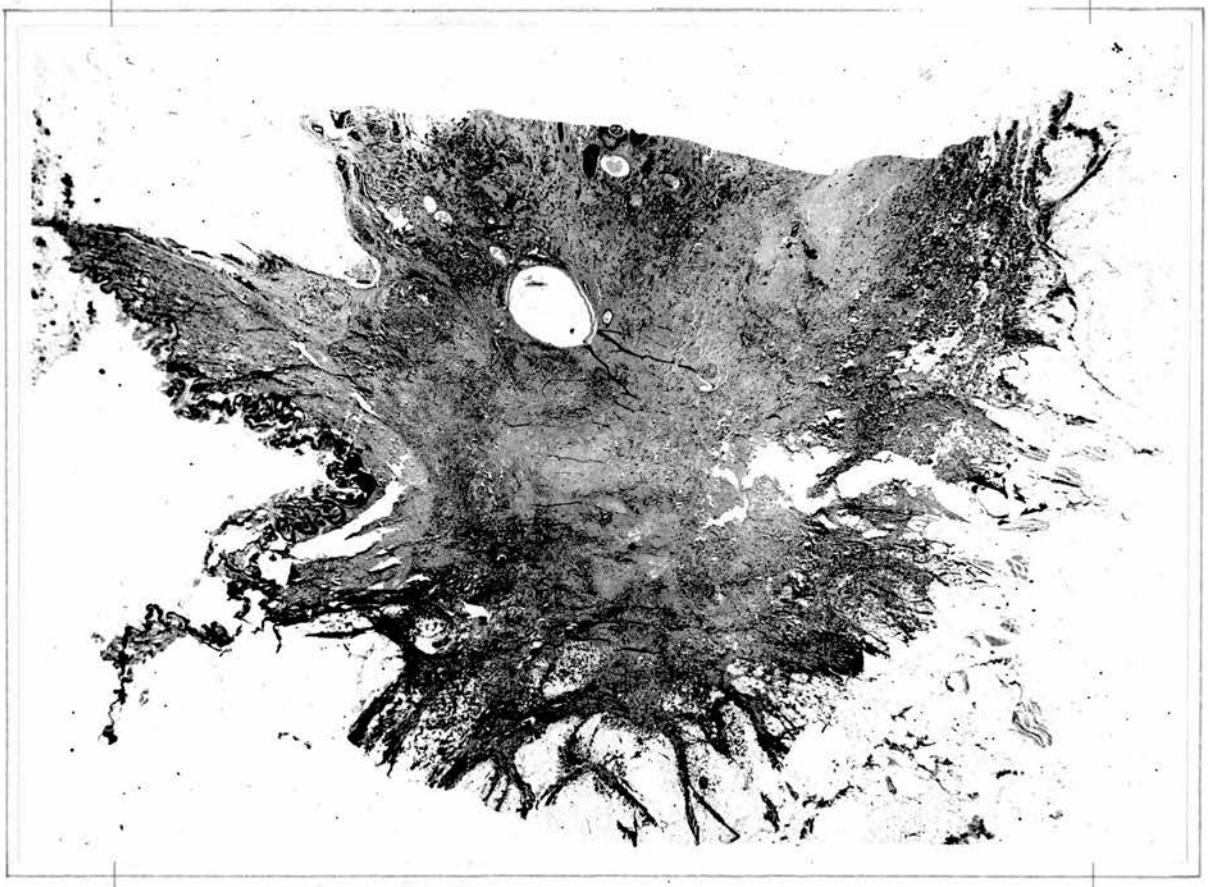

Plate 16

Tumour Contour

Irregular tumour. (x 5).

TABLE 36

Contour	Cases	%
Well-delimited	129	24
Irregular	411	76

TUMOUR CONTOUR (ALL CASES)

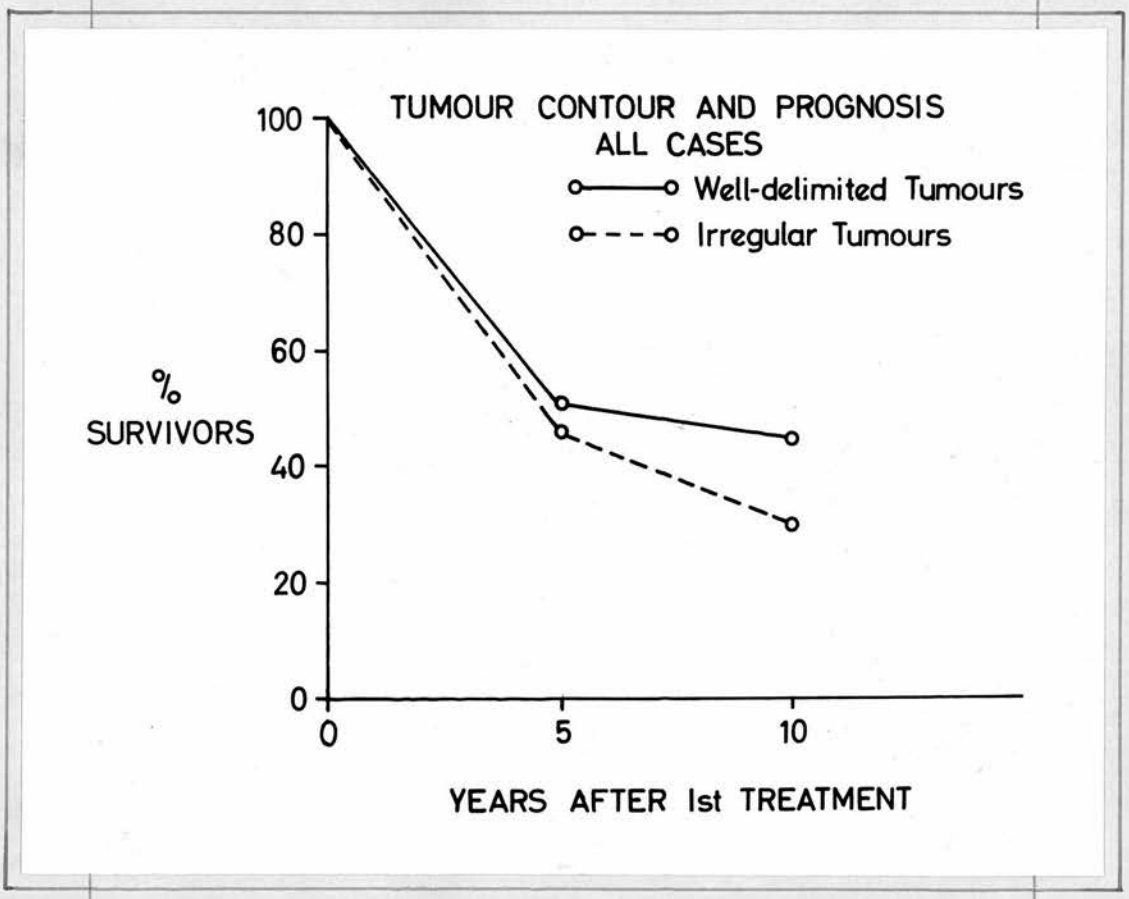
TUMOUR CONTOUR AND PROGNOSIS
ALL CASES
Well-delimited Tumours
Irregular Tumours
100
80
60
40
20
0
%
SURVIVORS
0
5
10
YEARS AFTER Ist TREATMENT

Figure 18

Contour and Prognosis

In Lane's series which consisted entirely of cases which were operable according to Haagensen's criteria, and had been followed up for a minimum of ten years, the survival rate of cases with well-delimited tumours was twice that of those with irregular tumours.

The overall figures for the present series confirms the better prognosis in the well-delimited group but the differences are not so striking (Table 37 and Fig. 18). It is interesting to note however that the greatest difference is in the ten-year figures where the survival rate for the cases with well-delimited tumours was one and a half times that of the cases with irregular tumours.

In order to establish whether the greater difference found in Lane's series was peculiar to the specific group considered, a more precise comparison was made.

Haagensen's criteria of operability (Haagensen, 1956) are fairly strict. It was felt that Clinical Stages I and II represented the best approximation to his operable group. Cases in these two stages who had been treated by simple mastectomy and radiotherapy and who had been followed up for a minimum of ten years were therefore used as the basis of this comparison (Table 38).

In/

TABLE 37

Follow-up period	Well-delimited			Irregular		
	Total cases	Survivors	% survival rate	Total cases	Survivors	% survival rate
5 years	129	66	51	411	188	46
10 years	78	35	45	225	68	30
15 years	14	3	21	51	10	20

TUMOUR CONTOUR AND PROGNOSIS

TABLE 38

	Present series	Series of Lane et al. (1961)
Number of cases	187	204
Stage	Clinical Stages I and II	"Operable"
Treatment	Simple mastectomy and radiotherapy	Radical mastectomy
Number with well-delimited tumours	53	46
Number with irregular tumours	124	158
10-year survival rate (well-delimited tumours)	55%	80%
10-year survival rate (irregular tumours)	44%	38%

TUMOUR CONTOUR AND PROGNOSIS -

COMPARISON WITH SERIES OF LANE ET AL. (1961)

In this group of cases the difference between the survival rates in the two types of tumour is very similar to that of the whole series (Table 37). The selection of this particular class of case does not therefore seem to be a factor of importance; the difference in survival rates remains less than that reported by Lane.

CONTOUR AND STAGE

Lane et al. found a 65 per cent incidence of axillary metastasis in the irregular group of tumours, compared with 41 per cent in the well-delimited group. In the present series the clinical staging reveals the opposite situation: 36 per cent of the well-delimited group were in Stage II whereas there were only 25 per cent of the irregular group in this stage. In the selected group defined above (Stages I and II, ten-year follow-up) the proportion in Stage II is almost the same for the two types of tumour (well-delimited 42 per cent, irregular 41 per cent).

It is contended by Lane and his colleagues that the higher rate of axillary involvement is a basic feature of the irregular type of tumour. But in this case it is possible that the axillary involvement rather than the contour of the tumour was the over-riding prognostic factor. In their series the rate of axillary involvement was almost equal in the survivors of the two groups (38 per cent in the well-delimited group, 37 per cent in the irregular/

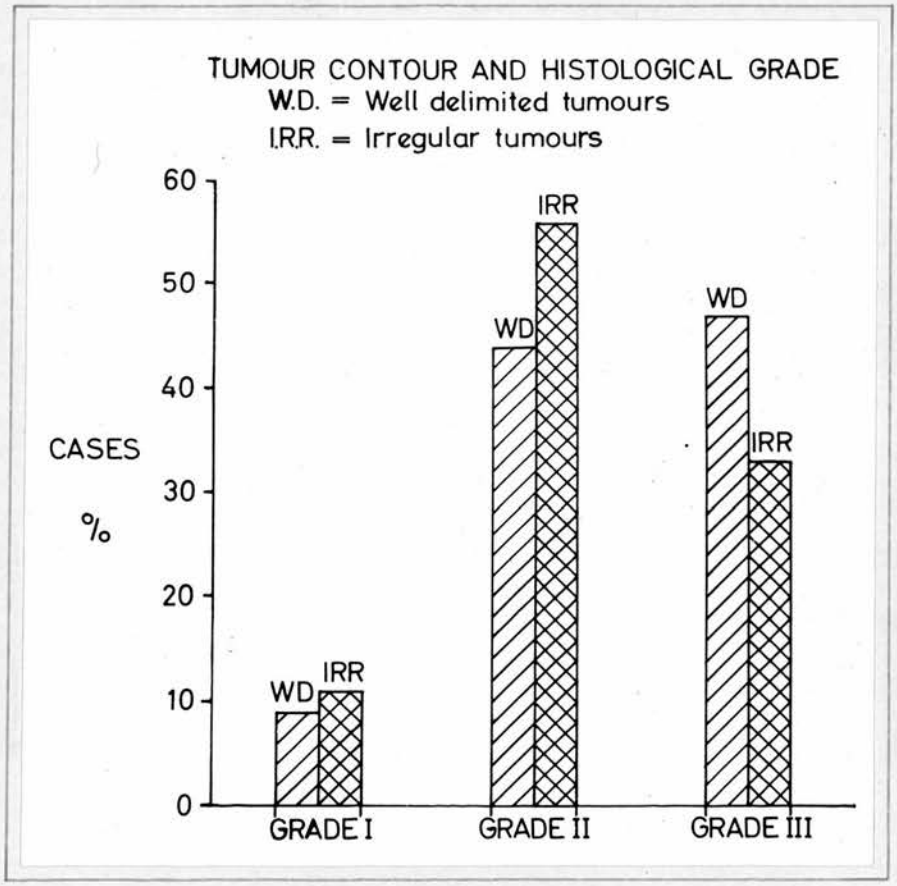
TUMOUR CONTOUR AND HISTOLOGICAL GRADE
W.D. = Well delimited tumours
I.R.R. = Irregular tumours
CASES
%
60
50
40
30
20
10
0
WD
IRR
WD
IRR
WD
IRR
GRADE I
GRADE II
GRADE III

Figure 19

irregular group). From this it can be calculated that in the non-survivors 82 per cent of the cases with irregular tumours had axillary involvement compared with 55 per cent in the well-delimited group. This would certainly suggest that the stage of the disease was more significant in determining survival than the contour.

CONTOUR AND GRADE

Rather surprisingly the cases with well-delimited tumours in Lane's series showed a lower incidence of differentiation and a higher incidence of nuclear atypism or pleomorphism. In fact they tended more towards the higher histological grades of malignancy than the apparently more malignant irregular tumours. The relationship between grade and contour in the present series tends to confirm these observations (Table 39, and Fig. 19). There is a slight preponderance of Grade I tumours in the irregular group and a very definite preponderance of Grade II tumours. Grade III tumours on the other hand are definitely commoner in the well-delimited group. However the prognostic significance of this is not as great as these observations would suggest for the differences in prognosis between Grades II and III are much less than between Grades I and II (see Fig. 10).

Conclusions/

TABLE 39

Grade	Well-delimited tumour		Irregular tumours	
	No. of cases	% of total	No. of cases	% of total
I	12	9	45	11
II	57	44	231	56
III	60	47	135	33
Total	129	100	411	100

TUMOUR CONTOUR AND HISTOLOGICAL GRADE

Conclusions

There seems to be a correlation between the gross contour of the tumour and prognosis as Lane and his colleagues have suggested. It is not however so strong in the present series as it is in theirs.

In this study however, unlike Lane's, the correlation cannot be explained by differences in the stage of the disease. Nor does it appear to be related to histological grade. Indeed the findings appear to be at variance with the grading and in this the present study agrees with Lane's findings.

While the method itself would appear to be simple it is not easy to apply in practice and is therefore not free of the possibility of error.

It must be concluded that the gross contour of the tumour as determined by inspection of the histological sections has not been proven to be of fundamental significance in gauging prognosis.

SECTION V

TREATMENT

TREATMENT

In the treatment of the individual patient with carcinoma of the breast a wide variety of methods may be considered. However, only a limited number of standard treatments are in general use.

It follows that quite large groups of patients will receive one form of standard treatment and of these the most important is the so-called operable group. Where the limits of this group are not too strictly defined it encompasses the majority of cases in a general hospital series. It is common practice for one mode of treatment to be applied to the whole of this group, with some limited exceptions.

In Edinburgh the principal mode of treatment is simple mastectomy with post-operative radiotherapy. The treatment policy is therefore one in which this method is applied as standard treatment to cases in the operable group. Its claims are based on this premise and not on the premise that it is the only treatment for carcinoma of the breast. This is in a sense obvious but confusion does arise from a tendency to equate the treatment with the treatment policy.

In the series under review the methods of treatment actually used were as shown in Table 40. In this table and in subsequent analyses male cases and cases presenting with/

TABLE 40

Method of treatment	No. of cases	% of cases
Simple mastectomy and radical radiotherapy	573	65
Simple mastectomy and palliative radiotherapy	53	6
Simple mastectomy and ovarian ablation or hormonal therapy	8	1
Simple mastectomy alone	71	8
Local excision only	13	1
Radical mastectomy	28	3
Radical mastectomy and radiotherapy	4	0.5
Modified radical mastectomy	7	1
Simple mastectomy with excision of pectoralis major and radiotherapy	8	1
Radiotherapy only	38	4
Radiotherapy with hormonal therapy	23	3
Hormonal therapy only	13	1
Endocrine ablation only	4	0.5
Chemotherapy only	1	0.1
Excision of metastasis only	1	0.1
No treatment	17	2
Exclusions (males etc.)	14	2
TOTAL	876	

SUMMARY OF TREATMENT METHODS USED

with simultaneous bilateral tumours are excluded. The methods of treatment used in the former cases have already been considered (Table 2). A further case in whom radical mastectomy was recommended but who was treated by simple mastectomy and radiotherapy is also excluded.

This breakdown illustrates the actual practice current in Edinburgh under the existing treatment policy. This is undoubtedly a true reflection of hospital practice in the area during the period under review, but since the series does not include private patients, it is not certain to what extent it reflects the position in private practice.

The two major factors determining the choice of treatment were age and stage. Their effect can be seen in the analyses of the two main groups shown in Tables 41 and 42, and in Figures 20 and 21. These show that the greater proportion of cases treated by methods other than simple mastectomy and radiotherapy were in the older age groups and the more advanced stages of the disease.

It will be noted that simple mastectomy and radiotherapy was used to some extent even in cases with advanced disease. In these cases the primary growth was removable even though there might be fixed axillary nodes, palpable supraclavicular nodes or in a few cases distant metastases.

Many of the patients who had simple mastectomy alone had early growths but were advanced in years. This was true/

TABLE 41

Age	Simple mastectomy and radiotherapy		Other methods	
	No. of cases	%	No. of cases	%
Under 40	78	14	23	8
41 - 50	165	29	36	13
51 - 60	144	25	46	16
61 - 70	147	26	65	22
Over 70	39	7	119	41
	573	÷ 100	289	100

AGE DISTRIBUTION IN RELATION TO TREATMENT

(Male and Bilateral Cases Excluded)

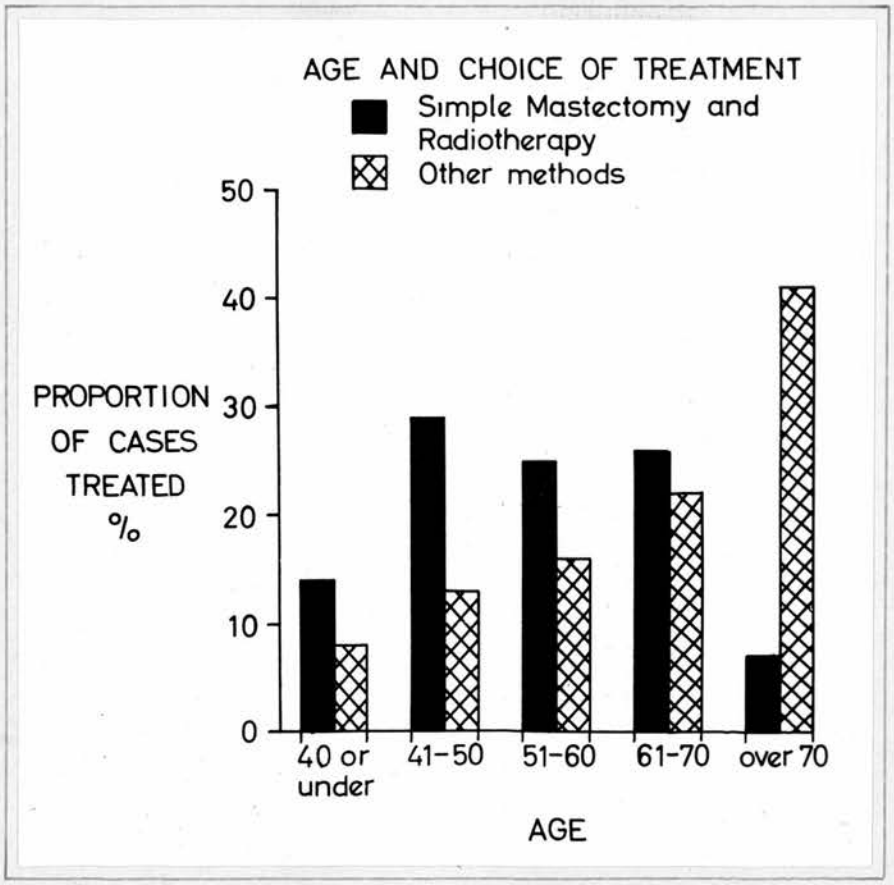
AGE AND CHOICE OF TREATMENT
Simple Mastectomy and Radiotherapy
Other methods
PROPORTION OF CASES TREATED %
50
40
30
20
10
0
40 or under
41-50
51-60
61-70
over 70
AGE

Figure 20

TABLE 42

Stage	Simple mastectomy and radiotherapy		Other methods	
	No. of cases	%	No. of cases	%
I	238	42	75	26
II	185	32	38	13
III	51	9	29	10
IVL	89	16	71	25
IVD	10	2	76	26
	573	≑ 100	289	100

STAGE DISTRIBUTION IN RELATION TO TREATMENT

(Male and Bilateral Cases Excluded)

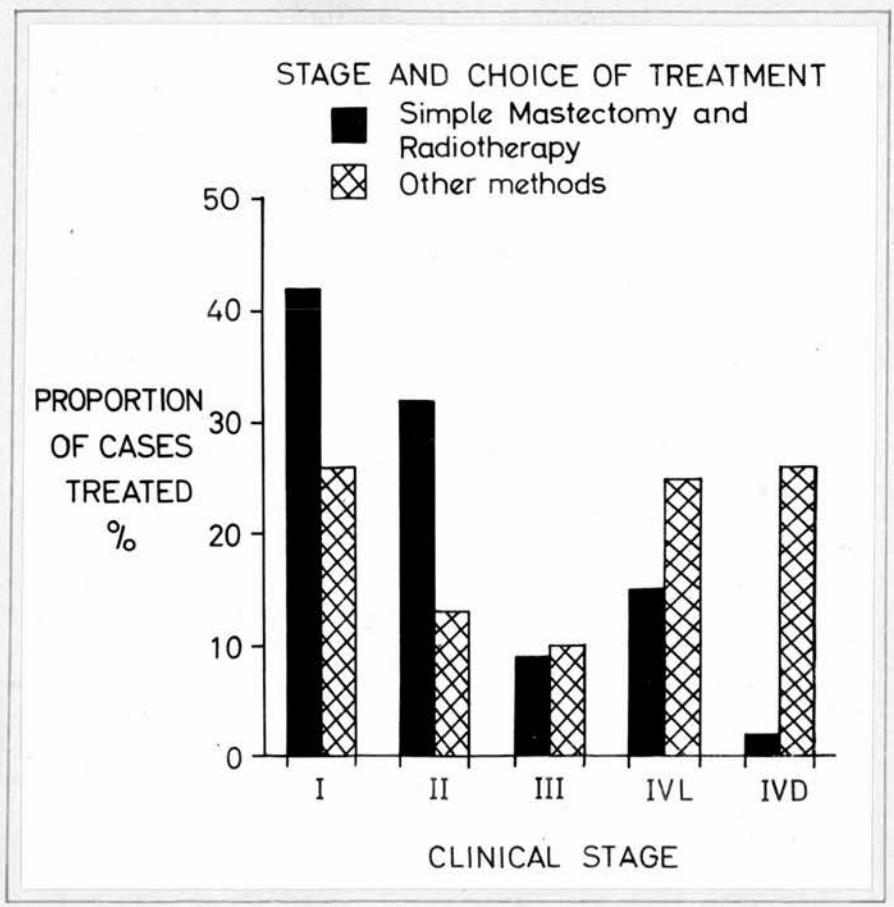
STAGE AND CHOICE OF TREATMENT
Simple Mastectomy and Radiotherapy
Other methods
PROPORTION OF CASES TREATED %
50
40
30
20
10
0
I
II
III
IVL
IVD
CLINICAL STAGE

Figure 21

true also of a number of those receiving palliative radiotherapy after simple mastectomy. These cases largely account for the number treated by "other methods" in Stage I. Simple mastectomy and palliative radiotherapy was however more often used in the advanced case with a resectable primary growth.

Of the patients not treated by simple mastectomy and radical radiotherapy, 47 nevertheless received a form of radical treatment for their disease. This group consists of those having radical mastectomy with or without radiotherapy, modified radical mastectomy, and simple mastectomy with removal of pectoralis major followed by radical radiotherapy. These cases comprised five per cent of the whole series and sixteen per cent of those not receiving the standard treatment.

Radical mastectomy alone was recommended by the radiotherapists in very obese patients whose configuration rendered effective irradiation difficult or impossible, in cases with tuberculosis and in those with peripheral vascular disease of the upper limbs. In some cases the surgeon's preference for radical mastectomy in the particular circumstances determined the treatment.

Cases Treated by Simple Mastectomy and Radical Radiotherapy

This group of cases, with the exclusion of male cases etc. as outlined above, will be termed for the sake of brevity the Standard Group.

At/

At first sight it would appear that as far as treatment is concerned this is a homogeneous group. There are in fact three principal sets of variations within it, which will be discussed under the headings of surgery, radiotherapy and ancillary treatment.

Variations in the Standard Treatment

Surgery

In certain respects the operative procedure was standardized. The main principles laid down (McWhirter, 1949) were that the axilla should not be entered, that primary skin closure should be achieved and that the pectoral fascia should not be removed unless the tumour was adherent to it.

In the majority of cases the axilla was in fact left unopened. Low subpectoral nodes lying outside the axillary fascia were however not infrequently removed, and this was recommended by the radiotherapists when the nodes concerned were considered to lie at the junction of two fields and might therefore not receive adequate irradiation. Sometimes the removal was more extensive than this, but where it approached axillary clearance the case was not considered to have had a simple mastectomy but rather a modified radical mastectomy.

It/

It was not possible to determine to what extent the pectoral fascia was left untouched. Where the tumour was adherent to the fascia or infiltrating the subjacent muscle a portion of that muscle was frequently removed. Such cases are also included unless the greater part of pectoralis was removed.

The actual extent to which removal of axillary nodes or of small parts of muscle was practised is indicated in Table 43 which shows that nearly three-quarters of the cases had a standard simple mastectomy.

Primary skin closure was routinely used although primary healing was not of course always achieved. The effect of this and other wound complications is considered in a later section.

A biopsy of the tumour, usually an excision biopsy, was carried out in 42 cases prior to the definitive treatment. In these cases the date of the biopsy was taken to be the date of first treatment.

Radiotherapy

The principles of treatment as defined by McWhirter (1950) were as follows:

1. Axillary and supraclavicular nodes must be treated as one continuous chain.
2. Internal mammary nodes must be treated in continuity with the chest wall.

3/

TABLE 43

Operation	No. of cases	%
Simple mastectomy without removal of nodes or portions of muscle	413	72
Simple mastectomy with removal of one or more axillary nodes	112	20
Simple mastectomy with removal of a portion of underlying muscle	41	7
Simple mastectomy with removal of both node or nodes and underlying muscle	7	1
TOTAL	573	

INCIDENCE OF EXTENSIONS TO SIMPLE MASTECTOMY

3. Hard quality radiation is essential.

4. Adequate dosage should be given to the whole of the area.

5. One course of treatment should be given.

It was also regarded as desirable to begin treatment within 14 days of the operation (McWhirter, 1948b).

To achieve these aims a technique was evolved in which the axilla and the supraclavicular fossa were irradiated by directly opposed fields, and the chest wall and internal mammary nodes by glancing fields. 250 kV irradiation was used with heavy filtration. A minimum tumour dose of 3750 r was given over a period of three weeks, the maximum being determined by the build of the patient, but the maximum tumour dose was not allowed to exceed 4500 r.

In 1956 following the introduction of 300 kV machines, this technique was modified. Slight alterations were made in the fields, the period of treatment was extended to four weeks and dosage was defined by the maximum rather than the minimum tissue dose. This maximum was 4250 r giving a minimum of 3370 - 3880 r (Garland, 1958).

In practice slight modifications of these techniques occurred.

The start of radiotherapy was often delayed. Only 21% of cases in the standard group began treatment within 15 days of the operation and in 42% the delay exceeded three weeks.

The/

The two main reasons for these delays were the heavy demands on the radiotherapy equipment resulting in a waiting list for treatment, and post-operative complications mainly related to wound healing. Failures of communication, breakdown of apparatus and personal difficulties of the patients were other but less frequent causes of delay.

The dosage occasionally fell below the specified level. Sometimes an excessive skin reaction led to the omission of the final one or two treatments. Sometimes the condition of the patient led to abandonment of the course. Breakdown of the apparatus occurring during the course of treatment not only caused the course to exceed the specified time but sometimes resulted in a smaller total dosage being given.

It is an accepted principle that in assessing the results of treatment, cases receiving incomplete courses should be included (McWhirter, 1948b). Patients whose total dosage fell short of the recommended level, whose course extended beyond the usual period or where there was delay in starting radiotherapy are therefore included in the standard group. However as the analysis of this group is intended to determine the effect of the standard treatment, cases where the dosage fell more than a few hundred rads below the prescribed level are excluded, as are those who received a palliative course or no radiotherapy at all in spite of an original decision to complete a radical course.

These/

These cases of course contribute to the overall figures, but it would be pointless to study the effect of a particular method of treatment except in cases where a reasonable approximation to that method was attained. It is also pointless, however, to restrict the analysis only to cases achieving a pre-determined ideal treatment where departures from that ideal are dependent on unpredictable factors such as the variable degree of skin sensitivity to irradiation.

Ancillary Treatment

In 1948 and 1949 ovarian irradiation was used as a routine ancillary treatment in cases having simple mastectomy followed by radiotherapy. 104 cases (18% of the cases in the standard group) were so treated in this series. These cases are subjected to a separate analysis in a later section. It was in fact concluded by McWhirter that no significant improvement in results was attained by this measure and its use was abandoned (McWhirter, 1957).

Summary

Under the Edinburgh treatment policy the basic method of treatment of simple mastectomy followed by radical radiotherapy is considered applicable in approximately 65 per cent of all cases presenting with primary breast carcinoma.

The/

The basic method has itself been subject to certain variations. The more important of these have been the removal of axillary nodes in certain circumstances, the occasional variations in the dosage of irradiation and the changes in technique introduced in 1956, and finally the use in 1948 and 1949 of prophylactic ovarian irradiation.

With the exception of the last these variations must be considered to lie within the practical as opposed to the ideal definition of the standard treatment.

S E C T I O N VI

RECURRENCE AND METASTASIS

RECURRENCE AND METASTASIS

Survival rates, crude or adjusted, have an established place in studies of the effectiveness of treatment. Recurrence rates are sometimes used as a substitute, particularly in short-term studies. A detailed study of the pattern of recurrent disease as a means of achieving the same object has however received less attention, although it is nearly 70 years since Halsted expressed the opinion that the effect of treatment was "measured truer in terms of local recurrence than of ultimate cure" (Halsted, 1895).

There are, of course, certain difficulties which tend to reduce the validity of conclusions drawn from such studies. The mode of spread of tumours is itself variable and the same manifestation may not have the same significance in all cases. Certain sites of recurrent disease are less accessible than others. In some the metastasis may proceed to an advanced stage before it is detectable at all, in others a very early stage may be recognizable. But, whatever the site, the early detection of recurrent disease depends on regular clinical examination.

Post-mortem studies alone reveal the full extent of the spread of the disease but by this time the disease is usually so advanced and the spread so complex that it is no longer possible to trace the earlier and more important stages. It is only in the living patient, with all the imperfections of clinical methods, that these stages can be studied.

Survival/

Survival rates on the other hand are based on the easily ascertained fact of death. Precise timing of the event is usually possible and there is no clinical dubiety. Nevertheless the fact of death is not in itself proof of recurrence of the disease. The latter is frequently obvious at the time of death, but where it is not it is either assumed that recurrence was present and the cause of death, as in crude survival rates, or adjustments such as those based on the probability of dying of intercurrent disease are made. Such adjustments can be made with tolerable accuracy, and as a means of comparison survival rates are unrivalled.

The pattern of recurrent disease however carefully observed cannot compete with survival rates as an overall measure of results. But under certain conditions it can throw light on the failure of treatment by indicating where and how that failure occurred. The principal conditions required are regular examination of the cases, accurate recording and large numbers. These conditions are fulfilled to a reasonable extent in the present series except where recurrence and metastasis at individual sites in patients of the same clinical stage are concerned. Here the numbers tend to become small and of doubtful significance.

The/

THE SPREAD OF CARCINOMA OF THE BREAST

In so far as treatment by simple mastectomy and radiotherapy is concerned, three phases of spread must be distinguished - spread limited to the tissues removed by the mastectomy, spread beyond this area but limited to the area irradiated, and spread beyond the confines of the treated area.

In the first case the spread can be no more than moderate extension by continuity. Such cases will be found mainly in Stage I although, because of the inaccuracies of clinical staging, some classified as Stage II and Stage III may fall into this category. Here the mastectomy alone completes the effective treatment.

Spread beyond the limits of the operation but confined to the irradiated area creates the situation of major importance in a study of this mode of treatment. Such cases are potentially curable but their cure will ultimately depend on the effectiveness of radiotherapy in eradicating the remaining tumour.

Spread by continuity is of some importance in this group since it includes those where skin or pectoral fascia is invaded. Microscopic invasion of the tissues at the margins of the resected specimen is a distinct possibility in such cases. Contamination of the wound with tumour cells liberated from the operation site contributes to this group, although/

although it probably occurs only in association with direct spread to limits of the resection, or with lymphatic or venous invasion. The study of this phenomenon is fraught with difficulties but there seems to be some correlation between the extent of the tumour and the discovery of tumour cells in wound washings (Nash et al., 1962).

The principal mode of spread which concerns us in this group is of course lymphatic spread. Willis, on whose monograph "The Spread of Tumours in the Human Body" (Willis, 1952) I have drawn heavily in this section, considers that in the first instance such spread is by embolism rather than permeation. In the later stages of spread, permeation both in the normal direction of flow and in retrograde fashion undoubtedly plays a part, as does retrograde lymphatic embolism. Willis finds little ground for believing that the lymph nodes form an effective barrier against further spread of the tumour, although this hypothesis continues to be mooted (e.g. Nicholls, 1960; Crile, 1961).

As was mentioned earlier, the researches of Sampson Handley (Handley, 1922) drew attention to the importance of spread to the internal mammary nodes in carcinoma of the breast. Turner-Warwick (1959) using a dye technique, found that 25 per cent of the lymphatic drainage of the breast was to the internal mammary nodes and that drainage to/

to these nodes occurred from all parts of the breast. The axillary nodes received almost all of the remaining 75 per cent of the lymph drainage, only a small and inconstant amount passing to the posterior intercostal nodes. Similar findings obtained by a radioactive tracer technique were reported by Hultborn and his colleagues in 1955.

The supraclavicular nodes are associated with the upper ends of both the internal mammary and axillary groups. Indeed as McWhirter (1950) has demonstrated they are virtually in continuity with the latter. Supraclavicular node metastasis is therefore generally to be regarded as a later phenomenon than axillary or internal mammary node metastasis, to which in fact it is usually secondary.

In the third group of cases - those in whom spread has passed beyond the confines of the treated area - dissemination by the blood-stream is the main mode to be considered.

Spread by continuity to this extent almost inevitably renders the case inoperable and excludes it from the standard treatment by simple mastectomy and radiotherapy.

Lymphatic spread beyond the treated area - to the mediastinum, for example - is less certain to be detected clinically and to affect the choice of treatment. Lymph channels not infrequently bypass the more proximal nodes and early spread from one node to another may also occur.

Lymphatic/

Lymphatic spread tends however to be a staged occurrence and the more advanced the involvement of the proximal and accessible nodes the more likely it is that further lymphatic spread will have occurred. It is reasonable to assume for example that lymphatic spread beyond the treated area is commoner in cases with matted or fixed axillary nodes (Stage IVL) than in those with palpable but mobile nodes (Stage II).

The vagaries of blood dissemination in cancer are well known. There is no means by which early blood spread can be detected or even, with any degree of certainty, predicted. In recent years much work has been done on the detection of tumour cells in the peripheral circulation (Engell, 1955; Malmgren et al., 1958; Seal, 1959; Moore, 1960; Cole et al., 1961). It has been shown that such cells can be detected even in apparently early cases and are found in increased numbers following manipulation of the tumour such as is entailed in clinical examination and diagnostic or operative procedures.

It seems likely therefore that the majority of such cells fail to give rise to metastases and the prognostic significance of these findings remains doubtful (Engell, 1959; Watne et al., 1961). Indeed some doubt has lately been/

been cast on the identity of these cells and it has been suggested that many may not be tumour cells at all (Alexander and Spriggs, 1960; Jackson, 1962).

Blood-borne metastases are undoubtedly the cause of many unpredictable failures of treatment in the early case. Although such spread may occur from cells liberated into the circulation at the time of operation the majority are probably present when the patient is first seen.

Spread Following Treatment

The manifestations of recurrent disease following the treatment of breast cancer fall into two main groups - those appearing in the erstwhile treated area and those appearing beyond that area. The former will be termed local recurrence and latter distant metastasis, while the term recurrent disease will, where suitable, be applied to cover both groups.

In relation to treatment by simple mastectomy and radiotherapy local recurrence refers to the reappearance of tumour on the affected side in the chest wall, the axilla, the supraclavicular fossa and in the relatively uncommon situation of the intercostal spaces in the parasternal region. These latter probably represent internal mammary metastases but are classified as chest wall recurrences for the purposes of the present study. Only/

Only four such were recorded in the standard group. All other sites are regarded as distant metastases including tumours appearing subsequently in the opposite breast.

Tumours in the opposite breast however constitute a special case for some of these may be independent primaries. The difficulty of distinguishing these has already been mentioned but in the standard group there were five cases in whom such a diagnosis seemed highly probable. Three of these survived over five years after the appearance of the second tumour, without evidence of further disease - one remaining alive at 10 years, one dying at 9 years of a coronary thrombosis and one at 6 years of a hepatocholangioma. Of the two remaining patients one who developed the second tumour 6 years after the first, died one and a half years later of a coronary thrombosis, and the other, whose second lesion appeared 14 years after the first was still alive at the end of the follow-up period two years later. These five cases are excluded from the total number considered to have developed recurrent disease.

Local Recurrence

Chest wall recurrence can be assumed to arise in most cases from local foci of tumour tissue either implanted at the time of operation or not included in the resected tissues. It has been noted that four cases showing parasternal nodules have been included amongst the chest wall/

wall recurrences and it may be that these arose by direct spread from foci in the internal mammary nodes or as Sampson Handley (1927) suggested, by retrograde lymphatic permeation.

Recurrence in the axilla is most likely to arise from tumour which was already present in the axillary nodes at the time of operation. It is of course possible as McWhirter (1954) has pointed out that previously uninvolved axillary nodes may be secondarily invaded from deposits of tumour in the chest wall or supraclavicular fossa. In view of the damage to lymph channels and to the nodes themselves produced by irradiation it seems unlikely that this path would be as freely available as in the normal individual. Spread by direct continuity from the chest wall into the axilla is a further possibility. This too seems unlikely since, where an extensive axillary clearance has been carried out as in Haagensen's technique, the incidence of axillary recurrence is very low (1 per cent) even in the presence of a fairly high chest wall recurrence rate of 10 per cent (Haagensen, 1956).

The significance of supraclavicular node recurrence is less easy to define. The most obvious source is again from foci of tumour present in these nodes at the time of operation. Subsequent spread may however occur from axillary or internal mammary node deposits, or from foci in the mediastinum which were either initially present or secondary to pulmonary or pleural metastases.

Internal Mammary Node Recurrence

In spite of the frequency with which the internal mammary nodes are now known to be involved even in apparently operable breast carcinoma, such metastases are seldom apparent on clinical examination. The reason for this is probably that these nodes are deeply placed and separated from the skin by well-defined fascial layers. Expansion of tumour in this situation will tend to be in a posterior direction into the anterior mediastinum. Although attempts have been made to demonstrate recurrences in these nodes radiographically (Massoud et al., 1964), satisfactory routine methods of detecting them are still lacking.

The presence of internal mammary node recurrences may perhaps be inferred in certain circumstances such as the presence of mediastinal tumour and pleural effusions. Spread to both mediastinum and pleura can occur in a variety of ways of which the most obvious is from tumour deposits in the lung. Willis (1952) is however of the opinion that pleural involvement in breast carcinoma more often affects the parietal pleura than the visceral pleura, and states that direct invasion of the serous surface by tumour is mainly responsible for this involvement rather than subserous lymphatic permeation. Such direct involvement may be from tumour deposits in the chest wall but may also arise/

arise from deposits in the internal mammary nodes. It seems a not unreasonable hypothesis that in the absence of tumour deposits in the lung (and possibly the abdomen), mediastinal and pleural involvement can be regarded as evidence of spread via the internal mammary nodes.

Distant Metastasis

The inaccessibility of many distant sites of metastasis and the size frequently attained before such metastases are detected, make deduction as to their significance hazardous. There are three circumstances in which distant metastases may appear - after local recurrence has become evident, at some time before a subsequent local recurrence appears, and finally in the complete absence of local recurrence.

When distant metastasis follows local recurrence it may represent spread from the latter. However, marked differences in the ease with which the two forms are detected make it possible that the distant lesions were already well established when the local recurrence became evident. When the local recurrence follows the distant metastasis it can be reasonably assumed that in most cases the distant lesions are not derived from the local recurrence but owe their existence to direct spread from the primary tumour. This is even more certain to be the case/

case when no local recurrence appears during the life of the patient. The remaining possibility is that local recurrence is derived secondarily from a distant metastasis. This, except perhaps in the case of supraclavicular metastases, is probably an uncommon event.

As to the significance of the various sites of distant metastasis speculation is for the most part pointless. The almost limitless possibilities of haematogenous spread and the phenomena of tertiary foci and retrograde dissemination render the pattern too complex. This is of course particularly true of post-mortem material. One may however assume that the commonest site of distant metastasis, the skeleton, represents in most cases blood-borne dissemination from the primary tumour.

It is therefore clear that local recurrence may generally be regarded as arising from tumour persisting in the treated area. Distant metastasis on the other hand when unassociated with local recurrence generally represents prior spread from the primary tumour. That exceptions occur is almost certain and might vitiate conclusions drawn from individual cases. One may however draw valid inferences from the behaviour of groups of such cases.

Distant metastasis followed by local recurrence is of less certain significance and the group of cases in which this was observed will therefore be analysed separately.

CASE MATERIAL

The material for this part of the study is drawn from the standard group as already defined but cases in Stage IVD are excluded since these presented with evident distant metastasis and were therefore beyond curative treatment.

Cases in Stage IVL who were treated by the standard method had, as far as could be determined clinically, disease confined to the treated area. This disease was however relatively advanced with matted or fixed axillary nodes or palpable supraclavicular nodes. The chances were high that disease had spread beyond the confines of the treated area. Nevertheless there was a small percentage of five-year survivors in this group.

Cases in Stages III and IVL (i.e. locally advanced) are considered together in the analyses in the later part of this section since the number of cases in the individual stages, being relatively small, are of less statistical significance.

The total number of cases in each Stage and the survival rates of the standard group are given in Table 44. Recurrent disease, local or distant, was observed in 314 of those which were included in Stages I to IVL.

TABLE 44

		STAGE					Total
		I	II	III	IVL	IVD	
5 year	Cases	238	185	51	89	10	573
	Survivors	167	102	26	13	1	309
	Survival rate (%)	70	55	51	15	10	54
10 year	Cases	144	102	28	46	5	325
	Survivors	71	50	7	3	-	131
	Survival rate (%)	49	49	25	7	0	40

STANDARD GROUP

SURVIVAL RATES - OVERALL AND BY STAGES

Incidence

The overall incidence of local recurrence in the series is based on the number of cases in whom a recurrence was observed in the treated area whether or not it was associated with a distant metastasis (Table 45 and Fig. 22).

The relative frequencies with which the different sites were affected are given in Table 46 and Figure 23. These figures include all cases showing recurrence at the given site and therefore overlap to some extent. (For full version of Table 46 see Appendix 3, Table 82). Recurrence confined to a single area was slightly less common in fact than recurrence appearing in two or more of the specified regions during the period of observation. The axilla is the most frequent site of recurrence in Stages II and IVL while in all stages supraclavicular recurrence is the least common. The chest wall is the commonest site of recurrence in Stages I and III though the differences are insignificant.

The site of first recurrence shows a rather similar distribution (Fig. 24). Axillary recurrence is however commonest in Stage I and strikingly so in Stages II and IVL. The predominance of chest wall recurrence in Stage III is also more evident. These cases include 6 in which a local recurrence and a distant metastasis were observed simultaneously as the first evidence of recurrent disease.

TABLE 45

	STAGE			
	I	II	III	IVL
No. of cases in Stage	238	185	51	89
No. of cases with local recurrence	57	72	16	53
% of cases with local recurrence in Stage	24	39	31	60

OVERALL INCIDENCE OF LOCAL RECURRENCE

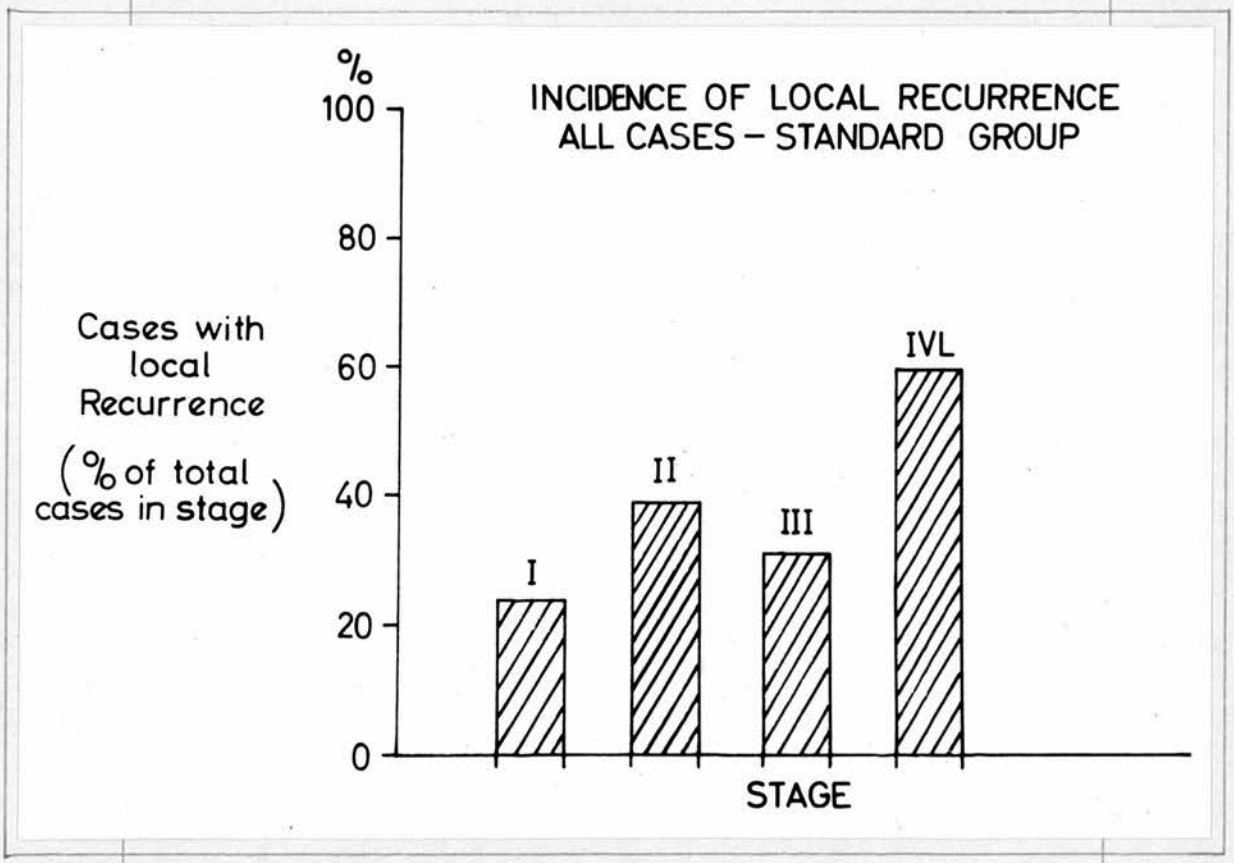
INCIDENCE OF LOCAL RECURRENCE
ALL CASES – STANDARD GROUP
%
100
80
60
40
20
0
Cases with local Recurrence
(% of total cases in stage)
I
II
III
IVL
STAGE

Figure 22

TABLE 46

SITE	STAGE			
	I	II	III	IVL
Axilla	14	28	16	40
Chest wall	15	25	20	29
Supraclavicular	11	18	10	25

SITES OF LOCAL RECURRENCES
IN RELATION TO STAGE

(Percentage of total cases in each stage having recurrence at given site)

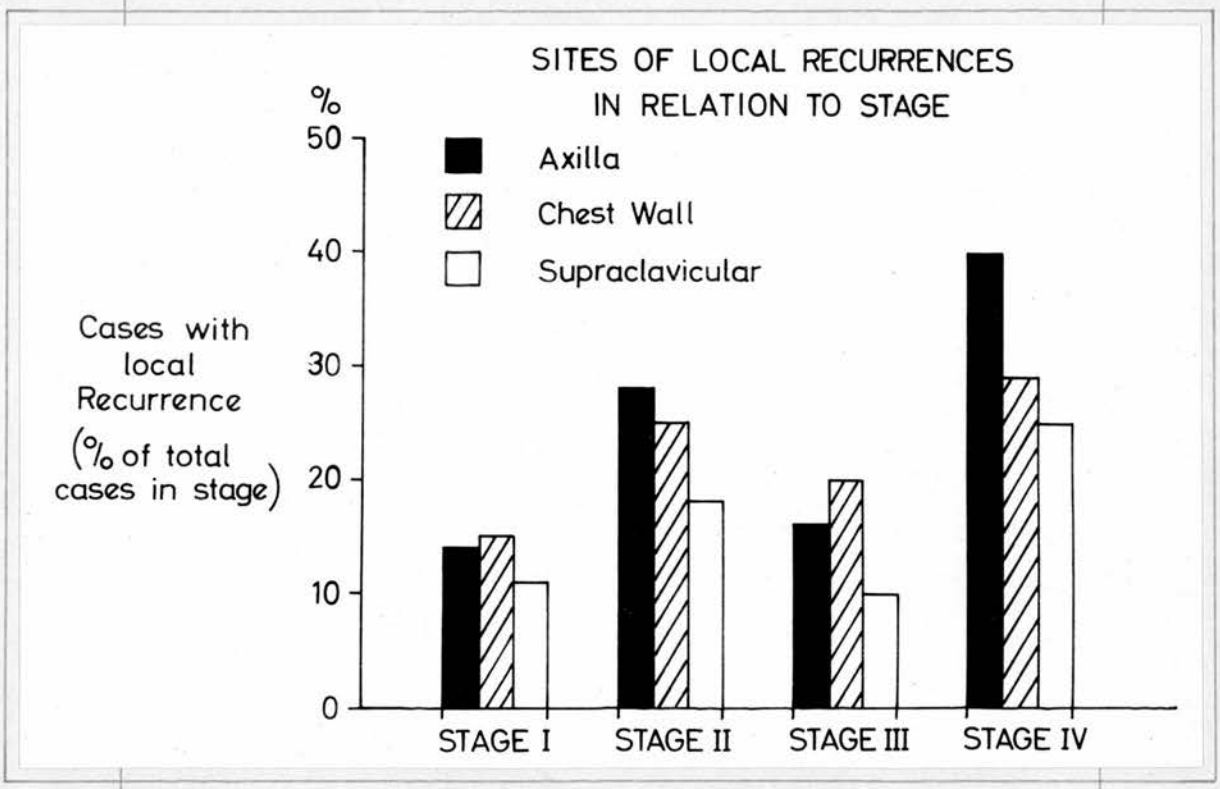
SITES OF LOCAL RECURRENCES
IN RELATION TO STAGE
%
50
40
30
20
10
0
Axilla
Chest Wall
Supraclavicular
Cases with local Recurrence (% of total cases in stage)
STAGE I
STAGE II
STAGE III
STAGE IV

Figure 23

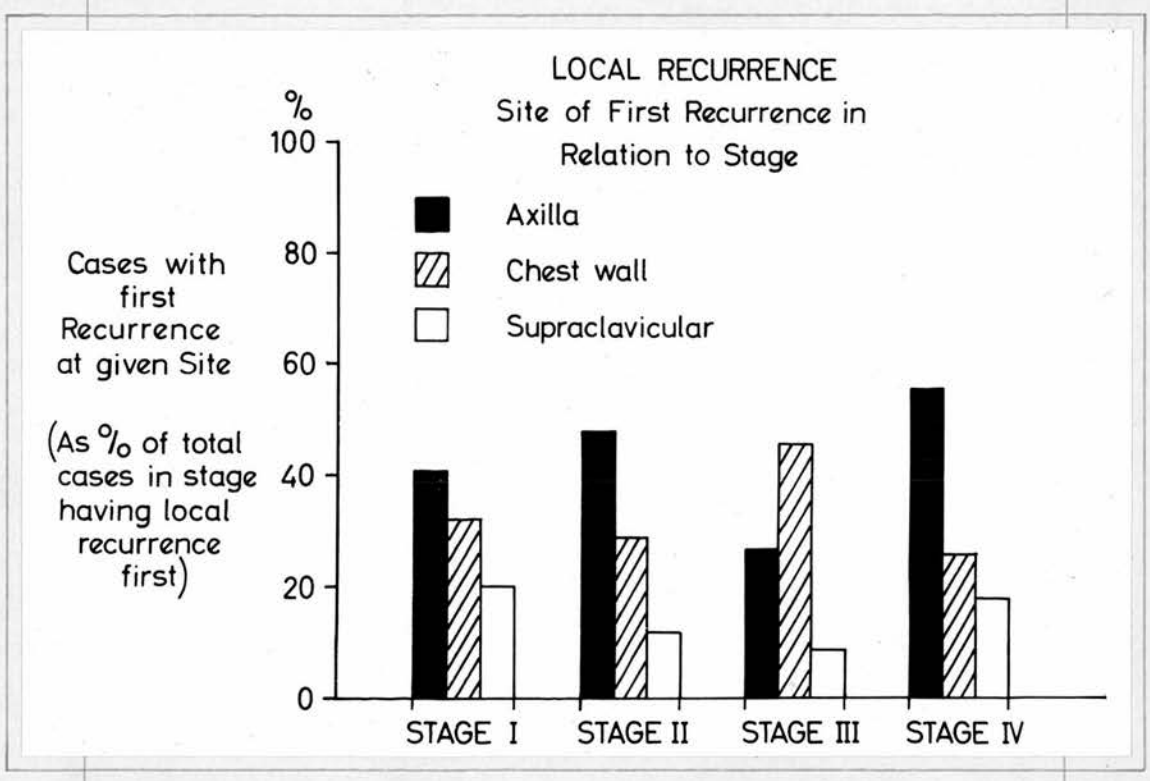
LOCAL RECURRENCE
Site of First Recurrence in Relation to Stage
%
100
80
60
40
20
0
Axilla
Chest wall
Supraclavicular
Cases with first Recurrence at given Site
(As % of total cases in stage having local recurrence first)
STAGE I
STAGE II
STAGE III
STAGE IV

Figure 24

In all the above analyses the total number of recurrences observed during the whole follow-up period is used. For comparative purposes however the five-year recurrence rate is commonly used. The five-year local recurrence rates for the standard group of the present series are given in Table 47.

Comparable figures are not available for McWhirter's 1955 series but in 1948 he noted a reduction in the five-year local recurrence rate after radical mastectomy, following the introduction of supplementary radiotherapy (McWhirter, 1948a). The definition of local recurrence was as used here and the cases were classified as Manchester Stages I-III. The recurrence rate for radical mastectomy alone was 40 per cent and for radical mastectomy followed by radiotherapy 14 per cent. In the present series even Stage I cases exceed this latter figure and the rate for Stages I to III combined is 25 per cent.

Certain difficulties are involved in comparisons with other series. The term local recurrence is used in different senses, the period of observation varies and the composition of the different series is not uniform. Further, where recurrence rates are given for separate sites the calculation of the total may not be possible because of the overlap of cases.

Haagensen/

TABLE 47

Stage	% of cases with local recurrence within 5 years	
I	16	Stages I-III 25%
II	35	
III	29	
IVL	58	

5-YEAR RECURRENCE RATES BY STAGES

CASES TREATED BY SIMPLE MASTECTOMY AND RADIOTHERAPY

Haagensen to whose personal series of radical mastectomies reference has already been made (Haagensen, 1956) gives detailed figures from which it can be calculated that his five-year local recurrence rate in the sense used here is about 20-25 per cent. The majority of his cases would undoubtedly fall within Manchester Stages I-III and probably represent the more favourable section of that group.

Haagensen's series also shows a striking difference in the distribution of local recurrence. Allusion has already been made to his very low incidence of axillary node recurrence. The commonest site for recurrence is in fact the chest wall, the supraclavicular fossa coming next in frequency. In the present series axillary recurrence is commonest, chest wall second and supraclavicular recurrence least common. Nohrman's (1949) figures which refer to radical mastectomy supplemented by radiotherapy are difficult to convert to similar terms but he appears to have a higher incidence of chest wall recurrence than the combined incidence of axillary and supraclavicular recurrence - this being in accord with Haagensen's findings. Truscott (1947) also found that chest wall recurrences exceeded the combined total of axillary and supraclavicular recurrences. The principal mode of treatment in his series was again radical mastectomy.

One/

One of the most interesting analyses of local recurrence is that published by Paterson and Russell (1960). In their series radical mastectomy was used throughout but was supplemented by post-operative radiotherapy in one half of the cases, these cases being chosen by random selection. The series is in two parts in each of which a different radiotherapeutic technique is used. In the earlier series irradiation was directed at the chest wall and axilla omitting most of the supraclavicular fossa - the quadrate technique. In the later series irradiation of the axilla, supraclavicular fossa and parasternal region was carried out but the remainder of the chest wall was omitted - the peripheral technique.

The five-year recurrence rates are given for the individual sites of chest wall, axilla and supraclavicular fossa but since some overlap of these cases must be assumed, a total cannot be calculated. The total local recurrence rate cannot however be less than that of the site showing the highest percentage. This latter figure ranges from 15 per cent in irradiated cases to 19.9 per cent in the unirradiated group. The totals are probably 5-10 per cent above these figures.

The site most commonly affected by local recurrence in Paterson's series varies according to the treatment regime, but in all groups the axilla is the least common site of recurrence/

recurrence. The chest wall is slightly more frequently affected than the supraclavicular region in both unirradiated groups and much more frequently in cases irradiated by the peripheral technique. In cases treated by the quadrate technique in which supraclavicular irradiation is minimal, the recurrences in this region exceed those in the chest wall. It is clear therefore that radiotherapy affects the pattern of local recurrence after radical mastectomy.

Two reports of the incidence of local recurrence after simple mastectomy and radiotherapy have appeared in the literature - Brinkley and Haybittle (1959) and Dahl-Iversen (1963).

In the former series local recurrence includes only chest wall and axilla. In Stage II cases the two-year recurrence rates were 8.6 per cent for cases treated by simple mastectomy and radiotherapy compared with 13.1 per cent for those treated by radical mastectomy and radiotherapy. From the published graph it appears that the recurrence rates (again at two years) for Stage I cases were approximately 4 per cent in each group. In the same series a group of cases treated by radical mastectomy alone had a 10 per cent two-year local recurrence rate in Stage I and a 19 per cent two-year local recurrence rate in Stage II.

The two-year recurrence rate is not a very reliable figure. Only 30% of the Stage I cases in the present series/

series, in whom local recurrence was the first sign of recurrent disease, developed that recurrence within 2 years. For Stage II the proportion was 60% (see Fig. 27).

Dahl-Iversen's report lists recurrences according to site and again a calculation of the overall incidence is not possible.

His series, like the present one, shows recurrence to be commonest in the axilla and least common in the supra-clavicular region after simple mastectomy and radiotherapy. However the results in cases treated by extended radical mastectomy show a similar distribution as well as a higher incidence in all three regions.

Conclusions

The results in the present series and the evidence of most of the reports in the literature seem to point to the conclusion that where tumour is left after surgical excision it is there that it is likely to recur.

The relatively low incidence of axillary node recurrence after radical mastectomy as compared with that after simple mastectomy and radiotherapy supports this conclusion. The relatively high incidence of supra-clavicular node metastasis after radical mastectomy seems to point in the same direction.

It/

It has been stated earlier that involvement of the supraclavicular nodes is generally secondary to that of axillary or internal mammary nodes. The incidence of supraclavicular involvement would therefore be less than in these other groups.

If the more commonly affected group of nodes, the axillary group, is removed and its removal is relatively more effective than the treatment of the remaining supraclavicular nodes, then the incidence of recurrence might be greater in the supraclavicular region. This situation appears to obtain after radical mastectomy. If on the other hand the axillary nodes are not removed and their treatment is comparable in effect to that of the supraclavicular nodes then the incidence of axillary node recurrence should exceed that of supraclavicular recurrence. This situation appears to obtain after simple mastectomy and radiotherapy.

It has already been noted that in the present series Stage III cases show a slightly higher incidence of chest wall recurrence than at the other two sites. The great majority of cases in this stage are so placed because of clinical evidence of fixation to pectoral fascia. Such cases frequently show involvement of the fascia or muscle by tumour at operation or only a narrow gap between tumour and fascia. The likelihood of microscopic deposits of tumour/

tumour being left behind in this region after simple mastectomy is quite high. Once again the commonest site of recurrence tallies with the likeliest site of incomplete removal of tumour.

One might expect that treatment by radical mastectomy with its more effective clearance of the chest wall would produce a lower incidence of chest wall recurrence than simple mastectomy. In the reports reviewed there is no clear evidence that it does. Comparison with the incidence of supraclavicular recurrence is probably not valid in this case since the relationship between local invasion and supraclavicular metastasis is more complex than that between axillary and supraclavicular metastasis.

Axillary recurrence thus appears to be more effectively prevented by surgery than by radiotherapy. There is no definite evidence that this holds for chest wall recurrence. The results of simple mastectomy and radiotherapy in the Stage III cases give no grounds for concluding however that radiotherapy is more effective than surgery in eradicating tumour from the chest wall.

The results published by Paterson and Russell and by Brinkley and Haybittle suggest that radiotherapy prevents or at least delays the appearance of local recurrence in a proportion of cases. That it does so as effectively as surgery as far as axillary recurrence is concerned is one of the/

the basic concepts on which the use of simple mastectomy and radiotherapy rests. It seems however that this is not the case for surgical clearance of the axilla achieves the lowest rates of axillary recurrence.

There seems to be no reason why this principle should hold true only for the axilla. As in the case of the axilla so also at other sites the incidence of local recurrence in cases treated by simple mastectomy and radiotherapy in the present series parallels the likelihood of tumour remaining behind after surgery - tumour whose eradication has depended on the subsequent irradiation. Nevertheless radical mastectomy does not achieve the same superiority over simple mastectomy and radiotherapy in preventing chest wall recurrence. Part of the difficulty lies in the lack of adequately staged series for comparison, but a possible explanation is that the additional clearance of tissue accomplished by a radical mastectomy is less significant in the chest wall than it is in the axilla.

THE/

THE TIME RELATIONSHIPS OF RECURRENCE AND METASTASIS IN BREAST CARCINOMA

Where radiotherapy fails to eradicate the tumour it often appears to delay the recurrence. A study of the time of appearance of recurrence and metastases is therefore of importance.

The date at which the first evidence of recrudescence of the disease was observed is known in all but four cases in the standard group. These four cases are therefore excluded from this part of the study except where utilized in the actuarial analyses.

Separate analyses are made of the groups already defined in relation to the site of the first evidence of recurrent disease. Cases where local recurrence was observed first include six with simultaneously observed distant recurrence. The number of cases in each group and in the subdivisions of each group are shown in Table 48. Where local recurrence was found to have appeared at more than one site when first observed, the site is listed as combined.

The sites of the first distant metastasis in cases in whom this was the first evidence of recurrent disease is shown in Table 49 and Figure 25. There is little difference between the two groups defined - those with and without subsequent local recurrence. As can be seen from Table 48 the numbers are too small to permit an analysis by/

TABLE 48

Site of 1st recurrence	Stage			
	I	II	III	IVL
Local recurrence				
Axilla	17	25	3	22
Chest wall	8	6	1	7
Supraclavicular fossa	13	15	5	10
Combined	0	6	2	0
Total	41	52	11	39
Distant metastasis (with subsequent local recurrence)				
Skeleton	6	7	3	5
Other sites	10	13	2	9
Total	16	20	5	14
Distant metastasis (with no local recurrence)				
Skeleton	21	17	4	8
Other sites	22	19	11	14
Total	43	36	15	22
Overall total	100	108	31	75

NUMBER AND DISTRIBUTION OF CASES WITH RECURRENCE AND METASTASIS

TABLE 49

SITE OF FIRST METASTASIS	TOTAL CASES (Stages I-IVL)
DISTANT METASTASIS (subsequent local recurrence)	
Skeleton	21
Lung	10
Pleura	4
Mediastinum	3
Other sites*	17
DISTANT METASTASIS (no local recurrence)	
Skeleton	50
Lung	13
Pleura	15
Mediastinum	1
Other sites*	37

* Other sites include abdomen, contralateral nodes, opposite breast, distant skin metastases and brain. Also included here are 7 cases with distant metastases at multiple sites.

CASES WITH DISTANT METASTASIS

SITES OF FIRST METASTASIS

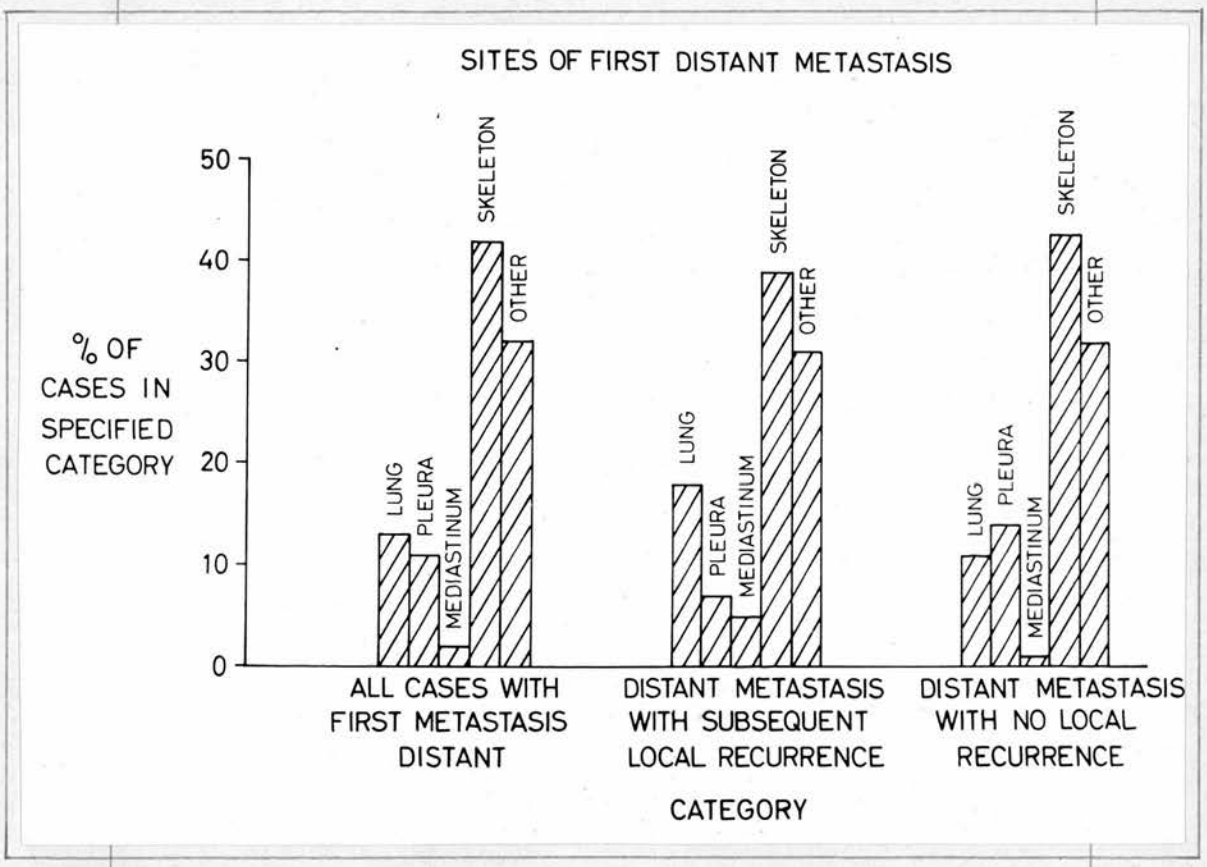
SITES OF FIRST DISTANT METASTASIS
% OF CASES IN SPECIFIED CATEGORY
50
40
30
20
10
0
LUNG
PLEURA
MEDIASTINUM
SKELETON
OTHER
ALL CASES WITH FIRST METASTASIS DISTANT
DISTANT METASTASIS WITH SUBSEQUENT LOCAL RECURRENCE
DISTANT METASTASIS WITH NO LOCAL RECURRENCE
CATEGORY

Figure 25

by stages.

The time relationships studied are the intervals from first treatment to the appearance of the first sign of recurrence (local or distant), and from the appearance of the first recurrence to death. The time of appearance of recurrent disease cannot of course be a very accurate parameter. However for a given site and with regular follow-up of the patients the averages are probably reliable.

The earlier periods from each of these starting points are divided into shorter intervals since the patients are seen more frequently at this stage and the number of cases recurring or dying is generally larger. The later periods are divided into intervals of one year.

The interval from treatment to first recurrence is plotted on a 10-year scale. The interval from first recurrence to death is plotted on a 5-year scale both because this interval is generally shorter and because the available follow-up time covering this phase is less.

The graphs dealing with the interval from treatment to recurrence are based on the percentage of cases remaining free of recurrence (or metastasis) at successive intervals of time. In the case of those dealing with the interval from recurrence (or metastasis) to death the percentages of cases remaining alive at successive intervals of time are plotted.

It/

It is possible to analyse such data in two ways. Either the number of patients remaining free of recurrence may be related to the total number observed to develop recurrence in the whole series or else allowance may be made by the method of actuarial analysis for cases dying without recurrence, ceasing to be followed up after a given period and so on. In the latter method the cases remaining free of recurrence are thus related to the whole population at risk - in this case the whole treated group. While the former enables a clearer picture of the interval from treatment to recurrence in recurring cases to be obtained, the latter allows the maximum use to be made of the material available and provides a closer approximation to overall recurrence rate. Both these methods are used in the presentation of data on the interval from treatment to recurrence.

In the case of the interval from recurrence to death however the population at risk consists only of those cases which have developed a recurrence. Here the correction for withdrawals obtained by actuarial analysis is insignificant since in the present series all but a very few of these cases are followed up to death. Only 13 out of 143 cases with local recurrence are not followed/

followed up to death and only 4 out of 116 of those with distant metastases. The data relating to this time interval are therefore only in the form of simple percentages of cases remaining alive in successive intervals of time from first recurrence.

As has already been pointed out the relation between recurrent disease and treatment is fairly clear in two groups of cases. These groups are the cases presenting with an initial recurrence in the treated area and the cases where an initial distant metastasis is not followed by a local recurrence. The pathological significance of the third group - those who develop a local recurrence after the appearance of a distant metastasis - is more obscure. This group has therefore been separated off from the cases with an initial distant metastasis. It is the smallest of the three groups amounting to only 55 cases in all and it is too small for separate analysis.

The tables from which these graphs are derived and the details of the statistical calculations are given in Appendix 3.

TIME/

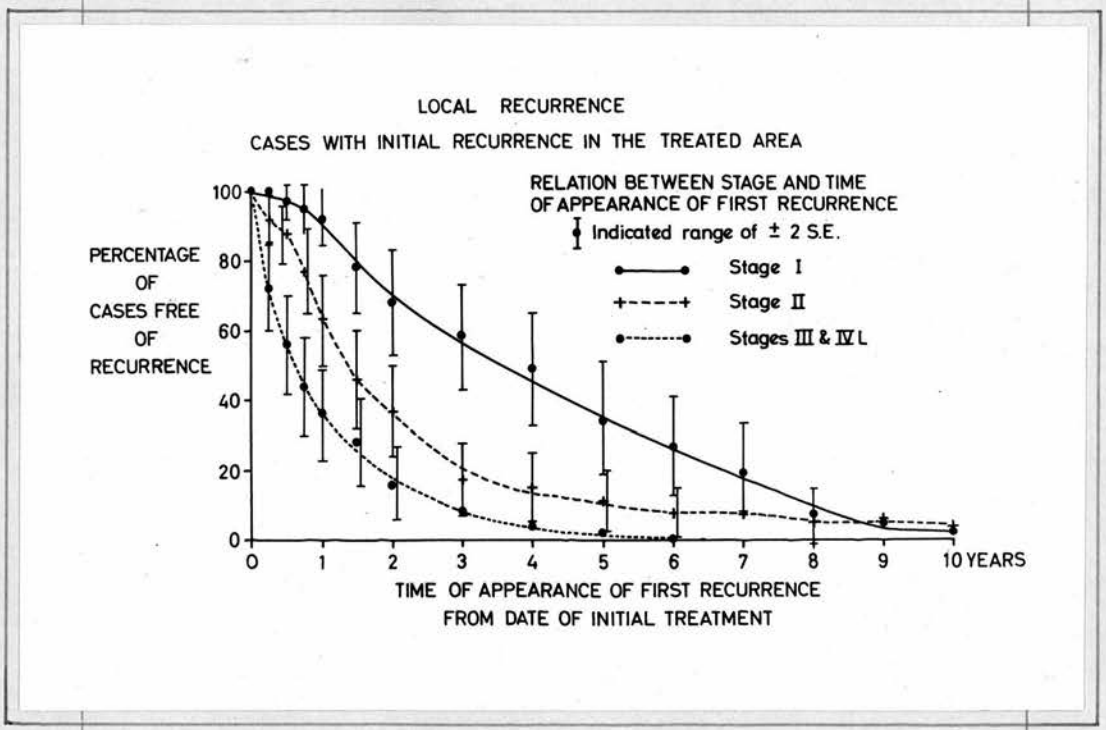
LOCAL RECURRENCE
CASES WITH INITIAL RECURRENCE IN THE TREATED AREA
RELATION BETWEEN STAGE AND TIME OF APPEARANCE OF FIRST RECURRENCE
Indicated range of ± 2 S.E.
Stage I
Stage II
Stages III & IV L
PERCENTAGE OF CASES FREE OF RECURRENCE
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 YEARS
TIME OF APPEARANCE OF FIRST RECURRENCE FROM DATE OF INITIAL TREATMENT

Figure 26

TIME OF APPEARANCE OF RECURRENT DISEASE

Local Recurrence

In cases where the first evidence of recurrent disease is a local recurrence, the time of appearance of that recurrence is analysed in relation to clinical stage in Figure 26.

The range is quite striking for whereas in Stage I less than 10% of the recurrences have developed at the end of one year, in cases in Stages III and IVL, i.e. with locally advanced disease, over 60% of the observed recurrences have already appeared. At five years the corresponding figures are 65% and 98% respectively.

There are few such estimates in the literature with which to compare these figures. Williams and his colleagues in their report from St. Bartholomew's Hospital in 1953 found that 74 per cent of their local recurrences appeared in two years. The cases treated were however a mixed group and a number of different methods of treatment were used. Haagensen (1956) gives a more detailed analysis of cases submitted to radical mastectomy. His figures show that 75% of the chest wall recurrences appeared between two and three years after treatment. A similar proportion of regional node (presumably axillary) recurrences were observed in the same time. The same result was obtained by Boyd and his colleagues/

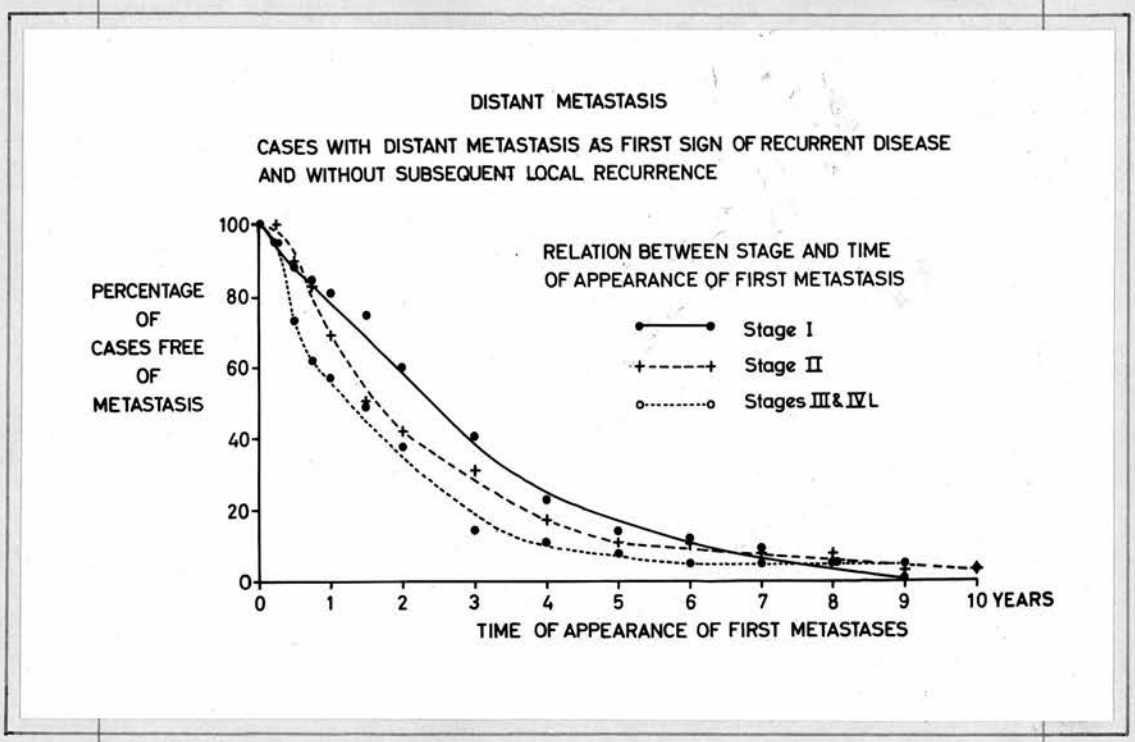
DISTANT METASTASIS
CASES WITH DISTANT METASTASIS AS FIRST SIGN OF RECURRENT DISEASE AND WITHOUT SUBSEQUENT LOCAL RECURRENCE
RELATION BETWEEN STAGE AND TIME OF APPEARANCE OF FIRST METASTASIS
Stage I
Stage II
Stages III & IV L
PERCENTAGE OF CASES FREE OF METASTASIS
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 YEARS
TIME OF APPEARANCE OF FIRST METASTASES

Figure 27

colleagues (1954) again in a series of radical mastectomies. Pawlias and his colleagues (1958) on the other hand, in a review of Mayo Clinic cases found that it took five years for 78% of the observed local recurrences to appear.

Distant Metastasis

If cases whose first sign of recurrent disease is a distant metastasis are analysed in a similar way certain differences from the pattern followed by local recurrence is seen (Fig. 27).

In the first place average time of appearance of distant metastases is earlier in Stage I cases than the corresponding time in relation to local recurrence. In the locally advanced group the reverse holds true. Secondly, the difference in time of appearance is not nearly so marked in the different stages as is the case with local recurrence.

DISCUSSION

General Considerations

Let us assume that local recurrence, at least in those cases where its appearance precedes that of distant metastasis, arises from foci of tumour remaining in the treated area. Let us further assume that distant metastasis/

metastasis, at least in those cases where no local recurrence subsequently appears arise by spread from the primary tumour and are in many cases already established at the time of treatment. The grounds for these assumptions and the exceptions which may occur have already been discussed (pp. 163-172).

Local Recurrence

The cases in whom recurrence in the treated area is the first sign of the failure of treatment are of considerable interest in relation to the effectiveness of that treatment. It has been shown that the time of appearance of these recurrences bears a definite relationship to the stage of the primary tumour. The limits of twice the standard error shown in relation to the curves in Figure 26 demonstrate the significance of the difference between Stage I and Stage II and between Stage I and the locally advanced cases (Stages III and IVL). The difference between Stage II and Stages III and IVL is less significant and is at several points only just in excess of the standard error itself. In general however the more advanced the primary tumour the earlier do the local recurrences appear.

It must of course be borne in mind that the actual incidence of these recurrences is also related to the stage/

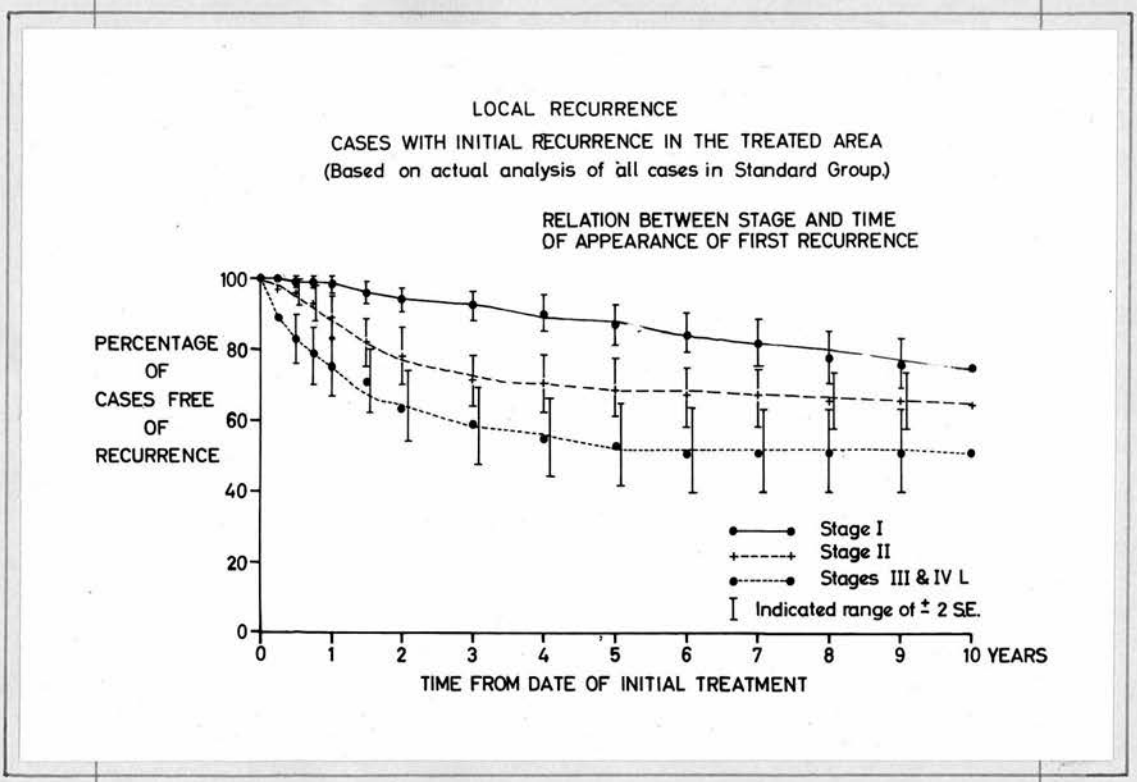
LOCAL RECURRENCE
CASES WITH INITIAL RECURRENCE IN THE TREATED AREA
(Based on actual analysis of all cases in Standard Group)
RELATION BETWEEN STAGE AND TIME
OF APPEARANCE OF FIRST RECURRENCE
PERCENTAGE OF CASES FREE OF RECURRENCE
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 YEARS
TIME FROM DATE OF INITIAL TREATMENT
Stage I
Stage II
Stages III & IV L
Indicated range of ± 2 S.E.

Figure 28

stage of the primary tumour and that treatment is successful in an increasing proportion of cases in the earlier stages. This can be shown if the cases with local recurrence are analysed by the actuarial method (Merrell and Shulman, 1955) in relation to the series as a whole (Fig. 28). From this graph it can be seen that the estimated local recurrence rate at five years (considering only those cases where local recurrence was the first sign of recurrent disease) is only 15% in Stage I, 30% in Stage II and 45% in Stages III and IVL combined. It is of interest to note that the differences in the rates between the different stages is of the same order of significance as previously calculated.

The study in the earlier part of this section of incidence of local recurrence at different sites has already shown that failure of treatment bears some relationship to the amount of tumour tissue left behind after the initial surgical excision. One must now consider why, where treatment does fail, this becomes apparent sooner in the case that was initially more advanced.

Effect/

Effect of Radiotherapy

Since simple mastectomy physically removes some of the tumour within the treated area and radiotherapy undoubtedly damages the remainder, this method of treatment cannot but effect a check, however temporary, on the progress of the disease. Where such treatment fails to eradicate the disease locally, local regrowth will occur and, after an interval of time, become apparent.

If the tumour remaining after simple mastectomy was unaffected by radiotherapy then, since the amount of such tumour is closely related to clinical stage, the observed relation between stage and time of appearance of local recurrence would be easily explained. It would merely reflect the shorter time taken by the larger residue of tumour tissue to grow into a mass which was clinically detectable. The same phenomenon has been observed in cases treated by radical mastectomy (Smithers et al., 1952; Haagensen, 1956). However it is quite apparent that the remaining tumour usually is affected by radiotherapy, since in the vast majority of cases clinically evident tumour deposits in the treated area disappear after treatment.

It can be accepted that in most cases where local treatment fails radiotherapy nevertheless produces a temporary arrest of the growth of the tumour remaining after simple/

simple mastectomy. The time of appearance of local recurrence however bears the same relationship to clinical stage as would occur if radiotherapy had no effect on the remaining tumour.

It must therefore be concluded that in these cases the same factor, that is the quantity of tumour tissue in the treated area, must govern the response to radiotherapy. This, it must be emphasized, applies only to this group of cases in which treatment fails - cases which are by implication radioresistant. It would not be justifiable to extend this argument to cases in which local treatment appears to be successful and to conclude that the success of treatment was due to the fact that the amount of tumour tissue remaining fell below a certain critical minimum. This may indeed be a factor but it is equally probable that biological factors intrinsic to the tumour itself are of importance.

Variation in Time of Appearance

It will be apparent from inspection of any of the graphs illustrating these observations that the range of time within which local recurrence first appears is very great. This applies to cases in all stages. Quantitative considerations such as have been advanced cannot do more than explain the differences in average behaviour. Other factors, again probably largely concerned with biological differences between different tumours, must play a part in this/

this wide range, and to some extent this also reflects the looseness of the concept of clinical stage.

It might be argued that biological differences themselves could account for the differences in the time of appearance of recurrence between the different stages. While this is impossible to refute with certainty there remains the fact that histological grading, at present the only available direct measure of the biological nature of the tumour, appears to be largely independent of clinical stage.

There remains the possibility that following treatment tumour growth, possibly after a short period of abeyance, proceeds at an accelerated rate in comparison with its growth prior to treatment.

Considering again the average behaviour of local recurrence, the rapid reappearance of local lesions is a characteristic of the more advanced primary tumours as judged by clinical stage. It has already been pointed out that clinical stage is essentially a statement of fact concerning the extent of a tumour at a point in time. It does not appear to measure any intrinsic property of tumour. Unless this were so it would seem unlikely that tumours which showed a biological change, such as an increase in growth rate as a response to treatment, would show any correlation with clinical stage.

The/

The hypothesis that early recurrence is due to an acceleration in growth rate resulting from treatment would therefore appear to be both unnecessary, since the former explanation seems to be adequate, and unlikely to be true. The matter is further discussed later in this section.

Distant Metastases

The incidence of distant but occult metastases at the time of initial treatment is presumably related to the stage of the primary tumour, for the more advanced the tumour the greater the opportunity for spread. The eventual appearance of these metastases will depend on their site, their size at the time of initial treatment and their rate of growth. It can be assumed that in most cases they are unaffected by the treatment of the primary tumour. The vagaries of haematogenous spread will however tend to obscure the relationship between the time of their appearance and the clinical stage of the primary tumour. It is not surprising therefore that this relationship is less striking than is the case with local recurrence.

Once again the phenomenon of distant metastasis is only seen in its proper perspective against the background of the whole case material of the series. This is illustrated/

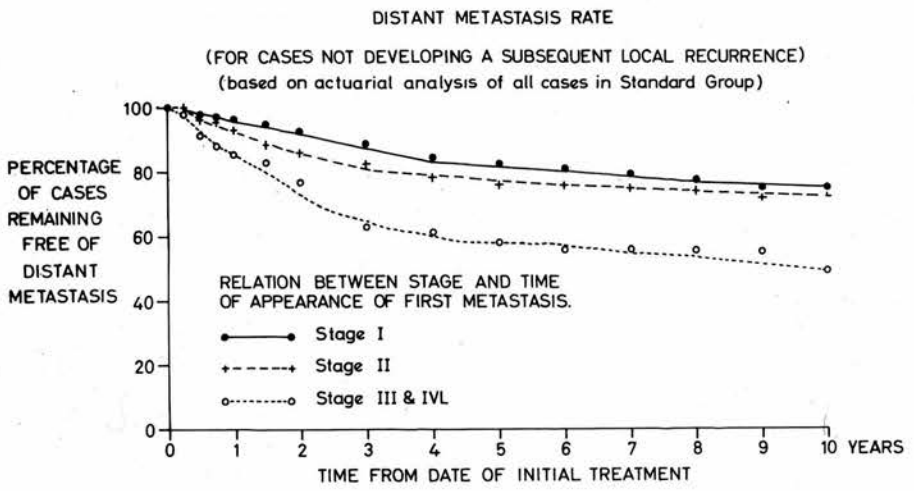
DISTANT METASTASIS RATE
(FOR CASES NOT DEVELOPING A SUBSEQUENT LOCAL RECURRENCE)
(based on actuarial analysis of all cases in Standard Group)
PERCENTAGE OF CASES REMAINING FREE OF DISTANT METASTASIS
100
80
60
40
20
0
RELATION BETWEEN STAGE AND TIME OF APPEARANCE OF FIRST METASTASIS.
Stage I
Stage II
Stage III & IVL
0 1 2 3 4 5 6 7 8 9 10 YEARS
TIME FROM DATE OF INITIAL TREATMENT

Figure 29

illustrated in Figure 29 based like Figure 28 on an actuarial analysis and referring only to cases where distant metastasis was not followed by local recurrence. The estimated 5 year distant metastasis rate (in this sense) is seen to be approximately 20% for Stage I, 25% for Stage II and 40% for Stages III and IVL combined.

THE ULTIMATE FATE OF PATIENTS WITH RECURRENT DISEASE

Of the patients who developed local recurrence or distant metastasis and analysed above, all but 17 were, as already mentioned, followed up to the time of death.

This interval from the appearance of recurrent disease to death was analysed in a similar fashion in terms of the percentage of cases remaining alive at successive intervals of time after the observation of the first recurrence or metastasis (Figs. 30 and 31).

Two features in these graphs are worthy of comment. The first is that while the interval from treatment to recurrence (or metastasis) was affected by the stage of the primary tumour at the time of treatment this has virtually no effect on the interval from recurrence to death. Secondly, a comparison of the two graphs shows that on average death occurs sooner after the appearance of a distant metastasis as first sign of recurrent disease than after a local recurrence. At two years for example 46% of the Stage I cases and 43% of the

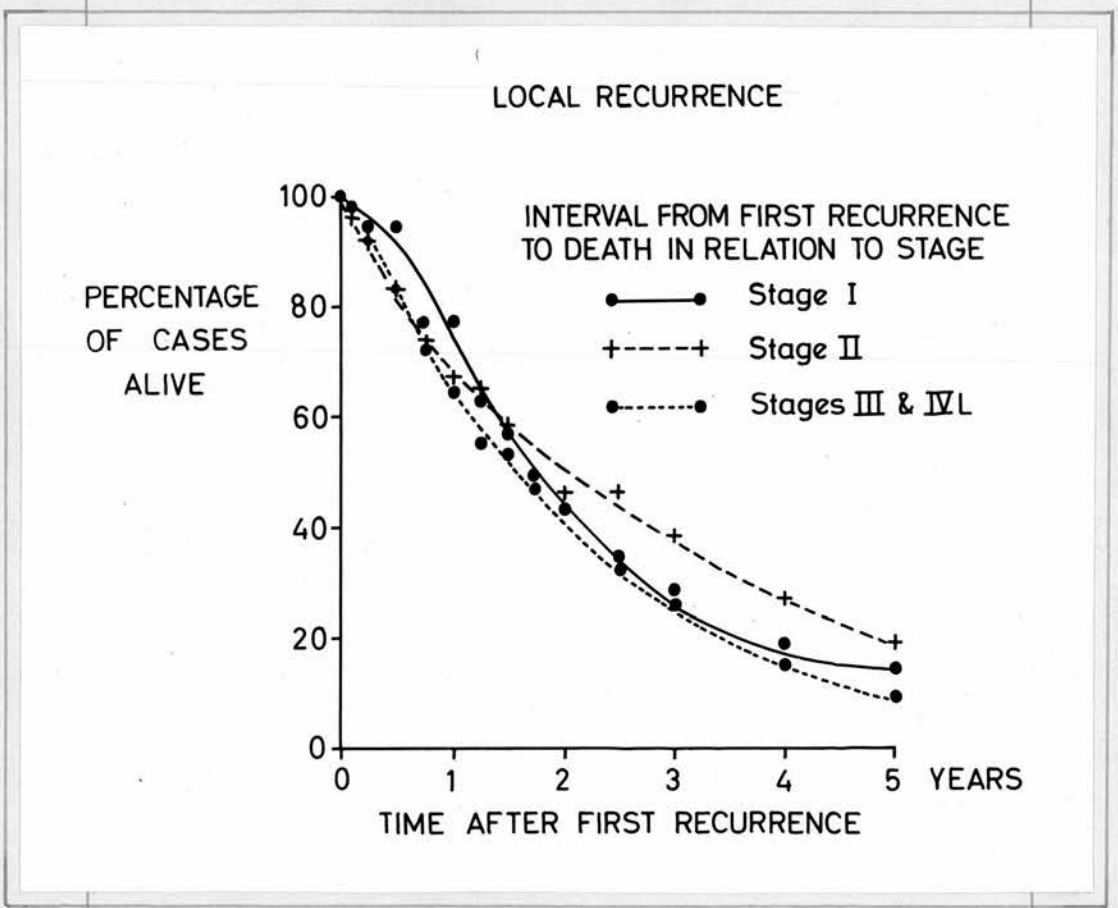
LOCAL RECURRENCE
INTERVAL FROM FIRST RECURRENCE
TO DEATH IN RELATION TO STAGE
Stage I
Stage II
Stages III & IVL
PERCENTAGE
OF CASES
ALIVE
100
80
60
40
20
0
0
1
2
3
4
5
YEARS
TIME AFTER FIRST RECURRENCE

Figure 30

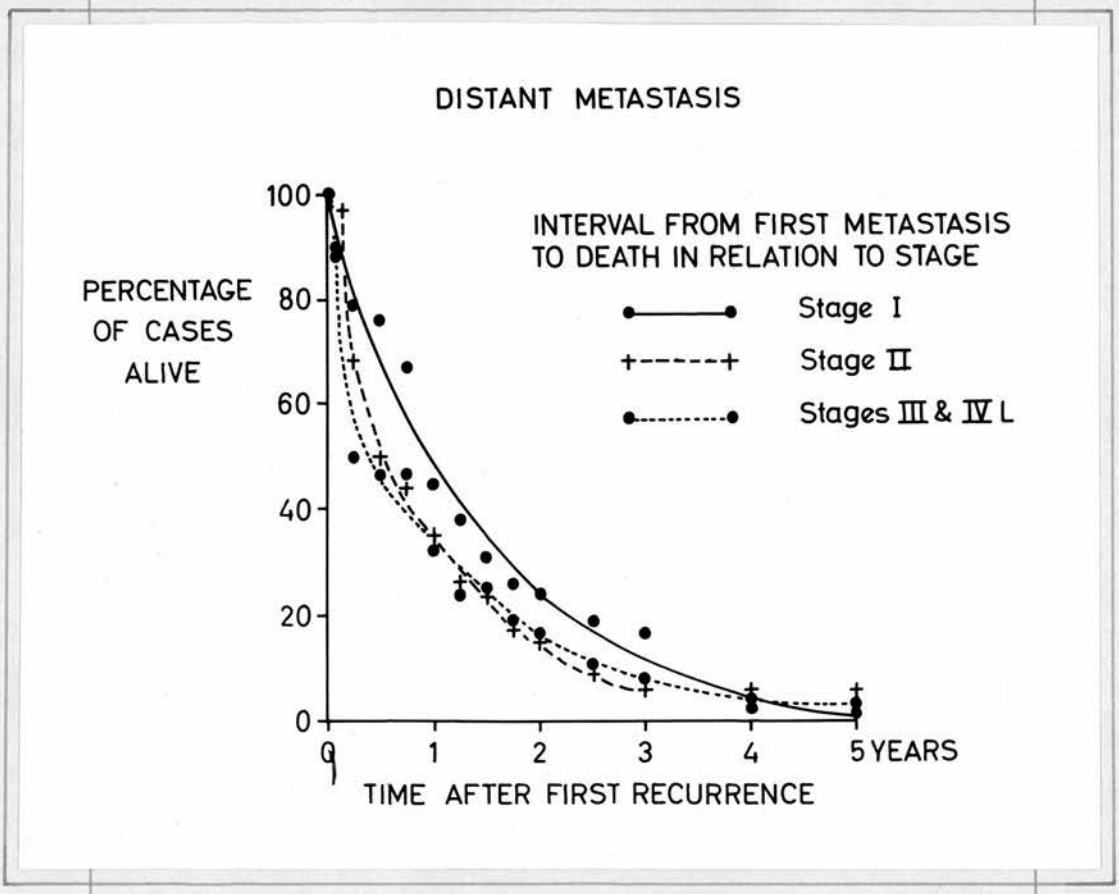
DISTANT METASTASIS
PERCENTAGE OF CASES ALIVE
100
80
60
40
20
0
INTERVAL FROM FIRST METASTASIS TO DEATH IN RELATION TO STAGE
Stage I
Stage II
Stages III & IV L
0
1
2
3
4
5 YEARS
TIME AFTER FIRST RECURRENCE

Figure 31

locally advanced cases remain alive after the appearance of a local recurrence. After the appearance of a distant metastasis however only 24% of the Stage I cases and 17% of the locally advanced cases remain alive at two years.

It can therefore be said the interval from the initial treatment to the appearance of recurrent disease is largely determined by the clinical stage of the primary tumour while the interval from the appearance of recurrent disease to death is largely determined by whether the recurrent disease is in the form of a local recurrence or a distant metastasis.

Other Factors affecting Time Relationships

It is obvious from a study of the preceding graphs that the time intervals observed are subject to a wide range of variation. The factors already discussed appear to affect the average interval and to be operative in a general way in all cases.

In the individual case a number of other factors must affect the outcome. These include the anatomical sites of the metastases, the physical size of the tumour mass, biological properties such as growth rate and metastasizing power, as well as the response to the various treatments applied during this phase.

With regard to the latter it may be noted that 83% of cases in the standard group who developed recurrent disease had some form of secondary treatment, 86% of those with local recurrence and 83% of those with distant metastasis.

DISCUSSION

Treatment and the Acceleration of Growth Rate

It has already been stated that the hypothesis that treatment in the advanced stages may accelerate growth is unnecessary to explain the earlier appearance of local recurrence in these cases. It has also been observed that the interval from the first evidence of local recurrence to the patient's death is unrelated to the original clinical stage (Fig. 30).

This is more direct evidence that acceleration of growth rate has not occurred. The more advanced cases in whom the tendency to earlier local recurrence has been demonstrated do not, on the average, die more quickly after the appearance of that recurrence, than the early cases whose local recurrence is much slower to appear.

This point has considerable therapeutic implications. On the basis of similar observations on the time of appearance of recurrence Haagensen (1956) concluded that in advanced cases operation accelerates the course of the disease. This view is in fact widely accepted.

If, as appears to be the case, such a hypothesis is neither necessary, nor indeed a satisfactory explanation of the facts, it ought not to influence the choice of treatment. It has been shown however that the more advanced the disease the/

the higher the incidence of recurrence and the shorter the interval before its appearance. These, not the hypothetical acceleration of the growth rate, are the probabilities which can provide a rational guide to treatment.

The Symptom-free Period

The life of a patient who ultimately dies of breast cancer may be divided into two phases following the primary treatment of her disease. These are the symptom-free period and the period from recurrence of disease to death. As Nissen-Meyer has recently stressed, the quality of life during these two periods may be very different (Nissen-Meyer, 1964).

While the object of the various forms of treatment of recurrent breast cancer is to extend the latter period and render it tolerable, it is the avowed object of primary treatment to avoid it altogether. It is unfortunately a foregone conclusion in our present state of knowledge that the primary treatment will fail in this aim in a considerable proportion of cases. Where it does so, and in the individual case this is unpredictable, it has a secondary standard of success - the achievement of the maximum symptom-free period.

Observations of the type made in the present series serve to indicate the probable symptom-free period which will/

will be achieved in given circumstances by a standard method of treatment. The published reports to which reference has been made above suggest that the pattern is similar for treatment by radical mastectomy.

As the probability of recurrence becomes higher and that of a long symptom-free period becomes less, then the cost to the patient of the means of achieving it becomes increasingly important. It is of course axiomatic that the untreated patient has no symptom-free period but it is obvious that in some circumstances no treatment is nevertheless the best policy. The important question of the morbidity of treatment is dealt with in a later section.

Finally there remains the possibility that, although local regrowth does not seem to be accelerated by local treatment, there are undoubtedly cases in whom any form of treatment appears to lead to widespread dissemination or to a reactivation of apparently dormant tumour. In fact there are well documented cases in which even incidental illness or an unrelated operation has produced such an effect (Gordon-Taylor, 1959). Such happenings are comparatively rare and it is difficult to be certain to what extent they should influence one's decision.

SUMMARY/

SUMMARY

The study of recurrence and metastasis after the treatment of breast carcinoma by simple mastectomy and radiotherapy shows that both the incidence and time of appearance of recurrent disease is broadly dependent on the clinical stage. The site of local recurrence seems to be closely related to the expected distribution of incomplete surgical removal of tumour. There is in this respect some evidence from comparisons with series treated by radical mastectomy that tumour in the axillary nodes is more effectively treated by surgery than by radiotherapy.

The rapidity with which local recurrence appears after treatment in advanced cases seems to be explained simply by the amount of tumour persisting in the treated area. No grounds were found for accepting the view that the treatment itself accelerated this regrowth. On the contrary a study of the interval from recurrence to death showed no correlation between it and the clinical stage as would be expected if this were the case.

Finally it may be observed that since the recurrence rate within a given period is closely related to the clinical stage, rates for short observation periods, particularly under five years, are very unreliable as a means of comparison where stage distribution is unknown.

MASSIVE CHEST WALL RECURRENCE

In 1952 Gatch and Culbertson drew attention to the phenomenon of diffuse skin recurrence in the chest wall following treatment by radiotherapy. This dramatic form of recurrence they attributed to loss of tissue resistance to cancer cells due to the effect of intensive radiotherapy.

A similar phenomenon has been observed in cases treated by simple mastectomy and radiotherapy in Edinburgh and has given rise to speculation concerning its nature. A striking feature of this type of recurrence is that diffusely scattered nodules of tumour sometimes appear to be limited to the treated area and indeed the boundary between irradiated and non-irradiated skin is sometimes outlined by the recurrence. Perhaps even more striking though less frequent is the appearance of nodular recurrence within the area of the posterior field of irradiation.

The nodules, which often become ulcerated, eventually spread beyond the treated area and are a particularly distressing and intractable form of recurrence.

This type of recurrence is uncommon - far less common than the usual localised chest wall recurrence from which, however, it seems sometimes to arise.

Nineteen cases of diffuse chest wall recurrence occurred within the group of cases treated by simple mastectomy and radiotherapy - an incidence of 3 per cent.

Since/

Since many possible factors may be involved, brief histories of these cases are presented. These are summarized in Table 50, p. 216.

CASE HISTORIES

Case 1.- A 69-year-old woman who presented with a 6 cm. Stage III carcinoma of left breast. The tumour was in the upper outer quadrant and was fixed to the skin and pectoral fascia.

At simple mastectomy a portion of pectoralis major was removed together with an axillary node. The tumour was Grade III. Wound healing was delayed and 45 days elapsed from mastectomy to radiotherapy but this delay was in part due to the radiotherapy waiting list. A minimum dose of 3500 r was given to the breast area and there were no adverse reactions. Prophylactic ovarian irradiation was also given.

Seven months after completion of radiotherapy a small skin recurrence appeared and at the same time metastases were found in the lumbar spine. Oestrogens were given with no response and four months later there was a diffuse recurrence over the whole chest wall. A pleural effusion also developed. The patient survived another nine months.

Case 2.- A 64-year-old woman with a 7 cm. carcinoma of the upper outer quadrant of the right breast. Invasion of skin with nodules of tumour (Stage IV). Simple mastectomy with removal of axillary node, no complications. Grade II tumour. Radiotherapy started 15 days later. Minimum dose 3750 r plus prophylactic ovarian irradiation. No complications.

Skin nodules appeared on chest wall in region of scar and mid-axillary line five months after completion of radiotherapy. No response to oestrogens. More extensive three months later. Opposite breast involved after further six months. Nodules progressed to ulceration. Patient survived two years after appearance of the first skin recurrence.

Case/

Case 3.- A 50-year-old woman with a 4 cm. carcinoma of the upper outer quadrant of the right breast. Axillary metastases present (Stage II); tumour fixed to skin. Simple mastectomy followed by radiotherapy 43 days later. No wound or radiotherapy complications. Minimum dose 3750 r plus prophylactic ovarian irradiation. Tumour - Grade II.

Recurrence appeared in region of scar five years after completion of treatment. Within two months had spread to involve chest wall diffusely. Oestrogens given without response. Died seven months after first appearance of skin nodules with tumour involving pleura and opposite breast and having developed oedema of the arm.

Case 4.- A 67-year-old woman with a 5 cm. Stage I carcinoma in the upper outer quadrant of the left breast. Skin fixation present.

Marked wound infection followed simple mastectomy. Radiotherapy (minimum dose 3750 r) started 24 days post-operatively. No complications. Tumour - Grade II.

Five years after completion of treatment oedema of the arm developed, followed five months later by chest wall recurrence. Within nine months recurrence diffusely spread over the chest wall. During this time treatment with oestrogens with no response and with androgens with slight response. Patient lived a further year.

Case 5.- A 50-year-old woman with a 5 cm. carcinoma in the upper inner quadrant of the left breast. Placed in Stage IV because of palpable node in the opposite axilla later found on biopsy to contain tumour. Tumour fixed to skin and pectoral fascia.

Slough developed in wound after simple mastectomy and a severe skin reaction followed radiotherapy (minimum dose 3750 r). Radiotherapy started 55 days after operation. Tumour not graded.

Tumour appeared in opposite (right) breast 10 months after completion of treatment and was treated by simple mastectomy and radiotherapy (minimum dose 3750 r). No post-operative complications but severe skin reaction after irradiation. This tumour was grade III.

Diffuse/

Diffuse recurrence appeared in right chest wall nine months after completion of treatment of that side and was followed by oedema of the right arm. Treatment by oestrogens produced an adverse response and a similar response followed treatment by androgens. There was a slight temporary response to adrenalectomy. Recurrence extended on to the posterior aspect of the shoulder and became ulcerated. Patient after further courses of oestrogens and androgens and after pituitary irradiation, all without response, died three years after the appearance of the chest wall recurrence.

Case 6.- A 36-year-old woman with a 4 cm. Stage II carcinoma of the upper outer quadrant of the left breast showing early skin fixation.

No complications after simple mastectomy, which included removal of axillary node, or after radiotherapy. Latter started 41 days after operation. Minimum dose 3750 r. Tumour - Grade III.

Axillary recurrence appeared eight months after end of treatment and was excised. Recurrence then appeared after a further eight months in the opposite axilla and, following ovarian irradiation, remained static for about a year. Axillary recurrence extended showing only a slight and temporary response to androgens. Two years after the first recurrence, the chest wall became diffusely infiltrated with tumour extending both inside and outside the treated area and proceeding to ulceration. The opposite breast also became involved. The patient lived five months after the appearance of the chest wall recurrence.

Case 7.- A 61-year-old woman with a 3 cm. Stage II carcinoma in the upper inner quadrant of the left breast showing early skin fixation.

No surgical or radiotherapy complications. Radiotherapy started 25 days post-operatively. Minimum dose 3750 r. Tumour - Grade II.

Axillary recurrence appeared two and a half years after completion of treatment and was followed seven months later by supraclavicular recurrence. There was some response to oestrogens.

After a further 15 months nodules appeared in relation to the scar, developing in two months into an extensive chest wall recurrence. Androgens produced no response and oedema of the arm developed. Opposite breast became involved/

involved and a pleural effusion appeared. There was a temporary response to adrenalectomy and oophorectomy. Patient lived 17 months after appearance of skin recurrence which ultimately ulcerated.

Case 8.- A 58-year-old woman with a 3 cm. Stage I carcinoma in the upper inner quadrant of the left breast.

Wound developed a small slough. Radiotherapy started 21 days post-operatively. Minimum dose 3750 r - no complications. Tumour - Grade II.

Axillary recurrence appeared two years after end of treatment, supraclavicular three months later and chest wall recurrence the following month. There was no response to oestrogens or androgens and in five months there were tumour nodules all over the treated area. The patient who also developed oedema of the arm lived a further five months.

Case 9.- A 47-year-old woman with a 1 cm. Stage I subareolar carcinoma of the right breast. Nipple retracted.

Simple mastectomy included removal of axillary node and was complicated by a large haematoma. Radiotherapy started 27 days later. Minimum dose 3750 r; no complications. Tumour not graded.

Fifteen months after completion of treatment a skin nodule appeared outside the treated area and was treated by radiotherapy. Nodule disappeared. Ten months later skin involvement commenced at the same site and extended into the treated area. Ovarian irradiation carried out but no response obtained. One year later recurrence noted to be diffuse within the treated area and confined to it. Adrenalectomy and oophorectomy carried out with good response lasting about a year. Ten months later tumour noted in opposite breast. After course of oestrogens which was without effect, hypophysectomy. Again good response lasting about six months. Patient died six years after first chest wall recurrence and three and a half years after recurrence became diffuse.

Case 10.- A 65-year-old woman with a 6 cm. centrally placed carcinoma of the left breast showing early skin fixation and associated with supraclavicular nodes and matted axillary nodes (Stage IV).

Radiotherapy/

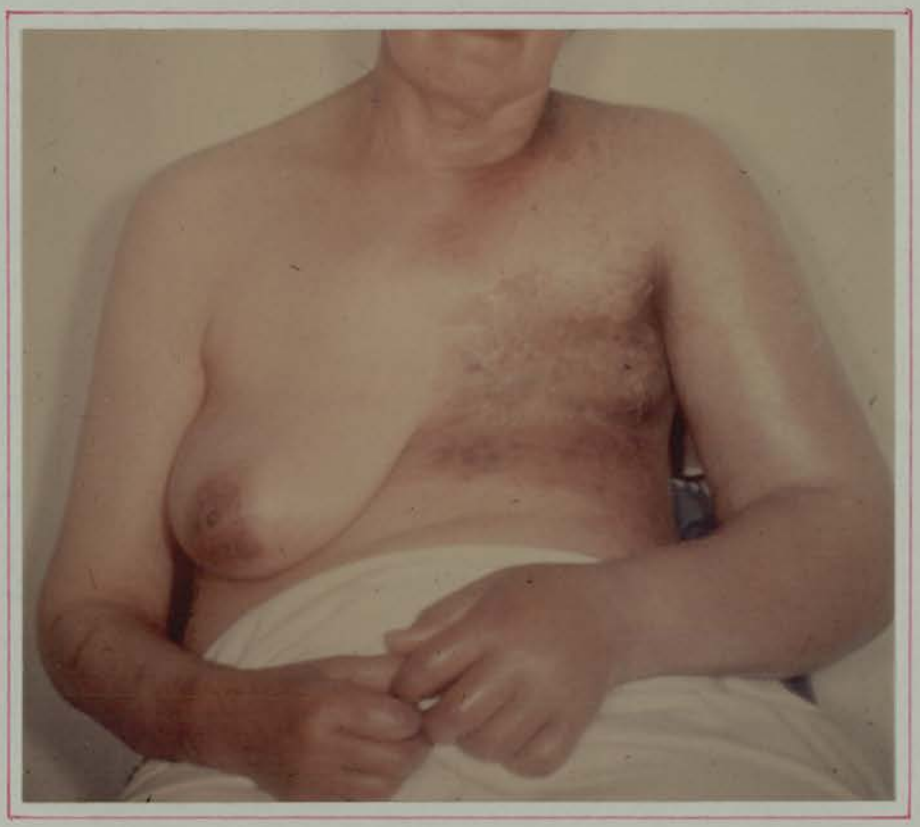

Plate 17

Massive Chest Wall Recurrence - Nodular Stage
(Note associated oedema of the arm - Case 10)

Radiotherapy started 20 days after simple mastectomy. No complications from either procedure. Minimum dose 3750 r. Tumour - Grade III.

Two years after end of treatment a 6 cm. area of diffuse recurrence noted on chest wall and arm became swollen. Slight response to oestrogens. No response to adrenalectomy. Recurrence spread over chest wall (Plate 17). Patient died a few days after implantation of radon seeds into the pituitary, one year after appearance of chest wall recurrence.

Case 11.- A 58-year-old woman with a 1.5 cm. Stage I carcinoma in the upper outer quadrant of the right breast showing complete skin fixation.

No complications followed surgery. Radiotherapy started 15 days later. Minimum dose 3750 r, no adverse reactions. Tumour - Grade II.

Six years after treatment oedema of arm noted in association with axillary recurrence. Diffuse chest wall recurrence appeared nine months after this within treated area and tumour also noted in opposite breast. No response to oestrogens. Lesions became ulcerative. Steroids produced a slight temporary response. Eighteen months after appearance of recurrence it had become very extensive but then showed good response to androgens. This was however temporary and patient died five months later.

Case 12.- A 46-year-old woman with a 4 cm. Stage II carcinoma in the lower outer quadrant of the left breast showing no fixation to skin.

Radiotherapy started within 14 days of operation. No complications from either. Minimum dose 3750 r. Tumour - Grade III.

Oedema of arm nine months after completion of treatment. Diffuse recurrence in treated area on chest wall four months later. No response to ovariectomy. Spread extended beyond treated area within two months progressing to involve posterior field. Lesions became ulcerative. Pleural effusion developed. Hypophysectomy six months after appearance of recurrence. No response. Patient died two months later.

Case/

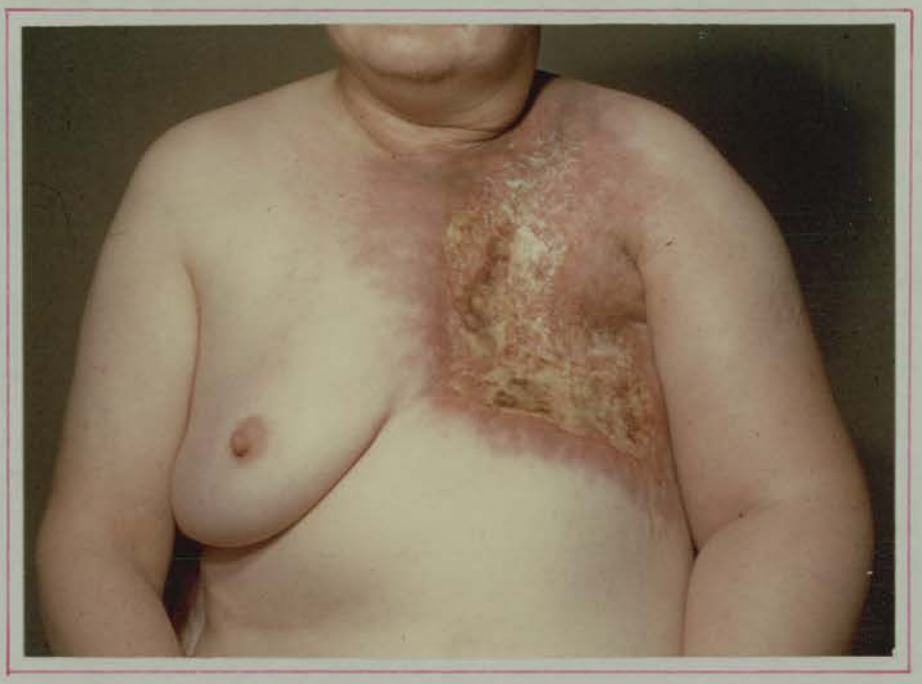

Plate 18

Massive Chest Wall Recurrence - Ulcerative Stage
(Note demarcation of recurrence medially and inferiorly corresponding to limits of irradiation - Case 14)

Case 13.- A 53-year-old woman with a 4 cm. carcinoma in the upper outer quadrant of the right breast showing extensive skin fixation and reddening. Axillary nodes palpable and matted (Stage IV).

Simple mastectomy which included removal of axillary node was complicated by incomplete healing and haematoma. Radiotherapy was not started until 34 days after operation and was followed by severe skin reaction. Minimum dose 3750 r. Tumour - Grade III.

Induration, considered to be largely due to oedema, persisted in the chest wall after treatment. Oedema of the arm developed. Skin nodules appeared in the treated area 18 months later and pelvic metastases noted at the same time. Ovarian irradiation was carried out and followed by androgens. A definite deterioration ensued and within three months there was extensive and ulcerated skin involvement. Four months later hypophysectomy was carried out with post-operative death.

Case 14.- A 49-year-old woman with a 3 cm. Stage II carcinoma in the upper inner quadrant of the left breast showing no skin fixation.

Post-operatively there was an area of skin necrosis but radiotherapy was started on the 15th day. No excessive reaction. Minimum dose 3750 r. Tumour - Grade III.

Diffuse chest wall recurrence appeared 11 months after the end of treatment and was associated with oedema of the arm. Ovarian irradiation produced no response. Two months later it had extended into the posterior shoulder field and a sharp line of demarcation was noted at the sternal margin corresponding to the limit of the treated area (Plate 18). A pleural effusion was also present. Hypophysectomy was carried out, apparently without response, three months after the appearance of recurrence and the patient died two months thereafter.

Case 15.- A 54-year-old woman with a 5 cm. Stage I centrally placed carcinoma of the left breast showing peau d'orange over a small area and oedema of the arm. Surgery and radiotherapy uncomplicated and separated by an interval of 23 days. Minimum dose 3500 r. Tumour - Grade III.

Recurrence appeared six months after the end of treatment in the opposite axilla and seven months later in the homolateral axilla and supraclavicular fossa. After a further/

further two months recurrence appeared in the region of the scar. This extended diffusely over the chest wall and into the posterior shoulder field within three months. A pleural effusion developed and the opposite breast became involved. Oestrogens were given with no response and the patient died six months after the appearance of the chest wall recurrence.

Case 16.- A 47-year-old woman with a 4 cm. Stage I carcinoma of the upper inner quadrant of the left breast showing partial skin fixation.

Mastectomy was followed by a wound abscess requiring incision. At operation a portion of pectoralis major was removed. Radiotherapy was started 45 days post-operatively and because of the size of the patient a small portion of the chest wall at the lower end of the scar could not be included. A severe skin reaction caused the omission of the last two treatments and resulted in a minimum dose of 3200 r. Tumour - Grade II.

Skin recurrence in the chest wall appeared at the lower end of the scar 14 months after the end of treatment and extended rapidly. Ulceration commenced within two months and oedema of the arm developed. A slight and temporary reduction followed ovarian irradiation and the administration of steroids but lesions were advancing again within a month. Opposite breast involved. Hypophysectomy five months after appearance of recurrence. No response. Patient survived a further six months.

Case 17.- A 41-year-old woman with a 7 cm. Stage II carcinoma in the upper outer quadrant of the right breast showing partial skin fixation.

Simple mastectomy complicated by necrosis of wound edges and radiotherapy delayed until the 22nd day. During treatment scar broke down again and last treatment was omitted. Minimum dose 3420 r. Tumour - Grade II.

Ten months after completion of therapy diffuse recurrence extending over the whole treated area on the chest wall appeared. At the same time supraclavicular, contralateral axillary and lumbar spine metastases were noted. No response followed ovarian irradiation and steroids. Oedema of arm developed. Recurrence extended during the following year into posterior field and pleural effusion developed. Opposite breast involved. Patient survived 16 months from time of appearance of chest wall recurrence.

Case 18.- A 65-year-old woman with a 5 cm. Stage IV carcinoma in the upper outer quadrant of the right breast with fixation to the skin, peau d'orange and an axillary node with spread into the adjacent tissues.

Wound infection occurred and radiotherapy delayed for 31 days. Minimum dose 3750 r - no complications. Tumour - Grade II.

Metastases appeared in posterior cervical chain two months after completion of treatment and were treated with further course of radiotherapy. Three months later diffuse infiltration of whole of treated area on anterior chest wall extending round to back and down over anterior abdominal wall. This associated with a pleural effusion and extensive recurrence in axillary and supraclavicular glands, and with oedema of the arm. Patient died a few days later.

Case 19.- A 36-year-old woman with a 3 cm. Stage II carcinoma in the upper inner quadrant of the right breast with early skin fixation. A node thought to be insignificant was noted in the opposite axilla.

Surgery was complicated by a large haematoma and radiotherapy by a severe skin reaction. Radiotherapy started within 14 days of operation. Minimum dose 3750 r. Tumour - Grade III.

Oedema of the arm developed one year after completion of treatment and a diffuse tumour infiltration of the anterior chest wall was observed four months later together with a definite metastasis in the opposite axilla. Ovarian irradiation given without response, and within a month ulceration had developed on the chest wall. After two further months tumour had spread to axilla, back, neck, and abdominal wall. Patient died seven months after the first appearance of chest wall recurrence.

Discussion

Certain factors in this series of cases show no striking difference from the pattern commonly found in carcinoma of the breast. This applies to age, size and site of tumour and, perhaps surprisingly, to clinical stage. However/

TABLE 50

Primary tumour			Clinical stage	Histo-logical grade	Mastectomy with removal at axillary node(s)	Wound compli-cations	Severe R/T skin reaction	Post-mastectomy oedema of arm	Metastases		Time of appearance of skin recurrence	Response to treatment
Site (quad-rant)	Skin involve-ment	Peau d' orange							Pleural	Opposite breast		
UO	+	-	III	III	+	+	-	-	+	-	7 m	Nil
UO	+	-	IVL	II	+	-	-	-	-	+	5 m	Nil
UO	+	-	II	II	-	-	-	+	+	+	5 yr	Nil
UO	+	-	I	II	-	+	-	+	-	-	5 yr	Slight
UI	+	+	IVD	III	-	-	+	+	-	+	9 m	Nil
UO	+	-	II	III	+	-	-	-	-	+	3 yr	Nil
UI	+	-	II	II	-	-	-	+	+	+	3½ yr	Slight
UI	+	-	II	II	-	+	-	+	-	-	2½ yr	Nil
C	+	-	I	N.K.	+	+	-	-	-	+	10 m	Good
C	+	-	IVL	III	-	-	-	+	-	-	2 yr	Nil
UO	+	-	I	II	-	-	-	+	-	+	7 yr	Good
LO	-	-	II	III	-	-	-	+	+	-	1 yr	Nil
UO	+	-	IVL	III	+	+	+	+	-	-	1½ yr	Nil
UI	-	-	II	III	-	+	-	+	+	-	11 m	Nil
C	+	+	I	III	-	-	-	-	+	+	15 m	Nil
UI	+	-	I	II	-	+	+	+	-	+	14 m	Nil
UO	+	-	II	II	-	+	-	+	+	+	10 m	Nil
UO	+	+	IVL	II	-	+	-	+	+	-	5 m	Nil
UI	+	-	II	III	+	+	+	+	-	-	16 m	Nil

MASSIVE CHEST WALL RECURRENCE

SUMMARY OF CASES

However in spite of the fact that some tumours were quite small and some were in Stage I all but two showed some degree of skin fixation. This skin involvement was not necessarily extensive and indeed skin oedema or reddening was only noted in four cases and skin nodules in one. The distribution of histological grades was also similar to the usual pattern.

The operation of simple mastectomy included the removal of one or more axillary nodes or a portion of pectoralis major in only a few cases and this was probably not a factor of importance. But complications of the wound occurred in over half of the cases.

The full dosage of radiotherapy as judged by the minimum dose received by the breast area was attained in all but four cases, but in spite of this severe skin reactions were few.

The time of appearance of the skin recurrence after the completion of treatment varied from five months to seven years, but in about half of the cases it was less than 15 months. The recurrence itself seemed to be diffuse almost from the start in some, but to spread from a small focus in others. In a number of cases it was preceded by axillary recurrence. Once established however it usually became extensive within a few months.

Oedema of the arm is a very frequent accompaniment of this type of recurrence and was noted in no less than 14 of/

of the 19 cases. Involvement of the opposite breast was also remarkably common being present in 10 of the cases. Pleural effusion developed in 8 cases.

Some quite long periods of survival with extensive chest wall recurrence were noted, a feature which in part accounts for the lasting impression such cases make. Yet very few indeed showed any response to a variety of methods of treatment.

The picture which emerges is by no means a homogeneous one. Gatch and Culbertson speak of early and sudden appearance of widespread cutaneous nodules but this is not the pattern seen in a number of the diffuse recurrences reported here. These authors however quote no specific cases and do not even make it clear that the irradiation was given after surgical removal of the breast.

It is difficult to attribute these recurrences to an effect of irradiation even in the case of those where an early recurrence was noted. Some of these cases were advanced at the time of treatment and would be expected to show early recurrence. Nevertheless the pattern of spread in relation to the treated area raises the possibility that tumour may spread more easily in irradiated skin. On the other hand many chest wall recurrences do not spread in this way and there is nothing in this series to suggest that these cases of diffuse recurrence differed in any way from the normal in their response to radiotherapy.

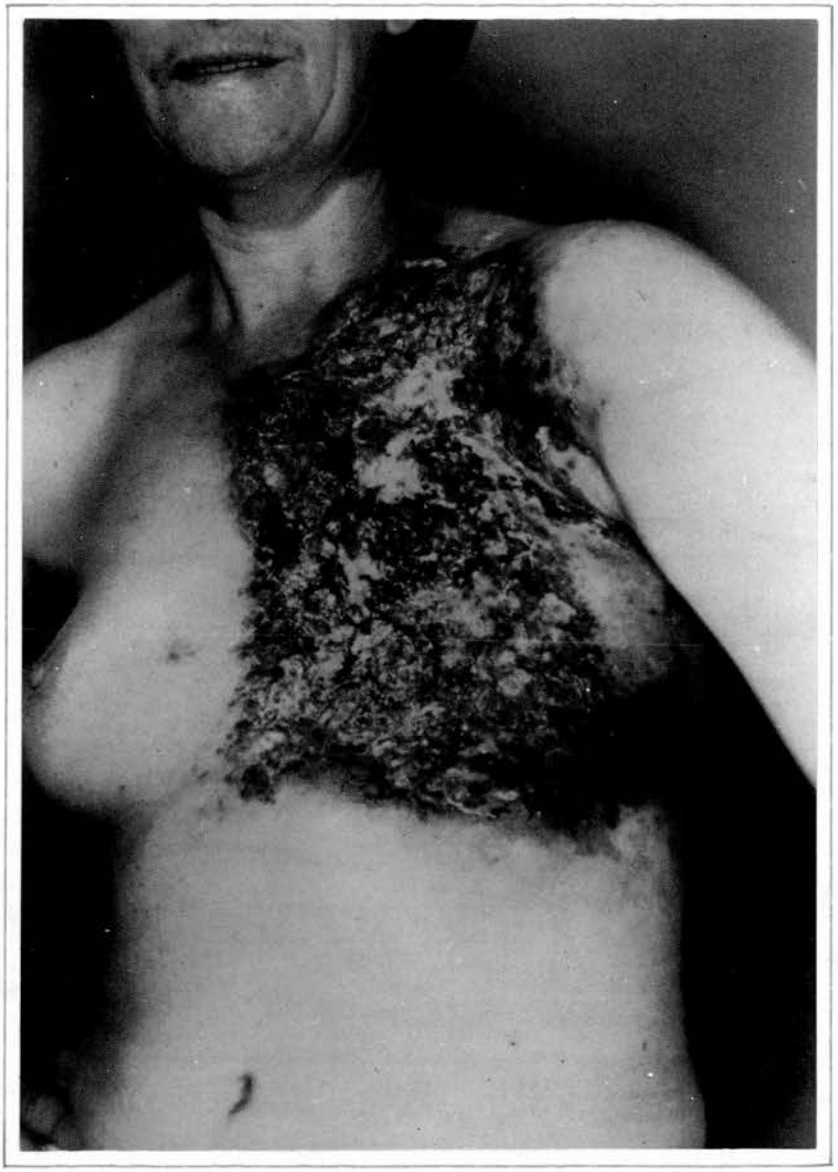

Plate 19

Diffuse Chest Wall Recurrence after Radical Mastectomy
(from Smithers, D.W. (1958). Amer. J. Roentgenol., 80, 740)

It is possible that the margin of the irradiated area may for a time present a barrier to further spread and temporarily confine the tumour to the limits of the irradiation. That the recurrence appears within the treated area itself cannot of course occasion surprise since it is within this area that local foci of tumour are most likely to be present.

The frequency of wound complications in these cases is a factor of interest which will be considered more fully in a later section. Suffice it to say that while such complications could conceivably predispose to the appearance of chest wall recurrence in general it is difficult to connect it with this particular type of chest wall recurrence. Such cases show for instance no striking tendency to early recurrence.

Finally this form of recurrence undoubtedly occurs after radical mastectomy and is illustrated, for example, by Cade (1950), in a case in which he attributes its appearance to the use of surgery in an advanced case, by Atkins (1956), and by Smithers (1958). The latter in fact refers to it as "that surgical disease of plaque-like chest recurrence" (Plate 19).

In conclusion it may be said that diffuse skin recurrence spreading widely over the chest wall is a rare type of recurrence. The cases demonstrating it show no pattern which would point to any particular factor as significant in its causation.

S E C T I O N VII

OTHER ASPECTS OF THE STANDARD GROUP

OTHER ASPECTS OF THE STANDARD GROUP

SITE OF THE TUMOUR AND RESULTS OF TREATMENT

Since the publication of the results of routine internal mammary node biopsy by R.S. Handley and Thackray in 1949 the importance of this route of spread has received much attention.

From this and similar studies, some of which are based on the examination of specimens removed by the extended radical or super-radical operation, a fairly clear picture has emerged of the pattern of such metastases. Handley's figures, the latest of which were published in 1964, remain among the most useful since they refer to routine biopsies carried out in cases undergoing conventional radical mastectomy. The special selection of cases which often enters into the picture where operations such as the super-radical mastectomy are used does not apply to Handley's series. Information as to the involvement of the axillary nodes is of course also available.

The site of the primary tumour is an important factor in determining the incidence of internal mammary node metastasis but the stage also plays a significant part.

Handley (1964) found internal mammary node metastases in about 30 per cent of all his cases with tumour in the medial half of the breast and in 20 per cent of those with lateral tumours. Where axillary metastases were found on pathological/

pathological examination of the resected specimen these percentages rose to approximately 50 per cent and 30 per cent respectively.

Dahl-Iversen (1963) in a smaller series of cases treated by extended radical mastectomy but selected according to accepted criteria for conventional radical mastectomy also found an incidence of internal mammary node metastases of about 30 per cent in medial tumours and only 10 per cent in lateral tumours.

Some differences undoubtedly arise from the inclusion of central tumours with those of the medial half of the breast. Handley, listing central tumours separately, found the incidence to be even higher than with medial tumours. Results from a series of super-radical mastectomies published by Bucalossi and Veronesi in 1959 show a similar high incidence in cases with central tumours although, in another such series published by Caceres (1959), the incidence was lower than in medial tumours.

Haagensen (1956) who lists central and medial tumours together found that the combined group had a higher incidence of internal mammary node metastases than the group with lateral tumours - the respective percentages being 31.6 per cent and 23.2 per cent - again similar to Handley's figures.

Some/

Some authors have however failed to confirm this, although in two such series - Hutchinson (1953) and Urban (1964) - there are very few cases in one or other group. In the latter's series this is due to selection of cases for extended radical mastectomy.

From the results obtained by those who have thus determined the presence of internal mammary node metastases, it would also appear that their existence has a marked effect on prognosis. This is particularly so if they are associated with axillary node metastases.

In Handley's 1964 report the five-year survival rate for cases with axillary metastases only, was 67 per cent while, for cases with both axillary and internal mammary metastases, it was 28 per cent. Urban found the corresponding figures to be 74 per cent and 43 per cent in a series of extended radical mastectomies (Urban, 1964). The difference was however less in Dahl-Iversen's extended radical mastectomy series - 63 per cent and 57 per cent for the corresponding groups (Dahl-Iversen, 1963). In the series of super-radical mastectomies of Bucalossi and Veronesi already referred to, 61 per cent of those cases with axillary involvement survived five years compared with 20 per cent of those in which internal mammary involvement was also present.

These/

These and similar results appear to justify measures taken to deal with possible spread to the internal mammary nodes, and to confirm the view that tumours on the medial side of the breast have a poorer prognosis.

The latter view is however open to some doubt. Nohrman (1949), Williams (1953), Berkson et al. (1957), Smithers et al. (1952) and Allen and Rigler (1962) all show a difference in prognosis in favour of lateral tumours. But apart from Nohrman's series the differences in prognosis is small. Smithers and his colleagues state in fact that in their cases it is not statistically significant. Nohrman, Berkson and Smithers (in a later series -Smithers, 1958-) all found the difference in prognosis to be confined to cases without axillary metastases. Williams on the other hand found no difference in these cases but a poorer prognosis for cases with medial tumours and axillary metastases. In Haagensen's series where the effect on prognosis of several locations is studied separately the prognosis for all tumours on the medial side is distinctly better than for those on the lateral side (Haagensen, 1956).

The importance of these views is considerable in relation to the effect of treatment of internal mammary metastases. McWhirter (1957) basing his argument on the view that prognosis in medial tumours is worse than in lateral tumours has expressed the opinion that the effect of radiotherapy/

radiotherapy on internal mammary node metastasis can be judged by the relative results in these groups of cases. He found in fact that the results obtained by simple mastectomy and radiotherapy were better in cases with medial tumours than in those with lateral tumours. The results for his "operable" group (Manchester Stages I and II) are shown in Table 51. In the present series the comparable figures for cases treated by simple mastectomy and radiotherapy are given in Table 52. The differences are smaller but the trend is the same, although in neither case are the differences statistically significant. If this group is broken down into its component stages the results are as shown in Table 53, and Figure 32.

It appears that in Stage I, where in most reported series the main difference in prognosis is found, that the same pattern is seen after simple mastectomy and radiotherapy. The five-year survival rate is worse in cases with medial tumours. In Stage II, where most authors have found no difference and Berkson and his colleagues report a slightly better prognosis for medial tumours, simple mastectomy and radiotherapy gives better results in cases with medial tumours. Again these differences are not statistically significant. It must be pointed out that one is now comparing clinical stage with pathological stage and that these two are not strictly comparable. No other comparison is however possible in the circumstances, and indeed it does not

seem/

TABLE 51

Site of tumour	Cases	% 5-year survivors
Medial half	263	64
Lateral half	595	59

5-YEAR SURVIVAL RATE AFTER SIMPLE MASTECTOMY AND RADIOTHERAPY ACCORDING TO SITE OF TUMOUR

(Stages I and II only - after McWhirter, 1957)

TABLE 52

Site of tumour	Cases	5-year survivors	5-year survival rate
Medial half	153	99	65%
Lateral half	216	136	63%

5-YEAR SURVIVAL RATE ACCORDING TO SITE

PRESENT SERIES - STANDARD GROUP - STAGES I AND II

TABLE 53

Stage	Site of tumour	Cases	5-year survivors	5-year survival rate %
Stage I	Medial half	106	71	67
	Lateral half	94	70	74
Stage II	Medial half	47	28	60
	Lateral half	122	66	54

5-YEAR SURVIVAL RATE IN RELATION TO BOTH STAGE AND SITE
PRESENT SERIES - STANDARD GROUP

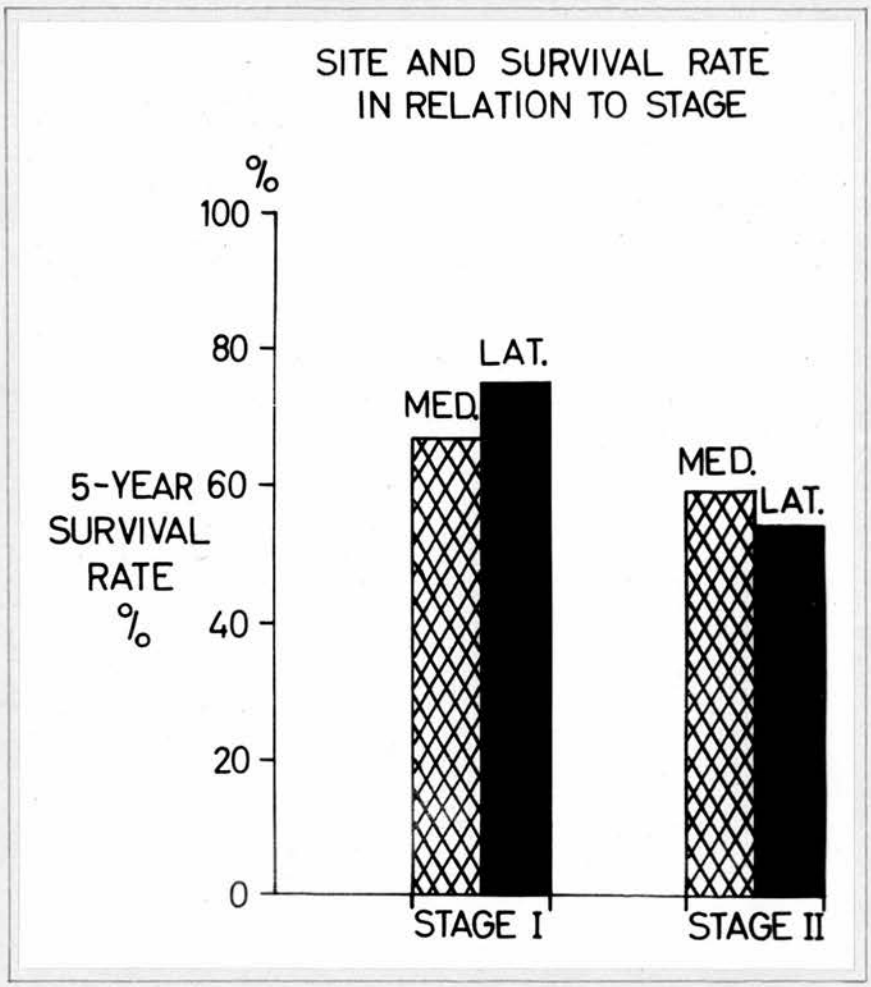
SITE AND SURVIVAL RATE
IN RELATION TO STAGE
%
100
80
60
40
20
0
5-YEAR
SURVIVAL
RATE
%
MED.
LAT.
MED.
LAT.
STAGE I
STAGE II

Figure 32

seem to be an unreasonable one in this case. It is clear however on statistical grounds that one is not justified in drawing from such data the conclusion that radiotherapy deals effectively with internal mammary node metastasis.

Other Evidence of Internal Mammary Node Involvement

It is difficult to determine the significance of internal mammary node involvement because we have few means of studying this region in the living patient. Arguments such as those used above are based largely on deductions. For this reason it seemed worthwhile to seek for further clinical evidence of such metastases.

Internal Mammary, Mediastinal and Pleural Metastasis

It has already been suggested that spread from the internal mammary nodes to the mediastinum and pleura probably occurs frequently and that, in the absence of pulmonary metastasis, spread to these sites could be considered to be evidence of spread by the internal mammary route. If this route is more commonly involved in medial tumours such metastases ought to be more frequent in these cases.

Cases showing this pattern of spread were therefore analysed in relation to the site of the tumour and the results are shown in Table 54. The four cases with parasternal nodules in the intercostal spaces are included in this group.

Contrary/

TABLE 54

		Total cases	Cases with mediastinal and pleural metastasis	Incidence of mediastinal and pleural metastasis (%)
Medial tumours	All cases	191	18	9
	Cases with local recurrence	66	11	17
	Cases with distant metastasis but no local recurrence	32	7	22
Lateral tumours	All cases	291	35	12
	Cases with local recurrence	105	27	26
	Cases with distant metastasis but no local recurrence	68	8	12

MEDIASTINAL AND PLEURAL METASTASES IN RELATION TO SITE OF PRIMARY TUMOUR - STAGES I-IVL ONLY

Contrary to expectation the incidence of mediastinal and pleural metastases is not higher in cases with medial tumours than it is in those with lateral tumours. The reverse is in fact the case except in the relatively small group of cases with distant metastasis and no local recurrence and in this group the difference is not statistically significant.

If one examines the relationship between local recurrence and mediastinal and pleural metastases, one finds (Table 55) that these metastases are found more frequently in association with local recurrence than without it, but once again the difference is not statistically significant. It has already been observed however (Table 54) these metastases only show this relationship in cases with lateral tumours and not, as one might expect, in cases with medial tumours. Taking these observations in conjunction it seems likely that such metastases arise by other routes than the internal mammary route. Indeed Willis (1952) avers that pleural involvement is commonly the result of direct spread through the chest wall. This is in keeping with the facts observed here.

One must therefore conclude that with one possible exception/

TABLE 55

	Total no. of cases in group	Cases with mediastinal and pleural metastasis	Incidence of mediastinal and pleural metastasis in group (%)
Cases with local recurrence	198	44	22
Cases with distant metastasis but no local recurrence	116	16	14

MEDIASTINAL AND PLEURAL METASTASIS IN RELATION TO LOCAL RECURRENCE

exception (cases with no local recurrence) one cannot use mediastinal and pleural metastases as good evidence of spread by the internal mammary chain of nodes.

PROPHYLACTIC OVARIAN IRRADIATION

As already mentioned prophylactic ovarian irradiation was used routinely for a short period (1948-1949) in conjunction with simple mastectomy and radiotherapy.

Only a small proportion of this series was given such treatment (12 per cent of whole series and 18 per cent of the standard group). It is nevertheless of importance to determine whether the overall results were affected by this procedure. Ackerman (1955) in his study of cases treated in Edinburgh comments on this as a possible criticism of the presentation of the results of simple mastectomy and radiotherapy. Garland (1958) has pointed out however that similar criticisms could equally be levelled at some series in which the results were primarily those of radical mastectomy.

McWhirter himself (1957) reviewing these cases came to the conclusion that ovarian irradiation had no significant effect on the five-year survival rates in Stages I and II. The cases in this series, which are in effect but a small sample of McWhirter's cases, are reviewed only to establish their effect on the results presented.

There/

There were 104 cases in the standard group who were given prophylactic ovarian irradiation. Seventy-five of these were in Stages I and II. Table 56 shows the results obtained in these cases compared with those of the standard group as a whole.

The only striking difference from McWhirter's figures lies in five-year survival rates in Stage II. He too found a small difference in favour of ovarian irradiation in Stage I.

Since, as has been pointed out, these cases are only a sample of a larger series one cannot attribute any significance to the difference in Stage II where in fact the larger series shows no such difference. It will also be seen that in the ten-year results the difference is considerably reduced.

It remains to be considered however whether this difference is sufficient to influence significantly the overall results in this series. Bearing in mind that these cases represent only 18 per cent of the standard group, the overall effect of a 20 per cent difference in survival rates in this small group would be to raise that of Stage II by about 4 per cent. This would not affect the conclusions drawn.

TABLE 56

	Follow-up	Cases with ovarian irradiation	Survivors	% survival rate	Survival rate of all cases in standard group
Stage I	5-year	39	30	77	70
	10-year	39	19	49	49
Stage II	5-year	36	27	75	55
	10-year	36	19	53	49

PROPHYLACTIC OVARIAN IRRADIATION

S E C T I O N VIII

MORBIDITY

MORBIDITY

The morbidity resulting from treatment to some extent can be regarded as the price exacted from the patient for the benefits conferred by that treatment. Where different forms of treatment confer similar benefits, as is the case with radical mastectomy and simple mastectomy with radiotherapy the relative morbidities assume in this respect considerable importance.

The present series provides an opportunity to assess the morbidity of both the surgical and radiotherapeutic aspects of the Edinburgh method, and to provide thereby a standard of comparison.

Morbidity is itself a relative term and impossible to define with precision. It is also difficult to find a common denominator that would render the very different types of morbidity of surgery and of radiotherapy comparable. The degree of distress suffered by the patient might be such a denominator, and this concept is in fact applied to the present assessment, but it is decidedly nebulous.

Definitions

In the pilot study which preceded the present work three categories of morbidity - nil, moderate and severe - were used. It soon became apparent that such distinctions were/

were not possible. In the present study only two categories are used - nil to moderate, and severe.

These categories are mutually exclusive, i.e. severe and not severe, and are best defined by detailing the former category.

Certain aspects of morbidity, particularly the psychological aspects, are very difficult to assess objectively.

The surgical removal of the breast is generally regarded as having a severe psychological effect on the patient, though it is remarkable how many patients appear, outwardly at least, to accept it with equanimity. Nevertheless this concept of mutilation was, as has already been said, one of the reasons which lead Keynes to adopt his radiotherapeutic approach. More recently Porritt (1964) has advocated, partly on these grounds, local excision of the tumour followed by radical radiotherapy.

A similar psychological disturbance may be associated with radiotherapy. To the lay mind radiotherapy is only too obviously associated with the diagnosis of cancer and to some extent with the more hopeless aspects of cancer. To some patients attendance at a radiotherapy department is a constant reminder of this.

Such aspects of morbidity cannot be assessed retrospectively and the present study is therefore devoted to the more objective forms of morbidity.

Surgical Morbidity

In general terms the morbidity of the surgical procedure was regarded as severe when it could be presumed to cause the patient considerable distress, when it considerably prolonged the recovery period, was potentially dangerous to the patient or caused death.

The surgical complications classified as severe were first of all those related to the wound - wound infection, large haematomas, necrosis and dehiscence, particularly if these required intervention such as drainage, excision, secondary suture or grafting, or were associated with appreciable delay in healing.

Other surgical complications regarded as severe were deep venous thrombosis, pulmonary embolism, severe post-operative chest or cardiac complications and such rarities as severe drug idiosyncrasies.

Radiotherapy Morbidity

In general the morbidity of radiotherapy was considered to be severe when, as in the case of surgery, the patient was caused considerable distress, the recovery period was unduly prolonged, the patient's life was endangered or death ensued.

Except/

Except in such broad terms, most of the conditions dealt with differ considerably from surgical complications and are not strictly comparable.

The complications of radiotherapy which were classified as severe were severe skin reactions as judged by the description in the records and particularly if moist desquamation developed in all fields, side-effects of some severity such as marked nausea or vomiting, severe tracheitis, pulmonary complications, or a combination of a number of such factors apparently sufficient to cause the patient considerable distress. The lesser degrees of the latter were not classified as severe morbidity nor were early skin reactions occurring during treatment which were dealt with by the omission of one or more treatments.

Certain late effects attributable to radiotherapy were also included under severe morbidity. These were extensive pulmonary fibrosis producing respiratory symptoms and irradiation bone necrosis or fracture causing significant pain. The mere presence of pulmonary fibrosis or rib fractures as demonstrated radiologically was not considered to amount to severe morbidity.

Other/

Other Types of Morbidity

Certain aspects of morbidity cannot be clearly attributed to one or other part of the treatment. Of these the two most important are oedema of the arm and limitation of shoulder movement. The former is dealt with separately. The latter, though of quite frequent occurrence, is more difficult to assess and probably less accurately recorded. It has not therefore been included in the analysis.

Incidence of Morbidity

Surgical Morbidity

Five hundred and seventy-three simple mastectomies were carried out in patients in the standard group (excluding second mastectomies for carcinomas of the opposite breast). Surgical morbidity was considered to be severe according to the above criteria in 121 cases - an incidence of 21 per cent. The surgical morbidity was not known in 17 cases (Table 57).

This incidence, which shows some variation with clinical stage, is relatively high and to some extent reflects the strictness of the criteria. However it is of interest to note that, in reporting the results of the Cancer/

TABLE 57

Stage	Number of cases	Number with severe surgical morbidity	Incidence of severe morbidity (%)
I	238	55	23
II	185	34	18
III	51	8	16
IV	99	24	24
Total	573	121	21

INCIDENCE OF SURGICAL MORBIDITY IN RELATION TO STAGE - STANDARD GROUP

Cancer Chemotherapy Trials in the United States, Noer (1963) found complication rates of 31 per cent and 34 per cent after radical mastectomy in two of his control groups (i.e. cases not receiving chemotherapy).

Certain cases with severe post-operative complications and cases who died post-operatively did not receive a radical course of radiotherapy and were therefore excluded from the standard group. Cases outwith this group also included a greater proportion of the aged. Both these factors would be expected to increase the incidence of morbidity in these cases. It was felt however that a true appreciation of the morbidity of simple mastectomy would not be obtained without reference to these cases. Their inclusion is also necessary to estimate the mortality of the operation.

One hundred and thirty-nine simple mastectomies were carried out in cases not included in the standard group. Surgical morbidity was rated as severe in 61 - an incidence of 44 per cent. Morbidity was unknown in one case. The overall incidence of severe morbidity following simple mastectomy is therefore 30 per cent.

There were 7 post-operative deaths after simple mastectomy, an overall incidence of 1 per cent. In five of these the patient was aged 69 or over. One patient who died on the twelfth post-operative day but in whom the cause was unknown was aged 47. The other, aged 55, died of/

of a pulmonary embolus. Death was related to pulmonary embolus in three cases and to chest infection in another two. The cause was unknown in two.

Radiotherapy Morbidity

The 573 cases in the standard group all received a radical course of radiotherapy. Severe morbidity, as defined above, resulting from that course occurred in 74 cases - an incidence of 13 per cent. Morbidity was unknown in five cases. The morbidity resulting from radiotherapy appears to be less than that resulting from simple mastectomy. Because of the different criteria used however the validity of the comparison is questionable. Again there was some variation in relation to clinical stage (Table 58), and again the more severe morbidity tended to be found in the less advanced cases.

The criteria of morbidity following irradiation vary widely in the studies reported in the literature. One of the most detailed of recent studies of the effects of radiotherapy is that of Fleming and his colleagues (1961). They found high incidences of constitutional symptoms, skin reaction and pulmonary effects but most of these were so mild that they could be accepted as normal concomitants of therapy and scarcely classifiable as morbidity. Ackerman (1955) found in the 719 Edinburgh cases which he studied, 47 with "extensive irradiation damage" - an incidence of 6.5 per cent. His observations covered only the late effects/

TABLE 58

Stage	Number of cases	Number with severe radiotherapy morbidity	Incidence of severe morbidity (%)
I	238	38	16
II	185	19	10
III	51	4	8
IV	99	13	13
Total	573	74	13

INCIDENCE OF RADIOTHERAPY MORBIDITY IN RELATION TO STAGE

effects of radiotherapy and are anatomical rather than symptomatic. Indeed some of the effects observed could be as readily attributed to surgery as to radiotherapy. Garland (1958) reviewing a small series of cases treated by simple mastectomy and radiotherapy quotes a five per cent incidence of morbidity. It is not clear however whether this refers to his own experience, nor is morbidity defined with any exactness.

There is no doubt that radiotherapy adds something to the morbidity of this method of treatment. The results in the present study would suggest that addition is a small but appreciable one. Since by no means all cases who suffer post-operative complications experience morbidity from radiotherapy, or vice-versa, it is difficult to make even hypothetical comparisons with radical mastectomy. That the morbidity of radical mastectomy exceeds that of simple mastectomy is undoubted. That it exceeds the combined morbidity of simple mastectomy and radical radiotherapy is by no means certain.

The position with regard to radiotherapy has perhaps been summed up best by Ralston Paterson, himself a radiotherapist. "Radical X-ray therapy, even in the best of hands, is not without an incidence of morbidity.....and it certainly entails three to four weeks of some discomfort." (Paterson, 1962). This is the price to be set against the results.

The Effect of Delay

It is obviously desirable that radiotherapy should be given as soon as possible after mastectomy, but a period of two weeks is generally considered to be an acceptable interval.

In practice however this interval was frequently exceeded. In the 573 cases in the standard group, radiotherapy followed surgery within 14 days in only 122 cases (21%). However nearly 60% commenced treatment within 21 days and it was decided to study the effect of delay by taking this interval as an arbitrary limit.

The effect of delays exceeding 21 days on the survival rate is shown in Table 59. Because of the relatively small numbers involved, Stages III and IVL are combined as a Locally Advanced category (McWhirter, 1955). Cases presenting with distant metastases are not considered.

So far as delay of this order is concerned, survival appears to be adversely affected only in the more advanced cases but the difference is not significant.

The two major causes of delay were the existence of a waiting list for radiotherapy - due to inadequate facilities, and a less important factor in later years - and the complications of surgery of which those affecting the wound were the commonest. Other causes of delay included breakdown of the radiotherapy equipment which at times was in use 12 hours a day, and delay in referral from the wards.

It/

TABLE 59

Stage	Interval - operation to radiotherapy not exceeding 21 days			Interval - operation to radiotherapy exceeding 21 days		
	Cases	5-year survivors	Survival rate (%)	Cases	5-year survivors	Survival rate (%)
I	125	85	68	113	82	73
II	108	62	57	77	40	52
Locally advanced	92	30	33	48	9	19

EFFECT ON SURVIVAL OF
DELAY IN COMMENCING RADIOTHERAPY

It is obvious that in any one case a combination of these factors may have been responsible and it was often difficult to determine their relative importance. However where wound complications occurred they almost invariably involved some delay unless they were insignificant. Although other factors also operated in some of these cases they are treated from the point of view of analysis as delays due to wound complications.

The Effect of Wound Complications

It seems not unlikely that the occurrence of necrosis, infection, delayed healing and so forth might in itself have a deleterious effect on the ultimate outcome, even though the delay as such did not affect the result.

The more serious wound complications were frequently associated with delays exceeding three weeks. Table 60 shows the survival rates of such cases compared with those in which the delay also exceeded three weeks but was unassociated with wound complications. The apparent difference is not statistically significant.

Finally it must be considered whether wound complications affect the incidence of local recurrence. Table 61 shows that there are no significant differences.

It appears then that neither delay nor wound complications have a significant effect on the survival rate and that wound complications do not promote local recurrence.

TABLE 60

Stage	No wound complications			Wound complications		
	Cases	5-year survivors	Survival rate (%)	Cases	5-year survivors	Survival rate (%)
I	65	46	71	48	36	75
II	51	29	57	26	11	42
Locally advanced	18	4	22	30	5	17

WOUND COMPLICATIONS IN RELATION TO SURVIVAL - CASES WITH DELAY EXCEEDING 21 DAYS

TABLE 61

Stage	Cases with wound complications			Local recurrence rate in standard group as a whole*
	Cases	Cases with local recurrence	Local recurrence rate (%)	
I	48	13	27	24
II	26	10	38	39
Locally advanced	30	16	53	49

* From Table 45

WOUND COMPLICATIONS IN RELATION TO LOCAL RECURRENCE

OEDEMA OF THE ARM

Oedema of the arm is undoubtedly the most important cause of late morbidity after radical mastectomy. One of the advantages claimed for treatment by simple mastectomy and radiotherapy is that following it, this complication seldom occurs (McWhirter, 1949; Garland, 1958).

In assessing the incidence of this condition as a complication of treatment it is necessary to exclude all cases with local recurrence of the disease. There were 52 such cases in this series and in all but one the time relationships indicated that recurrence and oedema of the arm were associated phenomena. In the remaining case the oedema developed immediately after treatment whilst the recurrence did not become apparent for another two and a half years. This case is included with those where the oedema was considered to be a complication of treatment.

An interesting finding in this group of cases where oedema was associated with local recurrence, was that it was much less common when local recurrence followed distant/

distant metastasis - 6 cases out of 55 (11%) - than when local recurrence appeared first - 45 cases out of 142 (32%). The explanation of this seems to be that oedema of the arm may take some time to develop after local recurrence appears. Those cases in whom distant metastasis appears first may therefore not survive long enough for oedema of the arm to occur.

There were also 12 cases in which transitory oedema of the arm was noted. Seven of these occurred within six months of treatment. These, while in all probability related to treatment, do not constitute an important degree of morbidity and if included would likewise distort the picture of this condition.

In the whole standard group there were 30 cases in whom permanent oedema of the arm developed unrelated to recurrent disease - an incidence of 5%. This figure undoubtedly reflects the extent to which this condition may be directly attributed to treatment.

Two possible aetiological factors were investigated in relation to this group - wound complications and local complications of radiotherapy. Five cases of each were found/

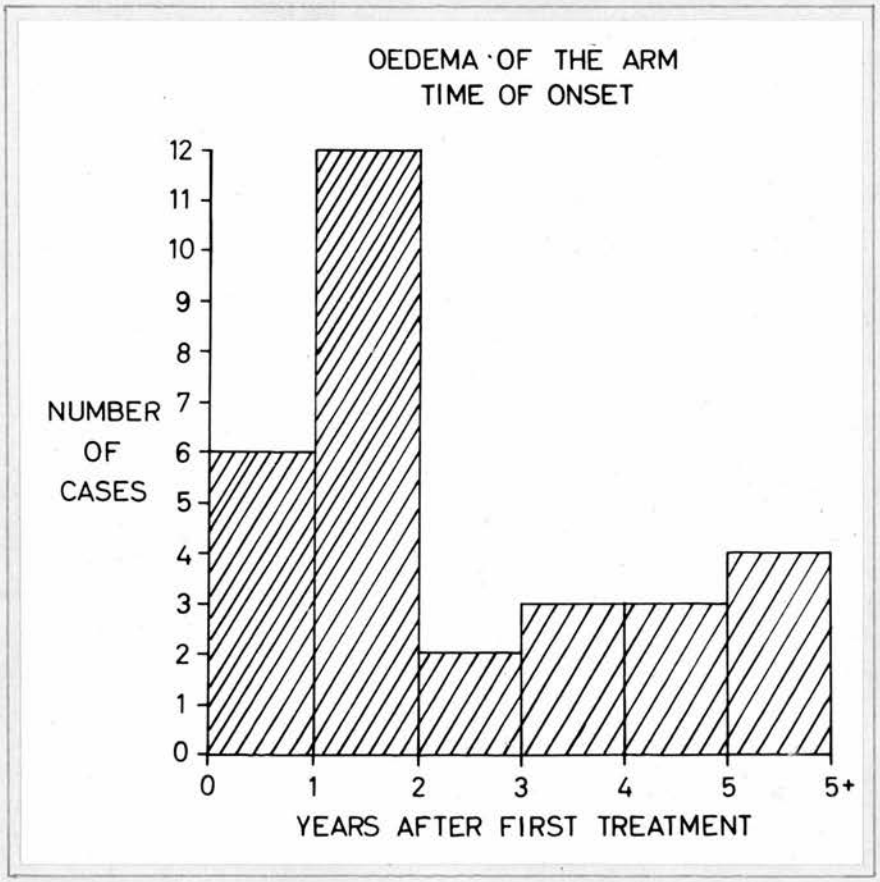
OEDEMA OF THE ARM
TIME OF ONSET
NUMBER OF CASES
0
1
2
3
4
5
6
7
8
9
10
11
12
0
1
2
3
4
5
5+
YEARS AFTER FIRST TREATMENT

Figure 33

found - a total of 10 in all - for in no case did both occur together. The incidence of each complication - about 15% - was less than the incidence of these complications in the whole series. Even the combined incidence was little more than the overall incidence of wound complications. There is therefore no evidence that either was of aetiological importance.

The time of onset of the oedema is also of interest and shown in Table 62 and Figure 33. Forty per cent of cases occurred between one and two years after operation, and very few occurred within six months.

DISCUSSION

The true incidence of post-mastectomy oedema of the arm is difficult to determine from the literature. Failure to exclude cases with recurrent disease, inclusion of transitory oedema, and variable periods of follow-up tend to confuse the issue. All of these as the above analysis shows could profoundly affect the incidence. Indeed the condition itself is subject to a number of definitions. Clinical observation, circumferential measurements and even (Tracy et al., 1961) volumetric measurements, have been used to define the degree of arm oedema and from them different incidences have been calculated.

It/

TABLE 62

Time of onset	Number of cases
Up to 6 months	3
6 months to 1 year	3
1-2 years	12
2-3 years	2
3-4 years	3
4-5 years	3
Over 5 years	4
Total	30

OEDEMA OF THE ARM

TIME OF ONSET

It is commonly stated that oedema of the arm follows radical mastectomy in about 30% of cases (Haagensen, 1956; Cutler, 1961). Some authors give much higher figures. Holman and his colleagues (1944) found an incidence of 67% in cases without local recurrences but in only 44% did the increase in circumference exceed 3 cm. Macdonald and Osman (1955) using an increase of 0.75 cm. as a criterion of swelling found an incidence of 72%, but when the limit was increased to 2 cm. the incidence was only 24%. Daland reviewed a series of 90 cases in 1950 in none of whom there was evidence of recurrent disease and found that oedema occurred, and the increase in circumference exceeded 2.5 cm., in 17% of cases. Amongst the lowest incidences are those of Dahl-Iversen (1963) for extended radical mastectomy (12%) and Atkins (1956) for conventional radical mastectomy (13%).

There have been a few reported figures for the incidence of oedema of the arm after simple mastectomy and radiotherapy. Williams and his colleagues taking cases of simple mastectomy with radiotherapy together with those who had no radiotherapy found an incidence of 5%. In the same series radical mastectomy with or without radiotherapy was followed by oedema of the arm in 14% of cases. They also observed that the incidence in all cases with radiotherapy was the same as that found in all cases where surgery was not followed by radiotherapy. Dahl-Iversen (1963), in his group of cases treated by simple mastectomy and radiotherapy using/

using the Edinburgh technique, had a 3% incidence of oedema of the arm. Crile (1961) found no case of oedema of the arm in 78 cases of simple mastectomy, 28 of whom received post-operative irradiation. In the same series, in which the follow-up did not exceed three years in the majority of cases but does not apparently exclude cases with recurrent disease, the incidence following radical mastectomy was 22%, while for radical mastectomy followed by radiotherapy it was 36%.

The 5% incidence found in the present series is similar to the experience of others using simple mastectomy and radiotherapy. There seems therefore little room for doubt that the incidence is appreciably lower than that found after radical mastectomy.

Many theories have been put forward to account for post-mastectomy oedema. Halsted, in 1921, believed that infection, either associated with wound complications or with a later, intercurrent infection was the precipitating factor. He postulated however that impaired lymphatic circulation was the underlying cause. Sampson Handley in his monograph published in the following year, 1922, further suggests that the lymphatics may be obstructed by perilymphatic fibrosis. He observed that division of the axillary vein did not of itself cause oedema and argued that the removal of the lymphatic trunks of the axilla should likewise fail to cause oedema since a collateral circulation existed in the shoulder region.

Venous/

Venous obstruction was considered by Veal (1938) to be a factor of importance and he attributed only 10% of his cases to primary lymphatic obstruction. On the other hand the studies carried out by Habif which are reported in Haagensen's monograph (Haagensen, 1956), showed evidence of delay in lymphatic absorption after radical mastectomy in all cases, even after a period sufficient for the development of a collateral circulation. Devenish and Jessop (1940) also found evidence of delay in the lymphatic circulation.

Most authors in fact seem to agree that lymphatic rather than venous obstruction is of major significance in cases attributable to treatment. Many of Veal's cases for instance were due to recurrence.

Haagensen however agrees with Halsted that infection is the most important precipitating factor. He, in fact, describes two varieties of this complication - post-operative surgical oedema and secondary surgical oedema. The former which occurs soon after operation, he attributes to wound complications, the latter occurring later, to incidental infections. A clear-cut distinction of this kind was not apparent in the present series. Very few cases, except those with transitory oedema, occurred soon after treatment.

Others have considered that radiotherapy is a factor of importance. Holman and his colleagues (1944) found a correlation/

correlation with X-ray therapy but only where there was a severe reaction. Treves (1957) likewise considered radiotherapy a significant factor whilst Crile's figures quoted above appear to support this contention. With regard to the latter, however, the inclusion of cases with recurrence and the tendency to select the more advanced cases for post-operative radiotherapy, renders them of doubtful significance. Devenish and Jessop concluded that neither infection nor radiotherapy were necessary aetiological factors.

It has already been pointed out that the present series shows no striking correlation with either wound infection or severe local reactions to radiotherapy. The occurrence of incidental infections was infrequently recorded and no conclusions can be drawn regarding its importance.

Summary

Oedema of the arm unassociated with local recurrence was found in 5% of the cases treated by simple mastectomy and radiotherapy. Most of these were late in appearance. There was no evidence that either wound complications or severe local reactions to radiotherapy were aetiological factors of importance.

S E C T I O N IX

GENERAL CONCLUSIONS

The "Null Hypothesis"

Those who, in the 1940's, found cause for optimism in the progress made in the treatment of breast cancer were soon to have their complacency shaken.

In 1951 a remarkable paper was published by Park and Lees in which, on the basis of certain assumptions and supported by a complex statistical argument, it was averred that there was no proof that treatment was effective in prolonging survival in breast cancer.

The factual basis of this claim was the result of a study of a large number of radical mastectomy specimens. The relationship between the delay in coming to treatment and the proportion of cases with involved axillary nodes was observed. It was found that 60% of cases who reported immediately on discovering the tumour had involved nodes while, if the period of delay was three years, the proportion had only increased to 75%. From this it was concluded that the maximum possible gain to be achieved by earlier diagnosis was a 7.5% increase in the five-year survival rate.

It was also considered that the five-year survival rate was an unreliable measure of the true effect of treatment since it credited to treatment those cases who would have survived 5 years without treatment. A small difference in the five-year survival rate of the order of 7.5% could have little significance in these circumstances.

While/

While therefore admitting by implication that cure of breast cancer is in certain circumstances possible, the conclusion drawn is that accepted measures fail to prove that this is in fact achieved.

These hypotheses did not stand unchallenged for long. Shimkin and his colleagues (1952) produced evidence that, while delay showed little correlation with the presence or absence of axillary nodes alone, it was clearly related to the more advanced stages of the disease. Both Kraus (1953) and McWhirter (1960) point out that Park and Lees, using a series of operable cases, fail to take into account those who during a three year delay either die or become inoperable. The proportion of early cases showing metastases is also challenged by Kraus, while Gillian (1952) pointed out that the existence of metastatic disease in the axilla might itself be a determining factor in the rapidity with which the patient sought treatment. Gillian's estimate for the true proportion of early cases with axillary metastasis is only 30%.

The essence of the criticism of Park and Lees is that from the nature of their material they greatly underestimated the effect of delay on the progress and curability of the disease. In consequence their strictures on the reliability of the five-year survival rate as a measure of the effectiveness of treatment (and these are basically correct) become much less relevant.

This/

This contribution to surgical thinking and the controversy which it stimulated have however served to place this problem in its proper perspective. While few would accept the tenet that treatment is not demonstrably effective in breast cancer, it is at least apparent that the range of effectiveness is less than the five-year survival rate had led one to believe. Earlier studies of survival in untreated cases (Greenwood, 1926; Daland, 1927; Nathanson and Welch, 1936; and Wade, 1946) and modern studies of long-term follow-up in breast cancer such as that of Ederer et al. (1963) also attest to this fact. Not only can the advanced untreated case survive many years but the early treated case may die of breast cancer after fifteen or twenty years or even longer with apparent eradication of the disease.

Biological Predeterminism

The concept that the result of treatment is predetermined by the biological nature of the tumour does not preclude the possibility that in some cases treatment may be effective. But it does imply that in some treatment is doomed, even in apparently early cases, to fail.

This idea, formulated by Macdonald in 1951 from an approach very similar to that of Park and Lees, was not new for it was implicit in the concepts from which histological grading was derived.

The/

The results in the present series have demonstrated that the biological properties of the tumour measured by grading determine prognosis independently of the stage of the disease. This relationship holds not only for the series as a whole but for cases treated by the same method and appears therefore to be, to some extent, independent also of treatment. The concept of biological predeterminism is not at variance with these facts.

Arising from this concept however is the idea that within the broad field covered by the term carcinoma of the breast, there are two specific groups which are biologically different. These are the rapidly growing highly malignant tumours and the slow growing relatively benign tumours or, as McKinnon (1955) has termed them - progressive and non-progressive.

All the evidence in the present series suggests that such distinctions are artificial. In almost every aspect studied an unbroken gradation is apparent. The relation of prognosis to clinical stage and to histological grade show this, the behaviour of recurrent growth and metastasis exhibit it also and, perhaps most important of all, the three histological grades are seen to be but three adjacent segments of a continuous scale.

Whilst the range of behaviour is indeed great there is no evidence in this study to suggest that it can be explained by the random intermingling of a limited number of well-defined/

well-defined types of breast cancer each with qualitatively different biological properties. If such types do, in fact, exist they will only be detectable by other measures. Indeed the biochemical techniques recently reported by Bulbrook and his colleagues (1960) appear to provide a further opportunity for exploring this problem, although here too there is already evidence of a fairly continuous gradation (Hayward, 1964).

With regard to histological grading this study has confirmed that it is an important biological parameter. While, as has been shown, it has definite limitations, it provides information of value in the study of the results of treatment of breast cancer. Its use would appear to be warranted wherever comparison between different groups of cases is contemplated.

The Role of Radiotherapy

The concepts discussed above were derived largely from observations on the results of radical mastectomy. The effectiveness of radiotherapy in association with less extensive surgery is the central theme of this study.

It has been pointed out that, within the limitations imposed by comparisons between different centres, no decisive difference between the results of radical mastectomy and simple mastectomy with radiotherapy has been found. In the absence of more satisfactory methods of comparison/

comparison one cannot accept it as proven that there is no difference. But on the other hand little is to be expected from further comparisons of this type.

It is not the intention of this study to make such comparisons, though it is of importance to establish, as has been done, that the series is comparable in material and results to the larger series published by McWhirter in 1955.

The restriction of surgery to simple mastectomy in cases in whom the tumour is known to extend beyond the confines of the operation, gives radiotherapy a decisive role in the treatment. The effect of radiotherapy should therefore be much easier to assess than in the circumstances obtaining when radiotherapy is used in association with radical mastectomy.

There are three possibilities as far as the effectiveness of radiotherapy is concerned. The first is of course that it has no effect at all. This hypothesis was put forward in the light of the finding that in the standard group the more anaplastic tumours which were presumably the more radiosensitive had the poorest prognosis in all stages.

These figures were of course relative, for not all well-differentiated tumours have a good prognosis, nor all anaplastic tumours a bad one. Indeed it is easy to disprove this hypothesis, for a proportion of cases with tumour beyond the confines of operation survived for considerable/

considerable periods and either had no local recurrence or experienced a delay before local recurrence became manifest.

The two remaining possibilities are that radiotherapy temporarily arrests the growth of the tumour but does not eradicate it, or that it eradicates the local growth completely.

Incontrovertible proof that radiotherapy eradicated local disease would require follow-up to death and autopsy evidence that the treated area remained free of tumour cells. The time relationships of local recurrence as revealed by this study show, however, that for cases in Stage II and more advanced stages the great majority of local recurrences are detectable within five years of first treatment. In these stages there will be a high proportion in whom final eradication of local disease will depend on radiotherapy.

The overall recurrence rates in the present series, in which all cases were followed up for five years, and over half for ten years or more, must give a fairly close approximation to the true picture of local recurrence after simple mastectomy and radiotherapy. In so far as they reflect failure in local eradication of the disease, and there is little reason to doubt that they do, these rates provide one with a measure of the efficacy of radiotherapy.

Although/

Although the overall local recurrence rate approaches 40% in Stage II and rises to 60% in Stage IVL it is evident that in an appreciable number of cases in these groups local eradication was achieved. It is extremely unlikely that the error of clinical staging is such that the cases who showed no local recurrence were those in whom there was in fact no tumour beyond the bounds of the simple mastectomy. The third possibility that radiotherapy can in some cases complete the local eradication of the disease is almost certainly true.

It is equally evident from a consideration both of local recurrence rates and the time of appearance of local recurrences, that in a proportion of cases radiotherapy temporarily arrests the growth but does not eradicate it. From further consideration of these two factors in relation to clinical stage, evidence has been presented to support the contention that where radiotherapy fails the duration of its effect is inversely related to amount of tumour tissue present.

Further confirmation of this was obtained in respect of recurrence in the axillary nodes. It was observed that the frequency of axillary recurrence was higher after simple mastectomy and radiotherapy than supraclavicular or chest wall recurrence. In most of the reported series in the literature the axilla was the least common site for recurrence/

recurrence following radical mastectomy. It seems therefore that surgical removal of axillary nodes is a more effective way of treating tumour in this site than radiotherapy.

It was not possible to draw similar conclusions regarding local recurrence at other sites, nor to make valid comparisons between the incidence of local recurrence after simple mastectomy and radiotherapy and the incidence after radical mastectomy. The objections to such comparisons in respect of survival rates are even more cogent when applied to local recurrence rates. However there is no evidence that local recurrence is significantly less common after simple mastectomy and radiotherapy.

Morbidity

Assuming that in terms of survival, simple mastectomy and radiotherapy is not inferior to radical mastectomy as a method of treating carcinoma of the breast, is this result achieved at a lesser cost in terms of morbidity? The evidence obtained from a study of the cases in this series show that the combination of simple mastectomy and radiotherapy entails an appreciable morbidity. While there are no substantial grounds for claiming that this morbidity exceeds that of radical mastectomy - and indeed an acceptable comparison would be very difficult to make - it seems likely that it is not strikingly less.

There is however one exception to this. As far as post-mastectomy oedema is concerned there is no doubt that this occurs between a half and one-third less frequently after simple mastectomy and radiotherapy than after radical mastectomy - taking the best figures in the relation to the latter as the standard of comparison.

Finally it can be said that there is no evidence that radiotherapy as such is responsible for massive chest wall recurrence after simple mastectomy and radiotherapy.

A P P E N D I X 1

STATISTICAL CALCULATIONS

1. Tests of Statistical Significance

The results of the tests as applied to the various tables in the text are listed below. In each case the degree of significance is indicated in the last column.

Tests/

Tests of Statistical Significance

Table no.	Page no.	Analysis	Chi-squared	Degrees of freedom	t	Limits of p	Significance
10	50	Menopausal cases against Others (41-60)	4.682	3	-	0.2-0.1	Not significant
15	61	2 cm. against 2-5 cm.	-	-	5.444	0.001	Very significant
		2-5 cm. " 5-10 cm.	-	-	7.046	0.001	Very significant
		5-10 cm. " 10 cm.	-	-	2.703	0.001-0.01	Significant
17	79	Stage I - Series (a) against Series (b)	-	-	1.506	0.1-0.2	Not significant
		Stage II " " " " "	-	-	No difference		-
		Stage III " " " " "	-	-	1.042	0.2-0.3	Not significant
		Stage IV " " " " "	-	-	0.292	0.7-0.8	Not significant
18	79	Operable - Series (a) against Series (b)	-	-	2.316	0.02-0.05	Significant
		Locally Advanced - Series (a) against Series (b)	-	-	0.287	0.7-0.8	Not significant
		Distant Metastasis - " " " " "	-	-	1.036	0.2-0.3	Not significant
19	80	All Cases - 5 yr. - Series (a) against Series (b)	-	-	No difference		-
		" " 10 yr. " " " " "	-	-	2.081	0.02-0.05	Significant
		Operable - 5 yr. " " " " "	-	-	No difference		-
		" 10 yr. " " " " "	-	-	1.439	0.1-0.2	Not significant
		Locally Advanced - 5 yr. " " " " "	-	-	2.417	0.02-0.05	Significant
		" " 10 yr. " " " " "	-	-	1.289	0.1-0.2	Not significant
		Distant Metastasis - 5 yr. " " " " "	-	-	0.474	0.6-0.7	Not significant
		" " 10 yr. " " " " "	-	-	No difference		-
22	89	5 yr. against 10 yr.	-	-	2.454	0.02-0.05	Significant
24	93	5-10 yr. against 10-15 yr.	-	-	0.930	0.3-0.4	Not significant
25/							

Table no.	Page no.	Analysis	Chi-squared	Degree of freedom	t	Limits of p	Significance
25	94	5 yr. - Stage I against Stage II	-	-	3.256	0.001-0.01	Significant
		" II " " III	-	-	1.082	0.2-0.3	Not significant
		" III " " IVL	-	-	5.082	0.001	Very significant
		" IVL " " IVD	-	-	2.903	0.001-0.01	Significant
		10 yr. - " I " " II	-	-	No difference		-
		" II " " III	-	-	3.333	0.001	Very significant
		" III " " IVL	-	-	2.340	0.02-0.05	Significant
		" IVL " " IVD	-	-	2.119	0.02-0.05	Significant
26	95	5 yr. - Grade I against Grade II	-	-	4.696	0.001	Very significant
		" II " " III	-	-	3.101	0.001-0.01	Significant
		10 yr. - " I " " II	-	-	1.370	0.1-0.2	Not significant
		" II " " III	-	-	0.192	0.8-0.9	Not significant
30	126	45 against 46-60	6.2995	2	-	0.02-0.05	Significant
		46-60 " over 60	0.732	2	-	0.5-0.7	Not significant
31	128	Stage I against Stage II	6.022	2	-	0.02-0.05	Significant
		" II " " III	3.306	2	-	0.1-0.2	Not significant
		" I " " IVD	12.023	2	-	0.001-0.01	Significant
		" I " " IV(L + D)	18.324	2	-	0.001	Very significant
32	130	Stage I - Grade II against Grades I and III	-	-	0.667	0.5-0.6	Not significant
		" II " " " " " " "	-	-	0.551	0.5-0.6	Not significant
		" III " " " " " " "	-	-	No difference		-
		" IV " " " " " " "	-	-	1.452	0.1-0.2	Not significant
33	132	5 yr. - Grade II against Grades I and III	-	-	1.35	0.1-0.2	Not significant
		10 yr. " " " " " " "	-	-	No difference		-
34	133	Stage I - Grade II against Grades I and III	-	-	0.926	0.3-0.4	Not significant
		" II " " " " " " "	-	-	0.253	0.7-0.8	Not significant
		" III " " " " " " "	-	-	0.456	0.6-0.7	Not significant
		" IV " " " " " " "	-	-	0.690	0.4-0.5	Not significant

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Table no.	Page no.	Analysis	Chi-squared	Degree of freedom	t	Limits of p	Significance
37	142	5 yr. - Well-delimited against Irregular	-	-	0.992	0.3-0.4	Not significant
		10 yr. " " "	-	-	2.340	0.01-0.02	Significant
39	146	Grade Distribution - Well-delimited against Irregular	7.992	2	-	0.01-0.02	Significant
44	174	5 yr. - Stage I against Stage II	-	-	3.18	0.001-0.01	Significant
		" II " " III	-	-	0.506	0.6-0.7	Not significant
		10 yr. " II " " III	-	-	2.51	0.01-0.02	Significant
45	176	Stage I against Stage II	-	-	3.111	0.001-0.01	Very significant
		" II " " III	-	-	1.081	0.2-0.3	Not significant
		" III " " IVL	-	-	3.233	0.001	Very significant
51	225	Survival - Medial against Lateral	-	-	1.397	0.1-0.2	Not significant
52	225	Survival - Medial against Lateral	-	-	0.395	0.6-0.7	Not significant
53	226	Stage I - Medial against Lateral	-	-	1.089	0.2-0.3	Not significant
		" II " " "	-	-	0.710	0.4-0.5	Not significant
54	228	All Cases - Medial against Lateral	-	-	1.068	0.2-0.3	Not significant
		Local Recurrence " " "	-	-	1.428	0.1-0.2	Not significant
		Distant Metastasis " " "	-	-	1.203	0.2-0.3	Not significant
55	230	Pleural Metastasis - Local against Distant	-	-	1.835	0.05-0.1	Not significant
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Table no.	Page no.	Analysis	Chi-squared	Degree of freedom	t	Limits of p	Significance
56	233	Stage I - 5 yr. Ovarian against No ovarian	-	-	0.951	0.3-0.4	Not significant
		" II - 5 yr. " " " "	-	-	2.469	0.01-0.02	Significant
		" II - 10 yr. " " " "	-	-	0.413	0.5-0.7	Not significant
59	245	Stage I - Not Exceeding against Exceeding	-	-	0.847	0.3-0.4	Not significant
		" II - " " " "	-	-	0.674	0.5-0.6	Not significant
		Locally Advanced - " " " "	-	-	1.869	0.05-0.1	Not significant
60	247	Stage I - No Wound against Wound	-	-	0.476	0.6-0.7	Not significant
		" II - " " " "	-	-	1.259	0.2-0.3	Not significant
		Locally Advanced - " " " "	-	-	0.419	0.6-0.7	Not significant
61	249	Stage I - No Wound against Wound	-	-	0.430	0.6-0.7	Not significant
		" II - " " " "	-	-	0.098	0.9	Not significant
		Locally Advanced - " " " "	-	-	0.398	0.6-0.7	Not significant

2. Relative Age-specific Incidence of Breast Carcinoma

The number of cases in each age group was divided by the number of females in the corresponding age group in the general population of Scotland according to the 1952 Csnsus (1952 being the nearest Census year to the median year of the study). The result was expressed as a rate per 100,000 and has been shown graphically in Figure 3.

This does not of course represent the actual age-incidence of breast carcinoma in Scotland. However assuming that the series is a representative sample of the disease and that the region from which it was drawn has a similar age distribution to Scotland as a whole, the result will give a relative age-incidence. This relative incidence will then reflect the pattern of the true age-incidence of the disease.

The figures from which the above graph was drawn are shown in Table 63.

3. Standard Deviation

The calculation of the standard deviation as used in the menopausal statistics (p. 42) was by the method described by Moroney (1956).

4. Age-corrected Mortality Rates

These have been derived from the Registrar-General's 1951 Life Tables (England and Wales) as shown in Tables

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64 and 71-74. Table 65 shows the derivation of the curve of natural mortality of a similar normal population used in Figure 8.

5. Data on Stage Distribution, Survival Rates and Histological Grading

The full versions of Tables 7, 9, 17, 18 and 19, from which the number of cases used in determining each percentage can be seen, are given in Tables 66-70. The full versions of Tables 30-34, relating to histological grading, are given in Tables 75-79.

TABLE 63

Age group	No. of females in population*	Cases of breast carcinoma in series	Relative incidence of breast carcinoma (per 100,000 females in specific age group)
21-25	191,355	3	2
26-30	197,696	8	4
31-35	171,913	27	16
36-40	194,469	65	34
41-45	188,453	87	46
46-50	180,031	117	65
51-55	159,771	91	57
56-60	142,355	102	72
61-65	123,342	105	85
66-70	104,224	110	106
71-75	80,479	81	101
76-80	49,600	49	99
81-85	23,582	24	102
86-90	8,229	5	61
91-95	2,420	2	83

* From 1952 Census (Scotland)

RELATIVE AGE-SPECIFIC INCIDENCE OF BREAST CARCINOMA

TABLE 64

(1) Age group x	(2) Mean age (estimated) $\bar{x}$	(3) No. of cases n	(4) $l_{\bar{x}}$*	(5) $l_{\bar{x}+5}$*	(6) $5p_{\bar{x}}$ (5)/(4)	(7) No. expected to survive 5 yrs. (3) x (6)		(8) Actual no. of cases surviving 5 yrs.	(9) Corrected 5-year survival rate (%) (8)/(7)
35 or under	30	38	95,311	94,650	0.99	38	102	47	46
36–40	38	65	94,161	93,087	0.99	64			
41–45	43	87	93,087	91,498	0.98	85	198	98	49
46–50	48	117	91,498	89,107	0.97	113			
51–55	53	91	89,107	85,530	0.96	87	183	94	51
56–60	58	102	85,530	80,177	0.94	96			
61–65	63	105	80,177	72,104	0.90	95	186	90	48
66–70	68	110	72,104	60,088	0.83	91			
71–75	73	81	60,088	43,592	0.73	59	99	43	43
76–80	78	49	43,592	24,952	0.57	28			
81–85	83	24	24,952	9,960	0.40	10			
86–92	(actual) 89	7	7,857	1,785	0.23	2			

* From Registrar-General's 1951 Life Tables (England and Wales).

AGE-SPECIFIC CORRECTED 5-YEAR SURVIVAL RATES (ALL CASES)

TABLE 65

NATURAL MORTALITY OF FEMALE POPULATION (EQUIVALENT IN AGE DISTRIBUTION TO PRESENT SERIES OF CASES)

(1) Age gp. x	(2) Mean age (estimated) $\bar{x}$	(3) No. of cases n	(4) $l_{\bar{x}}$*	(5) $l_{\bar{x}+5}$*	(6) $l_{\bar{x}+10}$*	(7) $l_{\bar{x}+15}$*	(8) $5p_x$ (5)/(4)	(9) $10p_x$ (6)/(4)	(10) $15p_x$ (7)/(4)	Expected survivors		
										5 yr. (3)x(8)	10 yr. (3)x(9)	15 yr. (3)x(10)
21–25	23	3	96,047	95,542	94,933	94,161	0.99	0.99	0.98	3	3	3
26–30	28	8	95,542	94,933	94,161	93,087	0.99	0.99	0.97	8	8	8
31–35	33	27	94,933	94,161	93,087	91,498	0.99	0.98	0.96	27	26	26
36–40	38	65	94,161	93,087	91,498	89,107	0.99	0.97	0.94	64	63	61
41–45	43	87	93,087	91,498	89,107	85,530	0.98	0.96	0.92	85	84	80
46–50	48	117	91,498	89,107	85,530	80,177	0.97	0.93	0.88	113	109	103
51–55	53	91	89,107	85,530	80,177	72,104	0.96	0.90	0.81	87	82	74
56–60	58	102	85,530	80,177	72,104	60,088	0.94	0.84	0.70	96	86	71
61–65	63	105	80,177	72,104	60,088	43,592	0.90	0.75	0.54	95	79	57
66–70	68	110	72,104	60,088	43,592	24,952	0.83	0.61	0.35	91	67	39
71–75	73	81	60,088	43,592	24,952	9,960	0.73	0.42	0.17	59	34	14
76–80	78	49	43,592	24,952	9,960	2,498	0.57	0.23	0.06	28	11	3
81–85	83	24	24,952	9,960	2,498	385	0.40	0.10	0.02	10	2	0
86–92	(actual) 89	7	7,857	1,785	251	24	0.23	0.03	0.003	2	0	0
Total		876								768	654	539
									Survival rates (%)	87.7	74.7	61.5

* From Registrar-General's 1951 Life Tables (England and Wales).

TABLE 66

AGE	STAGE I				STAGE II				STAGE III				STAGE IV			
	Cases	Expected survivors	Actual survivors	Corrected % survival rate	Cases	Expected survivors	Actual survivors	Corrected % survival rate	Cases	Expected survivors	Actual survivors	Corrected % survival rate	Cases	Expected survivors	Actual survivors	Corrected % survival rate
0 or under	31	31	22	71	42	42	21	50	8	8	3	38	22	22	1	5
41-50	73	71	52	73	62	60	33	55	15	15	9	60	54	53	4	8
51-60	68	65	50	77	57	54	33	61	17	17	6	35	51	48	5	10
61-70	80	69	52	75	36	31	20	64	25	21	11	52	74	65	7	11
Over 70	63	40	26	65	27	16	7	44	15	9	5	56	56	35	5	14

AGE AND PROGNOSIS
CORRECTED AGE-SPECIFIC 5 YEAR SURVIVAL RATES BY STAGE
(Full version of Table 7, p. 37)

TABLE 67

	Total in group	STAGE							
		I		II		III		IV	
		No. in stage	% in stage	No.	%	No.	%	No.	%
All cases 41-50	204	73	36	62	30	15	7	54	26
All cases 51-60	193	68	35	57	30	17	9	51	26
Cases at or within 5 yrs. of menopause	112	38	34	27	24	12	11	35	31

STAGE DISTRIBUTION IN RELATION TO MENOPAUSE

(Full version of Table 10, p. 50)

TABLE 68

Stage	McWhirter's 1955 series		Present series	
	No. of cases	% of total	No. of cases	% of total
I	582	31	315	36
II	481	26	224	26
III	250	13	80	9
IV	569	30	257	29
TOTAL	1882	100	876	≑ 100

STAGE DISTRIBUTION - MANCHESTER CLASSIFICATION
(Full version of Table 17, p. 79)

TABLE 69

Stage	McWhirter's 1955 series		Present series	
	No. of cases	% of total	No. of cases	% of total
Operable	1063	56	539	62
Locally advanced	546	29	241	28
Distant metastases present	273	15	96	11
TOTAL	1882	100	876	≑ 100

STAGE DISTRIBUTION - McWHIRTER'S MODIFICATION OF MANCHESTER CLASSIFICATION
(Full version of Table 18, p. 79)

TABLE 70

	McWhirter's 1955 series			Present series		
	Cases	Survivors	% survivors	Cases	Survivors	% survivors
All cases						
5 yr. surv. rate	1882	786	42	876	371	42
10 yr. " "	480	112	25	487	151	31
Operable						
5 yr. surv. rate	1063	612	58	539	315	58
10 yr. " "	254	99	39	307	138	45
Locally advanced						
5 yr. surv. rate	546	162	30	241	53	22
10 yr. " "	157	23	15	130	13	10
Distant metastases present						
5 yr. surv. rate	273	12	4	96	3	3
10 yr. " "	69	0	0	50	0	0

SURVIVAL RATES

COMPARISON WITH McWHIRTER'S 1955 SERIES
(Full version of Table 19, p. 80)

TABLE 71

(1)	(2)	(3)	(4)
Age group	Number of cases with 10-year follow-up n_{10}	$10p_{\bar{x}}$*	Expected survivors 10 yrs. (2) x (3)
35 and under ($\bar{x}$ = 30)	10	0.99	10
36-40	16	0.97	16
41-45	19	0.96	18
46-50	24	0.93	22
51-55	20	0.90	18
56-60	22	0.84	18
61-65	19	0.75	14
66-70	23	0.61	14
71-75	21	0.42	9
76-80	8	0.23	2
81-85	4	0.10	-
86-92 ($\bar{x}$ = 88)	1	0.04	-
			141
		Actual survivors	84
		Corrected 10-year survival rate	60%

* See Table 64 (l_{30} = 95,311, l_{40} = 93,778; l_{88} = 9,960, l_{98} = 385)

CORRECTED 10-YEAR SURVIVAL RATE FOR STAGE I CASES

TABLE 72

(1) Age group	(2) No. of cases with 10-year follow-up n_{10}	(3) $10p_{\bar{x}}$	(4) Expected survivors at 10 yrs. (2) x (3)
35 or under	9	0.99	9
36-40	15	0.97	15
41-45	15	0.96	14
46-50	14	0.93	13
51-55	14	0.90	13
56-60	17	0.84	14
61-65	10	0.75	8
66-70	13	0.61	8
71-75	7	0.42	3
76-80	2	0.23	-
81-85	4	0.10	-
86-92	-	0.04	-
			97
		Actual survivors	54
		Corrected 10-year survival rate	56%

CORRECTED 10-YEAR SURVIVAL RATE FOR STAGE II CASES

TABLE 73

(1) Age group	(2) No. of cases with 10-year follow-up n_{10}	(3) $10p_x$	(4) Expected survivors at 10 yrs. (2) x (3)
35 or under	7	0.99	7
36-40	12	0.97	12
41-45	17	0.96	16
46-50	24	0.93	22
51-55	22	0.90	20
56-60	29	0.84	24
61-65	32	0.74	24
71-75	22	0.42	9
76-80	8	0.23	2
81-85	6	0.10	1
86-92	1	0.04	-
			154
		Actual survivors	64
		Corrected 10-year survival rate	42%

CORRECTED 10-YEAR SURVIVAL RATE FOR GRADE II CASES

TABLE 74

(1) Age group	(2) No. of cases with 10-year follow-up n_{10}	(3) $10p_x$	(4) Expected survivors at 10 yrs. (2) x (3)
35 or under	6	0.99	6
36-40	11	0.97	11
41-45	12	0.96	12
46-50	18	0.93	17
51-55	16	0.90	14
56-60	15	0.84	13
61-65	17	0.75	13
66-70	13	0.61	8
71-75	12	0.42	5
76-80	7	0.23	2
81-85	1	0.10	-
86-92	1	0.04	-
			101
		Actual survivors	41
		Corrected 10-year survival rate	41%

CORRECTED 10-YEAR SURVIVAL RATE FOR GRADE III CASES

TABLE 75

Age	Grade I		Grade II		Grade III	
	Number of cases	Percentage of cases graded in age group	Number of cases	Percentage of cases graded in age group	Number of cases	Percentage of cases graded in age group
35 or under	2		11		13	
36-40	6 } 16	11	18 } 56	40	24 } 68	49
41-45	8		27		31	
46-50	10		45		39	
51-55	4 } 27	11	43 } 133	53	27 } 92	36
56-60	13		45		26	
61-65	8		51		27	
66-70	8 } 31	11	48 } 166	56	28 } 98	33
71-75	9		36		18	
over 75	6		31		25	

GRADE DISTRIBUTION IN DIFFERENT AGE GROUPS

TABLE 76

Stage	Grade I		Grade II		Grade III	
	Cases	% of graded cases in stage	Cases	% of graded cases in stage	Cases	% of graded cases in stage
I	39	15	145	54	82	31
II	20	10	91	48	79	42
III	8	11	41	59	21	30
IVL	4	3	64	53	53	43
IVD	3	7	14	34	24	59

GRADE DISTRIBUTION IN EACH CLINICAL STAGE

TABLE 77

Stage	Grade I			Grade II			Grade III		
	Cases	5-year survivors	5-year survival rate	Cases	5-year survivors	5-year survival rate	Cases	5-year survivors	5-year survival rate
I	39	33	85	145	96	66	82	42	51
II	20	15	75	91	45	48	79	37	47
III	8	5	63	41	17	41	21	7	33
IV	7	2	28	78	11	14	76	4	5

PROGNOSIS IN RELATION TO GRADE AND STAGE (ALL CASES)

TABLE 78

Follow-up period	Grade I			Grade II			Grade III		
	Cases	Survivors	Survival rate	Cases	Survivors	Survival rate	Cases	Survivors	Survival rate
5 years	53	43	81	257	144	56	192	80	42
10 years	32	15	47	149	59	40	100	38	38
15 years	7	3	42	35	7	20	15	3	20

GRADE AND PROGNOSIS

(STANDARD GROUP)

TABLE 79

Stage	Grade I			Grade II			Grade III		
	Cases	5-year survivors	5-year survival rate	Cases	5-year survivors	5-year survival rate	Cases	5-year survivors	5-year survival rate
I	28	24	86	114	81	71	67	38	57
II	18	15	83	72	42	57	69	33	48
III	4	3	75	28	15	54	13	5	38
IV	3	1	33	43	7	16	43	4	9

PROGNOSIS IN RELATION TO GRADE AND STAGE

(STANDARD GROUP)

APPENDIX 2

DETAILS OF DIFFERENCES IN CLINICAL STAGING

TABLE 80

Radiotherapy Stage	I				II				III				IVL				IVD			
Stage determined from surgical records	II	III	IVL	IVD	I	III	IVL	IVD	I	II	IVL	IVD	I	II	III	IVD	I	II	III	IVL
Number of cases	34	21	1	3	48	12	6	1	5	7	5	1	7	18	12	7	0	1	1	4

DIFFERENCES IN CLINICAL STAGING

TABLE 81

Differences between stages	Number of cases	Percentage of total differences
I and II	82	40
I + II and III	50	25
I and III	29	14
II and IVL	25	12
II and III	21	10
III and IVL	18	9
I and IV	12	6
IVL and IVD	11	5
II + III and IVD	5	2

DIFFERENCES IN CLINICAL STAGING

RELATIVE FREQUENCY OF DIFFERENCES

APPENDIX 3

TABLES FOR SECTION VI (RECURRENCE AND METASTASIS)

TABLE 82

SITE		STAGE I	STAGE II	STAGE III	STAGE IVL
Total no. of cases in stage		238	185	51	89
Axillary Recurrence	No. of cases	33	52	8	36
	%	14	28	16	40
Chest Wall Recurrence	No. of cases	36	46	10	26
	%	15	25	20	29
Supraclavicular Recurrence	No. of cases	27	33	5	22
	%	11	18	10	25

SITES OF LOCAL RECURRENCES IN RELATION TO STAGE
(Full version of Table 46, p. 177)

TABLE 83

CASES WITH LOCAL RECURRENCE

Years after initial treatment	Cases without recurrence observed in given period	Cases developing recurrence in following period	% of cases remaining without recurrence at end of given period	Standard error
0	41	0	100	-
0.25	41	1	100	-
0.5	40	1	98	2.4
0.75	39	1	95	3.4
1	38	6	93	4.1
1.5	32	4	78	6.5
2	28	4	68	7.3
3	24	4	59	7.7
4	20	6	49	7.9
5	14	3	34	7.4
6	11	3	27	6.9
7	8	5	20	6.2
8	3	1	7	4.1
9	2	1	5	3.4
10	1	-	2	2.4

RATE OF APPEARANCE OF RECURRENCE
STAGE I

TABLE 84

CASES WITH LOCAL RECURRENCE

Years after initial treatment	Cases without recurrence observed in given period	Cases developing recurrence in following period	% of cases remaining without recurrence at end of given period	Standard error
0	52	4	100	-
0.25	48	2	92	3.7
0.5	46	6	89	4.4
0.75	40	7	77	5.8
1	33	9	63	6.8
1.5	24	5	46	6.9
2	19	10	37	6.7
3	9	1	18	5.3
4	8	2	15	5.0
5	6	2	12	4.4
6	4	0	8	3.7
7	4	1	8	3.7
8	3	0	6	3.2
9	3	1	6	3.2
10	2	-	4	2.7

RATE OF APPEARANCE OR RECURRENCE
STAGE II

TABLE 85

CASES WITH LOCAL RECURRENCE

Years after initial treatment	Cases without recurrence observed in given period	Cases developing recurrence in following period	% of cases remaining without recurrence at end of given period	Standard error
0	50	14	100	-
0.25	36	8	72	6.3
0.5	28	6	56	7.0
0.75	22	4	44	7.0
1	18	4	36	6.8
1.5	14	6	28	6.3
2	8	4	16	5.2
3	4	2	8	3.8
4	2	1	4	2.8
5	1	1	2	2.0
6	0	-	0	-
7	-	-	-	-
8	-	-	-	-
9	-	-	-	-
10	-	-	-	-

RATE OF APPEARANCE OF RECURRENCE
STAGES III & IVL

TABLE 86

CASES WITH DISTANT METASTASIS
(no subsequent local recurrence)

Years after initial treatment	Cases without metastasis observed in given period	Cases developing metastasis in following period	% of cases remaining without metastasis at end of given period
0	43	2	100
0.25	41	3	95
0.5	38	2	88
0.75	36	1	84
1	35	3	81
1.5	32	6	74
2	26	9	60
3	17	7	40
4	10	4	23
5	6	1	14
6	5	1	12
7	4	2	9
8	2	2	5
9	0	-	0
10	-	-	-

RATE OF APPEARANCE OF METASTASIS
STAGE I

TABLE 87

CASES WITH DISTANT METASTASIS
(no subsequent local recurrence)

Years after initial treatment	Cases without metastasis observed in given period	Cases developing metastasis in following period	% of cases remaining without metastasis at end of given period
0	36	0	100
0.25	36	4	100
0.5	32	2	89
0.75	30	5	83
1	25	7	69
1.5	18	3	50
2	15	4	42
3	11	5	31
4	6	2	17
5	4	0	11
6	4	1	11
7	3	0	8
8	3	2	8
9	1	0	3
10	1	-	3

RATE OF APPEARANCE OF METASTASIS
STAGE II

TABLE 88

CASES WITH DISTANT METASTASIS
(no subsequent local recurrence)

Years after initial treatment	Cases without metastasis observed in given period	Cases developing metastasis in following period	% of cases remaining without metastasis at end of given period
0	37	2	100
0.25	35	8	95
0.5	27	4	73
0.75	23	2	62
1	21	3	57
1.5	18	4	49
2	14	9	38
3	5	1	14
4	4	1	11
5	3	1	8
6	2	0	5
7	2	0	5
8	2	0	5
9	2	1	5
10	1	-	3

RATE OF APPEARANCE OF METASTASIS
STAGES III and IVL

TABLE 89

Years after initial treatment (X)	Number of cases observed X or more years after initial treatment ($_0W_x$)	Withdrawals† ($_nW_x$)	Number developing local recurrence as first sign of recurrent disease ($_nR_x$)	Estimated proportion of cases reaching this X who:-		% of cases treated who develop local recurrence as first sign of recurrent disease (P_x)
				Develop local recurrence before next stated X yrs. ($_nQ_x$)*	Survive without local recurrence to next stated X yrs. ($_nP_x$)	
0	238	4	0	0.000	1.000	100
0.25	234	4	1	0.004	0.996	100
0.5	229	3	1	0.004	0.996	99.6
0.75	225	3	1	0.004	0.996	99.1
1	221	6	6	0.028	0.972	98.8
1.5	209	9	4	0.020	0.980	96.0
2	196	19	4	0.021	0.979	94.1
3	173	10	4	0.024	0.976	92.0
4	159	11	6	0.039	0.961	89.7
5	142	27	3	0.023	0.977	86.2
6	112	12	3	0.028	0.972	84.0
7	97	12	5	0.055	0.945	81.6
8	80	15	1	0.014	0.986	77.3
9	64	4	1	0.016	0.984	76.0
10	59	-	-	-	-	74.7

† Withdrawals: Cases ceasing to be followed up after a given year, cases dying without recurrence or metastases, and cases developing a distant metastasis as first sign of recurrent disease.

LOCAL RECURRENCE (as first sign of recurrent disease)
RECURRENCE RATE - ACTUARIAL ANALYSIS
STAGE I CASES

TABLE 90

Years after initial treatment (X)	Number of cases observed X or more years after initial treatment ($_0W_x$)	Withdrawals ($_nW_x$)	Number developing local recurrence as first sign of recurrent disease ($_nR_x$)	Estimated proportion of cases reaching this X who:- Develop local recurrence before next stated X yrs. ($_nQ_x$)	Survive without local recurrence to next stated X yrs. ($_nP_x$)	% of cases treated who develop local recurrence as first sign of recurrent disease (P_x)
0	185	2	4	0.022	0.978	100.0
0.25	179	6	2	0.011	0.989	97.8
0.5	171	3	6	0.035	0.965	96.6
0.75	162	9	7	0.044	0.956	93.2
1	146	16	9	0.065	0.935	88.9
1.5	121	6	5	0.042	0.958	82.8
2	110	6	10	0.093	0.907	79.4
3	94	6	1	0.011	0.989	71.7
4	87	6	2	0.024	0.976	70.8
5	79	5	2	0.026	0.974	69.0
6	72	9	0	0.000	1.000	67.2
7	63	4	1	0.016	0.984	67.2
8	58	9	0	0.000	1.000	66.0
9	49	5	1	0.022	0.978	66.0
10	43					64.5

LOCAL RECURRENCE (as first sign of recurrent disease)
RECURRENCE RATE - ACTUARIAL ANALYSIS
STAGE II CASES

TABLE 91

Years after initial treatment (X)	Number of cases observed X or more years after initial treatment ($_0x$)	Withdrawals ($_nW_x$)	Number developing local recurrence as first sign of recurrent disease ($_nR_x$)	Estimated proportion of cases reaching this X who:-		% of cases treated who develop local recurrence as first sign of recurrent disease (P_x)
				Develop local recurrence before next stated X yrs. ($_nQ_x$)	Survive without local recurrence to next stated X yrs. ($_nP_x$)	
0	140	4	14	0.103	0.897	100.0
0.25	122	10	8	0.068	0.932	89.7
0.5	104	7	6	0.059	0.941	83.5
0.75	91	6	4	0.045	0.955	78.6
1	81	8	4	0.052	0.948	75.0
1.5	69	11	6	0.095	0.905	71.0
2	52	14	4	0.089	0.911	64.1
3	34	2	2	0.061	0.939	58.5
4	30	3	1	0.035	0.965	55.0
5	26	4	1	0.042	0.958	53.1
6	21	3	0	0.000	1.000	50.9
7	18	3	0	0.000	1.000	50.9
8	15	4	0	0.000	1.000	50.9
9	11	3	0	0.000	1.000	50.9
10	8					50.9

LOCAL RECURRENCE (as first sign of recurrent disease)
RECURRENCE RATE - ACTUARIAL ANALYSIS
STAGE III and IVL CASES

TABLE 92

Years (X)	0^1_x $(0_x - \frac{1}{2}nW_x)$	$0^1_x - {}_nR_x$	$\frac{{}_nR_x}{(0^1_x)(0^1_x - {}_nR_x)}$	$\sum \frac{{}_nR_x}{(0^1_x)(0^1 - {}_nR_x)}$	S.E.
0	236	236	0	0	-
0.25	232	231	0.000019	0.000019	0.44
0.5	227.5	226.5	0.000019	0.000038	0.61
0.75	223.5	222.5	0.000020	0.000058	0.75
1	218	212	0.000130	0.000188	1.3
1.5	204.5	200.5	0.000098	0.000286	1.6
2	186.5	182.5	0.000118	0.000404	1.9
3	168	164	0.000145	0.000549	2.2
4	153.5	147.5	0.000265	0.000814	2.6
5	128.5	125.5	0.000186	0.001000	2.7
6	106	103	0.000275	0.001275	3.0
7	91	86	0.000641	0.001916	3.6
8	72.5	71.5	0.000193	0.002109	3.6
9	62	61	0.000264	0.002373	3.7
10	-	-	-	-	-

STAGE I
CALCULATION OF STANDARD ERROR FOR TABLE 89

TABLE 93

Years (X)	o^1_x $(o_x - \frac{1}{2}nW_x)$	$o^1_x - n^R_x$	$\frac{n^R_x}{(o^1_x)(o^1_x - n^R_x)}$	$\sum \frac{n^R_x}{(o^1_x)(o^1_x - n^R_x)}$	S.E.
0	184	180	0.000121	0.000121	1.1
0.25	176	174	0.000066	0.000187	1.3
0.5	169.5	163.5	0.000217	0.000404	1.9
0.75	167.5	160.5	0.000261	0.000665	2.4
1	138	129	0.000506	0.001171	3.0
1.5	118	113	0.000375	0.001546	3.2
2	107	97	0.000961	0.002507	4.0
3	91	90	0.000121	0.002628	3.7
4	84	82	0.000290	0.002918	3.8
5	76.5	74.5	0.000351	0.003269	4.0
6	-	-	0.000000	0.003269	3.8
7	61	60	0.000273	0.003542	4.0
8	-	-	0.000000	0.003542	3.9
9	46.5	45.5	0.000474	0.004016	4.2
10	-	-	-	-	-

STAGE II
CALCULATION OF STANDARD ERROR FOR TABLE 90

TABLE 94

Years (X)	O^1_x $(O_x - \frac{1}{2}nW_x)$	$O^1_x - {}_nR_x$	$\frac{{}_nR_x}{(O^1_x)(O^1_x - {}_nR_x)}$	$\sum \frac{{}_nR_x}{(O^1_x)(O^1_x - {}_nR_x)}$	S.E.
0	138	124	0.00082	0.00082	2.8
0.25	117	109	0.00063	0.00145	3.4
0.5	100.5	94.5	0.00063	0.00208	3.8
0.75	88	84	0.00054	0.00262	4.0
1	77	73	0.00071	0.00333	4.3
1.5	63.5	57.5	0.00164	0.00497	5.0
2	45	41	0.00216	0.00713	5.4
3	33	31	0.00196	0.00909	5.6
4	28.5	27.5	0.00127	0.01136	5.8
5	24	23	0.00182	0.01318	6.1
6	19.5	19.5	0	0.01318	5.8
7	16.5	16.5	0	0.01318	5.8
8	13	13	0	0.01318	5.8
9	9.5	9.5	0	0.01318	5.8
10	-	-	-	-	-

STAGES III and IVL
CALCULATION OF STANDARD ERROR FOR TABLE 91

TABLE 95

Years after initial treatment (X)	Number of cases observed X or more years after initial treatment ($_0x$)	Withdrawals* ($_nW_x$)	Number developing distant metastasis (without subsequent local recurrence) ($_nR_x$)	Estimated proportion of cases reaching this X who:-		% of cases treated who develop distant metastasis (P_x)
				Develop distant metastasis before next stated X yrs. ($_nQ_x$)	Survive without distant metastasis to next X yrs. ($_nP_x$)	
0	238	2	2	0.008	0.992	100
0.25	234	2	3	0.013	0.987	99.2
0.5	229	2	2	0.009	0.991	97.9
0.75	225	2	1	0.004	0.996	96.9
1	222	8	3	0.014	0.986	96.3
1.5	211	7	6	0.029	0,971	94.9
2	198	14	9	0.047	0.953	92.0
3	175	7	7	0.041	0.959	87.6
4	161	14	4	0.026	0.974	84.0
5	143	28	1	0.008	0.992	81.8
6	114	15	1	0.009	0.991	81.1
7	98	15	2	0.022	0.978	80.3
8	81	14	2	0.027	0.973	78.5
9	65	5	0	0.000	1.000	76.3
10	60	-	-	-	-	76.3

* Withdrawals: Cases ceasing to be followed up after a given year, cases dying without recurrence or metastasis, cases developing a local recurrence as first sign of recurrent disease and cases whose distant metastasis was later followed by a local recurrence.

DISTANT METASTASIS (no subsequent local recurrence)
METASTASIS RATE - ACTUARIAL ANALYSIS
STAGE I

TABLE 96

Years after initial treatment (X)	Number of cases observed X or more years after initial treatment ($_0x$)	Withdrawals ($_nW_x$)	Number developing distant metastasis (without subsequent local recurrence) ($_nR_x$)	Estimated proportion of cases reaching this X who:-		% of cases treated who develop distant metastasis (P_x)
				Develop distant metastasis before next stated X yrs. ($_nQ_x$)	Survive without distant metastasis to next X yrs. ($_nP_x$)	
0	185	7	0	0.000	1.000	100
0.25	178	3	4	0.023	0.977	100
0.5	171	7	2	0.011	0.989	97.7
0.75	162	10	5	0.032	0.968	96.6
1	147	18	7	0.051	0.949	93.5
1.5	122	8	3	0.026	0.974	88.6
2	111	12	4	0.038	0.962	86.3
3	95	2	5	0.053	0.947	83.0
4	88	6	2	0.024	0.976	78.5
5	80	7	0	0.000	1.000	76.5
6	73	8	1	0.014	0.986	76.5
7	64	5	0	0.000	1.000	75.4
8	59	5	2	0.035	0.965	75.4
9	50	4	0	0.000	1.000	72.7
10	44	-	-	-	-	72.7

DISTANT METASTASIS (no subsequent local recurrence)
METASTASIS RATE - ACTUARIAL ANALYSIS
STAGE II

TABLE 97

Years after initial treatment (X)	Number of cases observed X or more years after initial treatment (O_x)	Withdrawals* ($_nW_x$)	Number developing distant metastasis (without subsequent local recurrence) ($_nR_x$)	Estimated proportion of cases reaching this X who:-		% of cases treated who develop distant metastasis (P_x)
				Develop distant metastasis before next stated X yrs. ($_nQ_x$)	Survive without distant metastasis to next X yrs. ($_nP_x$)	
0	140	16	2	0.015	0.985	100
0.25	122	10	8	0.068	0.932	98.5
0.5	104	9	4	0.040	0.960	91.9
0.75	91	8	2	0.026	0.974	88.0
1	81	9	3	0.039	0.961	85.6
1.5	69	13	4	0.064	0.936	82.3
2	52	9	9	0.190	0.810	77.0
3	34	3	1	0.031	0.969	62.2
4	30	3	1	0.035	0.965	60.3
5	26	4	1	0.042	0.958	58.1
6	21	3	0	0.000	1.000	55.6
7	18	3	0	0.000	1.000	55.6
8	15	4	0	0.000	1.000	55.6
9	11	2	1	0.100	0.900	55.6
10	8	-	-	-		50.0

DISTANT METASTASIS (no subsequent local recurrence)
METASTASIS RATE - ACTUARIAL ANALYSIS
STAGES III and IVL

TABLE 98

CASES WITH LOCAL RECURRENCE

Years after initial treatment	Cases observed to end of given period	Cases dying in following period	% of cases remaining alive at end of given period
0	35	1	100
0.08	34	1	97
0.25	33	0	94
0.5	33	6	94
0.75	27	0	77
1	27	5	77
1.25	22	2	63
1.5	20	3	57
1.75	17	1	49
2	16	4	46
2.5	12	3	34
3	9	2	26
4	7	2	19
5	5	-	14

MORTALITY RATE AFTER APPEARANCE OF RECURRENCE
STAGE I

TABLE 99

CASES WITH LOCAL RECURRENCE

Years after initial treatment	Cases observed to end of given period	Cases dying in following period	% of cases remaining alive at end of given period
0	48	2	100
0.08	46	2	96
0.25	44	4	92
0.5	40	5	83
0.75	35	3	73
1	32	1	67
1.25	31	3	65
1.5	28	2	58
1.75	26	4	54
2	22	0	46
2.5	22	4	46
3	18	5	38
4	13	4	27
5	9	-	19

MORTALITY RATE AFTER APPEARANCE OF RECURRENCE
STAGE II

TABLE 100

CASES WITH LOCAL RECURRENCE

Years after initial treatment	Cases observed to end of given period	Cases dying in following period	% of cases remaining alive at end of given period
0	47	1	100
0.08	46	3	98
0.25	43	4	92
0.5	39	5	83
0.75	34	4	72
1	30	4	64
1.25	26	1	55
1.5	25	3	53
1.75	22	2	47
2	20	5	43
2.5	15	2	32
3	13	6	28
4	7	3	15
5	4	-	9

MORTALITY RATE AFTER APPEARANCE OF RECURRENCE
STAGES III and IVL

TABLE 101

CASES WITH DISTANT METASTASIS
(no subsequent local recurrence)

Years after initial treatment	Cases observed to end of given period	Cases dying in following period	% of cases remaining alive at end of given period
0	42	4	100
0.08	38	5	90
0.25	33	1	79
0.5	32	4	76
0.75	28	9	67
1	19	3	45
1.25	16	3	38
1.5	13	2	31
1.75	11	1	26
2	10	2	24
2.5	8	1	19
3	7	5	17
4	2	1	5
5	1	-	2

MORTALITY RATE AFTER APPEARANCE OF METASTASIS
STAGE I

TABLE 102

CASES WITH DISTANT METASTASIS
(no subsequent local recurrence)

Years after initial treatment	Cases observed to end of given period	Cases dying in following period	% of cases remaining alive at end of given period
0	34	1	100
0.08	33	10	97
0.25	23	6	68
0.5	17	2	50
0.75	15	3	44
1	12	3	35
1.25	9	1	26
1.5	8	2	24
1.75	6	1	18
2	5	2	15
2.5	3	1	9
3	2	0	6
4	2	0	6
5	2	-	6

MORTALITY RATE AFTER APPEARANCE OF METASTASIS
STAGE II

TABLE 103

CASES WITH DISTANT METASTASIS
(no subsequent local recurrence)

Years after initial treatment	Cases observed to end of given period	Cases dying in following period	% of cases remaining alive at end of given period
0	36	4	100
0.08	32	14	89
0.25	18	1	50
0.5	17	0	47
0.75	17	5	47
1	12	3	33
1.25	9	0	25
1.5	9	2	25
1.75	7	1	19
2	6	2	17
2.5	4	1	11
3	3	2	8
4	1	0	3
5	1	-	3

MORTALITY RATE AFTER APPEARANCE OF METASTASIS
STAGES III and IVL

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