The association of cytosol oestrogen and progesterone receptors with histological features of breast cancer and early recurrence of disease

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Summary Two hundred and eighty-eight primary breast tumours were examined for the presence or absence of oestrogen (RE) and progesterone (RP) receptors. Analysis has shown a relative interdependence between the steroid receptor status of primary breast cancer and other prognostic variables such as histological grade, lymphocytic infiltration and tumour elastosis. There were significant associations between epithelial cellularity, stromal fibrosis and the value of RE in those tumours in which the receptor was present. Cellularity and fibrosis were unrelated to the presence or absence of oestrogen receptor. By contrast, neither the presence or absence nor the value of RP could be related to cellularity or fibrosis. The value of RE and RP analysis as an indicator of prognosis was examined in a sub-group of 175 patients receiving no additional treatment following mastectomy. Overall relapse-free survival (RFS) was no different for those patients with receptors compared to those without them (RE, P = 0.11, RP, P = 0.7). There was no difference in RFS of receptor positive and negative tumours when the axillary node status was taken into account.

Increased recognition of the importance of selective hormone binding in initiating steroid action in target tissues has led to the study of oestrogen and progesterone binding by human breast cancer. Though the receptor content of the primary tumour is reported to be independent of factors such as tumour site or size, age of patient or degree of axillary node involvement (Knight et al., 1977) it is not known to what degree tumour differentiation is under endocrine control. Studies linking receptors and hormone-dependent proteins with morphological and clinical features may help clinicians to recognise tumours which are hormone-sensitive. In early studies of this nature there was no consistent relationship between specific histopathological features of the tumour and either the presence or the value of RE (Sander, 1968; Korenman & Dukes, 1970; Johansson et al., 1970; Feherty et al., 1971; Wittliff et al., 1971; LeClercq et al., 1973; Terenius et al., 1974; Aspergren & Hakansson, 1974). However, in some of these studies numbers were small and methods of RE analysis and morphological examination were inconsistent. More recent studies have shown that RE may be closely related to tumour grade (Maynard et al., 1978; Martin et al., 1979b; Rasmussen et al., 1981; Thoresen et al., 1981), to the histological type and degree of lymphocytic infiltration of primary tumour (Rosen et al., 1975) and to the presence or absence of elastosis in the tumour stroma (Masters et al., 1976). Similar links have been recognised between the progesterone receptor (RP) and histological grade and elastosis (Martin et al., 1979b; Rolland et al., 1980), but a relationship between RP and other aspects of tumour morphology has not been reported.

Most investigators who have studied the relationship between RE and freedom from recurrence and survival, have suggested that an earlier recurrence and shorter survival may be expected in those patients who lack RE in their primary tumour, although data vary as to which patients obtain the greatest benefit (Knight et al., 1977; Maynard et al., 1978; Bishop et al., 1979; Cooke et al., 1979; Allegra et al., 1979; Forrest et al., 1980; Westerberg et al., 1980; Croton et al., 1981). As the RE is said to be independent of other prognostic variables in breast cancer, the measurement of this receptor has been advocated as a means of selecting patients likely to benefit most from systemic adjuvant therapy (Cooke et al., 1980). By contrast, Hilf and his colleagues (1980) were unable to confirm that RE has any beneficial effect on the disease process.

Similar studies which link the presence or absence of RP to relapse-free survival (RFS), have also produced conflicting results (Pichon et al., 1980; Allegra et al., 1979; Kinne et al., 1981) and the role

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of this receptor as a prognostic factor in breast cancer remains uncertain.

The objectives of this single centre study were twofold: to test the hypothesis that the presence or absence of RE$\text{c}$ and RP$\text{c}$ is a reflection of certain morphological features of the tumour, some of which are of prognostic significance in their own right and to investigate the role of RE$\text{c}$ and RP$\text{c}$ as indicators of early recurrence.

Materials and methods

Oestrogen and progesterone receptor assay

Samples of histologically proven primary tumours from women with breast cancer were studied. Portions for oestrogen (RE$\text{c}$) and progesterone (RP$\text{c}$) receptor measurement were selected at the time of surgery by the pathologist who received tissue for frozen section. They were stored in liquid nitrogen until required for analysis, and then homogenised and centrifuged. The receptor content of the cytosol was measured by incubation with either tritiated oestradiol in the presence or absence of diethyl-stilboestrol as a competitor for specific oestrogen receptor sites, or tritiated R5020 and radio-inert R5020, a synthetic progesterin, for specific progesterone receptor sites. Non-receptor bound $[^3]$H-hormone was separated from hormone bound to receptors by adsorption on to Dextran-coated charcoal (DCC). The activity of the receptor-bound radio-labelled hormone remaining in the supernatant was measured in a scintillation counter and the data analysed according to Scatchard (1949). Values > 5 fM mg$^{-1}$ for RE$\text{c}$ and > 15 fM mg$^{-1}$ for RP$\text{c}$ of cytosol protein were regarded as positive (Barnes et al., 1977; Skinner et al., 1980). Negative results from tumours where the cytosol protein was < 0.7 mg ml$^{-1}$ were not accepted as valid and were excluded from the study.

Histology

The pathological features of 288 unselected primary malignant breast tumours were reviewed retrospectively by one pathologist who was unaware of the receptor status. His observations were based on the examination of routine paraffin wax embedded sections stained with haematoxylin and eosin and sections stained for elastic tissue with Miller's Victoria blue and Van Geison stain. The following pathological observations were made: the maximum diameter, the nature of the margin (circumscribed or stellate), and the histological type of the primary tumour. The grade of infiltrating duct tumours was assessed on a scale of 1 (well-differentiated) to 3 (poorly-differentiated) taking into account tubular differentiation, nuclear pleomorphism and mitotic activity according to the method recommended by Scarff & Torloni (1968) which is essentially that of Bloom & Richardson (1957). The degree of lymphoid reaction in and around the primary tumour was evaluated on a scale of 1 (slight or none) to 3 (marked), and the epithelial cellularity of the middle and the edge of the tumour, the stromal reaction or fibrosis within the tumour and the degree of elastic tissue formation within the stroma were similarly assessed. This is a semi-quantitative visual assessment based on the experience of the pathologist.

Assessment of recurrence

The relationship of the RE$\text{c}$ and RP$\text{c}$ status to the development of early recurrence of the disease was studied in a subgroup of 175 patients with operable disease $(T_1-3 N_0-1 M_0)$. Each had a Patey modified radical mastectomy. After histological examination of the axillary nodes, the patients were classified into three groups: those with no nodes containing tumour; those with 1–3 nodes containing tumour; and patients with 4 or more nodes containing tumour. Patients with bilateral tumours, or distant metastases and those receiving adjuvant hormone or cytotoxic therapy were excluded from this part of the study.

The patients were examined one month after operation, then every 6 weeks for 2 years and thereafter annually. Local recurrence and nodal disease was confirmed where possible by biopsy while distant bone and visceral metastases were diagnosed on unequivocal radiological evidence.

Statistical methods

The Chi-squared test was used to test for association between histological features and receptor status in $r \times c$ contingency tables. The relationship between RE$\text{c}$ and RP$\text{c}$ content and degrees of cellularity, fibrosis, lymphocytic infiltration, elastosis and histological grade was examined by means of the Kruskal Wallis non-parametric one-way Analysis of Variance (ANOVA).

For studies of RFS time-based curves were computed by actuarial methods and compared by the log-rank test (Peto et al., 1977).

Results

Receptor status and age

The subgroups of patients analysed in relation to histology (288) or recurrence of disease (175) were shown statistically to be similar in composition in terms of age, menopausal status, and frequency of receptor-positive tumours, to an overall group of
523 consecutive patients with breast cancer studied in a 4-year period, but in whom complete histological or follow-up data was not available. Sixty per cent of the patients had tumours containing $\text{RE}_c$ and $40\% \text{ RP}_c$. Fifty-three per cent of premenopausal and $62\%$ of postmenopausal patients possessed $\text{RE}_c$. Absolute values of $\text{RE}_c$ showed a statistically significant association with age, being higher in older women and confirming a previous observation from our laboratory (Skinner et al., 1980). For $\text{RP}_c$ the proportions of receptor-positive premenopausal ($43\%$) and postmenopausal ($38\%$) patients were similar and age had no influence on the value of $\text{RP}_c$.

### Receptor status and pathological parameters

The morphological and histological features of 288 primary tumours were studied in relation to both the receptor status, and in receptor-positive tumours, to the value of $\text{RE}_c$ and $\text{RP}_c$. There was no relationship between the presence or absence of $\text{RE}_c$ and $\text{RP}_c$ and either the diameter of the tumour or whether the margins were circumscribed or infiltrative. The relationship between receptor status and histological type of tumour is shown in Table I. All of the tubular carcinomas contained $\text{RE}_c$ and $\text{RP}_c$, and $70\%$ of the infiltrating lobular carcinomas contained $\text{RE}_c$. However, the numbers of some types of tumour were too small to permit statistical evaluation.

### Table I Relationship of histological type of primary tumour to oestrogen and progesterone receptor status

| Histological type   | $\text{RE}_c$ No. positive ($\%$) | $\text{RP}_c$ No. positive ($\%$) |
|---------------------|----------------------------------|----------------------------------|
| Intraduct           | 5/9 (55)                         | 3/9 (33)                         |
| Infiltrating duct*  | 148/248 (60)                     | 100/233 (43)                     |
| Infiltrating papillary | 1/1 (100)                       | --                               |
| Mucoïd              | 5/8 (63)                         | 1/8 (13)                         |
| Medullary           | 0/3 (0)                          | 0/3 (0)                          |
| Infiltrating lobular| 7/10 (70)                        | 4/10 (40)                        |
| Tubular             | 7/7 (100)                        | 5/5 (100)                        |
| Sarcoma             | 0/2 (0)                          | 0/2 (0)                          |

*All grades.

### Histological grade

$\text{RE}_c$ was measured in 157 and $\text{RP}_c$ in 142 infiltrating duct carcinomas in which grade was assessed. There was a highly significant association between the presence or absence of both types of receptor and the histological grade ($\text{RE}_c$ vs. grade $P=0.0004$; $\text{RE}_c$ vs. grade $P=0.0001$). $\text{RE}_c$ and $\text{RP}_c$ occurred most frequently in grade 1 (well-differentiated) tumours whereas there were relatively few receptor-positive tumours in grade III (poorly-differentiated) (Figure 1). In receptor-positive tumours there was no association between grade and value of either $\text{RE}_c$ ($P=0.6$) or $\text{RP}_c$.

![Figure 1](image-url)  
**Figure 1** Relationship of $\text{RE}_c$ and $\text{RP}_c$ to grade of infiltrating duct tumours.
Specific types of tumours, e.g. lobular, medullary and tubular, were not graded and were excluded from this section.

**Cellularity and fibrosis**

In those tumours in which receptors were found there was a significant association between cellularity, both at the centre and at the edge of the tumour, and the value of \( RE_c \) \((P < 0.0001)\) (Figure 2) although cellularity was unrelated to the presence or absence of \( RE_c \) \((RE_c \ vs. \ cellularity \ edge, \ P = 0.7; \ centre, \ P = 0.1)\). Tumour cellularity was not related to either the value of \( RP_c \) \((edge, \ P = 0.2; \ centre, \ P = 0.3)\), or to the presence or absence of this receptor \((RP_c \ vs. \ cellularity \ centre, \ P = 0.5; \ edge, \ P = 0.8)\). In \( RE_c \)-positive tumours there was an inverse association between the degree of stromal fibrosis and value of \( RE_c \), those tumours with most fibrosis containing lowest values of receptor \((P < 0.0001)\) although there was no association between the degree of fibrosis and the presence or absence of \( RE_c \) \((P = 0.2)\). Fibrosis was not related to either the presence or the value of \( RP_c \) \((P = 0.2, \ P = 0.5)\).

**Elastosis**

\( RE_c \) and \( RP_c \) were found in 72% (32/44) and 59% (23/39) respectively of those tumours with a marked degree of elastic tissue within the stroma compared with 67% (37/55) and 36% (17/47) of tumours with moderate elastosis and 49% (36/73) and 26% (18/68) of those with none. For both \( RE_c \) and \( RP_c \) these were statistically significant associations \((RE_c \ vs. \ elastosis, \ P = 0.02; \ RP_c \ vs. \ elastosis, \ P = 0.004)\) (Figure 3). There was no association between degree of elastosis and value of either \( RE_c \) or \( RP_c \) \((P = 0.4)\).
**Lymphocytic infiltration**

Only 30% (9/30) of tumours with a marked lymphocytic infiltrate were found to contain $R_{Ee}$ in contrast with 73% (69/94) of tumours with no lymphocytic reaction ($P = 0.0001$). A similar inverse association was found for $R_{Pc}$. Ninety-three percent of tumours with a marked lymphocytic reaction were $R_{Pc}$ negative ($P = 0.0004$) (Figure 4). There was no association between the degree of lymphocytic infiltration and the value of either receptor ($RE_e, P = 0.9; RP_c, P = 0.3$).

**Inter-relationships of grade, lymphocytic infiltration and elastosis**

There was a highly significant association between the degree of lymphocytic infiltration and histological grade of infiltrating duct tumours (Table II). High grade tumours contained the most marked lymphoid reaction ($P < 0.0001$). Table III summarizes the inverse association between the degree of elastosis and histological grade, elastosis being most marked in grade I tumours ($P = 0.0001$).

**Receptor status and node metastases**

There was no association between the receptor status of the primary tumour and the number of axillary lymph nodes containing metastases ($RE_e$ vs. nodes, $P = 0.3$; $RP_c$ vs. nodes, $P = 0.7$). The histological findings are summarized in Table IV.

**Receptors and recurrence rates**

When the follow-up data were analysed neither age nor menopausal status at the time of first presentation had any influence on the recurrence.

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**Table II** Frequency of concurrence of each degree of lymphocytic infiltration and histological grade in 183 infiltrating duct tumours

| Lymphocytic infiltration | None | Moderate | Marked |
|--------------------------|------|----------|--------|
| Grade I (n=49)           | 34   | 14       | 1      |
| Grade II (n=94)          | 52   | 29       | 13     |
| Grade III (n=40)         | 4    | 20       | 16     |

($P = <0.0001$).

**Table III** Frequency of concurrence of each degree of elastosis and histological grade in 172 infiltrating duct tumours

| Elastosis | None | Present | Marked |
|-----------|------|---------|--------|
| Grade I (n=48) | 14   | 12      | 22     |
| Grade II (n=85) | 30   | 35      | 20     |
| Grade III (n=39) | 25   | 12      | 2      |

($P = 0.0001$).
Table IV  Summary of relationship of REc and RPc receptor status to histological observations

| Histological observation | Association with oestrogen receptor (REc) | Association with Progesterone receptor (RPc) |
|--------------------------|------------------------------------------|-------------------------------------------|
| Diameter of primary tumour | None                                     | None                                      |
| Margin of primary tumour | None                                     | None                                      |
| Histological type        | Statistically none, but all tubular and most lobular tumours REc + ve | Statistically none, but all tubular tumours RPc + ve |
| Grade of infiltrating duct tumours | REc occur most frequently in grade I (well-differentiated) tumours (P=0.0004) | RPc occur most frequently in grade I (well-differentiated) tumours (P=0.0001) |
| Lymphocytic infiltration | Inverse association between lymphoid reaction and presence of REc (P=0.0001) | Inverse association between lymphoid reaction and presence of RPc (P=0.0004) |
| Epithelial cellularity:   | In REc + ve tumours, highest values in most cellular tumours (postmenopausal) (P<0.001) but unrelated to receptor status. | None |
| Stromal fibrosis          | In REc + ve tumours, lowest values in those tumours with marked fibrosis (postmenopausal) (P<0.0001) but unrelated to receptor status. | None |
| Elastosis                 | REc occur most frequently in tumours with elastosis (P=0.02) | RPc occur most frequently in tumours with elastosis (P=0.004) |
| Number of axillary nodes containing tumour | None | None |

rate of the tumour. The presence or absence or REc and RPc was analysed with respect to the RFS 15 and 29 months after the last patient entered the study. At a median observation period of 24 months, a statistically significant increase in RFS was found for patients who possessed REc compared with those who lacked this receptor (P = 0.02). This difference was no longer significant at a median period of observation of 34 months (Figure 5). When the patients were divided into 4 groups according to the REc content of the tumour (REc negative, 5–30, 31–100, >100 FM mg⁻¹ cytosol protein) there was no statistical relationship between RFS and the REc value at any time (Figure 6). In 163 patients RPc was also measured. The presence of this receptor was not related to RFS (Figure 7). This was noted in both REc positive and REc negative tumours, although the number of patients who possessed RPc and lacked REc was very small.

The importance of the presence of metastases in the ipsilateral axillary nodes in determining the prognosis in breast cancer has been emphasised (Say & Donegan, 1974; Fisher et al., 1975). This was confirmed in the present study. The overall recurrence rate was significantly higher in node + ve patients regardless of their receptor status (P<0.001). Three years after mastectomy 80% of patients without axillary node involvement remained free from recurrence compared with 56% of those who had 1–3 involved nodes and less than 30% of patients with 4 or more nodes containing tumour.

RFS was analysed in relation to receptor status and axillary node involvement (Figure 8). There was no statistically significant difference in the RFS between REc + ve and REc – ve tumours in patients without axillary metastases (P>0.9) or in patients with extensive nodal disease (≥4) (P=0.2). In patients with 1–3 axillary nodes involved, REc + ve tumours were associated with a longer RFS than REc – ve tumours at a median observation period of 24 months (P=0.05), but not at 34 months (P=0.07). There were no differences between the RFS of RPc + ve and RPc – ve tumours in any axillary node subgroup.

Discussion

Breast cancer varies in its responsiveness to hormones, and is the first disease in which estimation of tissue receptors at the time of initial surgery has been advocated as a method of identifying patients with the greatest risk of recurrence. The purpose of this study was to examine inter-relationships between steroid receptor activity and a variety of histological features, and to
assess the value of $RE_c$ and $RP_c$ as independent factors in the prognosis of breast cancer.

We have shown $RE_c$ and $RP_c$ to be independent of certain factors known to influence the natural history of the disease, for example tumour size, and the nature of its margin and axillary metastases (Fisher et al., 1975). Although we could not show a statistical relationship between receptors and the histological type it is interesting to note that all tubular carcinomas had both $RE_c$ and $RP_c$. This confirms the observation of Antoniades & Spector (1979). We also confirmed reports of a high incidence of $RE_c$ in invasive lobular tumours (Rosen et al., 1975; Antoniades & Spector, 1979; Martin et al., 1979b; Rasmussen et al., 1981). Other workers have failed to demonstrate any such association (Johansson et al., 1970; Feherty et al., 1971; Wittliff et al., 1971; LeClercq et al., 1973; Aspegren & Hakansson, 1974), but in most series the majority of tumours were infiltrating duct carcinomas and, as in the present study, the number of uncommon histological types was too small to permit statistical evaluation. The finding that both invasive lobular and tubular carcinomas have a high incidence of $RE_c$ supports the hypothesis that they are extreme variants of the same histological entity (Eusebi et al., 1979).

Although in the past it was generally accepted that there was no association between the presence of $RE_c$ and the histological features of infiltrating duct tumours (Johansson et al., 1970; Feherty et al., 1971; Rosen et al., 1975), only Feherty used the W.H.O. recommended system of grading. More recently, using this method exclusively, Maynard et al. (1978), Martin et al. (1979b), Rasmussen et al. (1981) and Thoresen et al. (1981) have shown a definite relationship between histological grade and $RE_c$.

Our data agree with the latter reports and in addition have confirmed the findings of Martin et al. (1979b) that the possession of $RP_c$ is also linked to histological grade. Terenius et al. (1974) was unable to show a relationship between the presence or absence of $RE_c$ and grade, but found that $RE_c$ values were statistically higher in well-differentiated tumours. The method of grading was not specified. In the present study, as in that of Heusen et al. (1975) and Thoresen et al. (1981), the mean value of the receptors was similar in all three grades, and thus the significance of the association between grade and presence or absence of receptor is difficult to interpret. Silvestrini et al. (1979) using thymidine-labelling indices have shown that tumours with rapid rates of cell division have a low

![Figure 5](image)

**Figure 5** Effect of $RE_c$ status on relapse-free survival.
incidence of $RE_c$. This, and the frequency with which receptors are found in low grade tumours suggests that receptors are associated in some way with low rates of cellular replication.

Cellularity, when assessed both at the centre and the edge of the tumour to avoid sampling errors, was unrelated to the presence of $RE_c$ and $RP_c$. However, in receptor-positive tumours, there was a significant association between the highest values of $RE_c$ and those tumours with the most abundant epithelial component. This was found both in the overall group and post-menopausal patients but not in pre-menopausal patients. Conversely, those tumours with the most marked stromal reaction had the lowest $RE_c$ values. Once again this was not seen in the pre-menopausal patients. By contrast,
Figure 7  Effect of $RP_c$ status on relapse-free survival.

Figure 8  Effect of $RE_c$ status and node involvement on relapse-free survival.
the mean value of the progesterone receptors was similar for all degrees of cellularity. These findings are identical with those of Masters et al. (1978) and similar, in part, to the results of Terenius et al. (1974), Antoniades & Spector (1979) and Martin et al. (1979a). Rosen et al. (1975) observed some association between cellularity and $R_E$ value but did not consider it significant. Feherty et al. (1971) and Rasmussen et al. (1981) were unable to show this association. The failure to demonstrate such a link may be the result of unavoidable variation in methods used to assess cellularity (Antoniades & Spector, 1979).

It seems that although cellularity does not affect the frequency with which receptor-positive tumours are identified, it does influence the value of $R_E$ when present and therefore $R_E$ negativity, based on a low receptor value, should be considered with caution in tumours of low cellularity for it may only reflect the lack of epithelial cells (Martin et al., 1979a). As the presence of $R_P$ is normally closely linked with $R_E$ (Martin et al., 1979b) the dissociation of $R_E$ and $R_P$ in relation to cellularity is unexplained.

There is no readily apparent explanation for the observation that receptors occur infrequently in tumours with a prominent lymphocytic infiltration, a relationship which has been reported previously (Rosen et al., 1975). It seems unlikely that lymphocytes per se are responsible for the absence of receptors within a tumour and this inverse association may merely reflect the observed statistically significant association between heavy lymphoid infiltration and poorly differentiated tumours. A lymphoid reaction is known to be closely related to the degree of malignancy (Fisher et al., 1975).

The association of hormone receptors with the presence of elastic tissue within the tumour stroma may have a similar explanation for there was a statistical association between histological grade and elastosis, the latter being most marked in well-differentiated (grade I) tumours. Masters and his colleagues (1976, 1978) and Rasmussen et al. (1981) have also found an association between $R_E$ and elastosis, a feature which occurs frequently in postmenopausal patients, and an association has been reported between $R_P$ and elastosis (Rolland et al., 1980). They could give no satisfying explanation for their results.

Shivas & Douglas (1972) have shown that patients whose tumours contain elastic tissue survive longer than those who lack it. They are also more likely to respond to endocrine therapy (Masters et al., 1979). Well-differentiated (grade I) tumours have similar properties (McGuire et al., 1977). These reports taken with the present data emphasise that hormone-dependent cells in breast tumours can be demonstrated both biochemically and histologically and many of the features of breast cancer are interdependent. Steroid receptors cannot be considered in isolation when planning treatment.

The relationship between receptor status and prognosis is not a simple one. Several reports have suggested that early relapse of breast cancer is clearly associated with a lack of $R_E$ (Maynard et al., 1975; Cooke et al., 1979, 1980; Allegra et al., 1979; Hahnel et al., 1979; Forrest et al., 1980; Westerberg et al., 1980). Patients who have $R_E$ are reported to live longer than those who lack it (Bishop et al., 1979; Croton et al., 1981). Kinne et al. (1981) and Samaan et al. (1981) found no overall difference in the RFS of patients with and without $R_E$, but have found small significant differences in subgroups based on node or menopausal status. The data from the present study, like those of Hilf et al. (1980) fails to demonstrate any clear prognostic value for disease recurrence. Similarly there is conflicting evidence that the progesterone receptor is a reliable indicator of prognosis. Pichon et al. (1980) demonstrated an increase in RFS for patients with $R_P$, whereas Allegra et al. (1979) and Kinne et al. (1981) as in the present study, found no association between the $R_P$ and RFS.

The reasons for these conflicting results are not clear. Variations in the method of receptor analysis may be important and Forrest et al. (1980) showed that by merely moving the “cut-off point” separating receptor-rich (+ve) from receptor-poor (low +ve and -ve) tumours, the prognostic value for $R_E$ could be eliminated. However, there is good qualitative agreement between centres using the DCC technique, including our own (King et al., 1978), and the present study has employed similar criteria for receptor positivity to previous reports.

Hilf and his colleagues (1980) stressed that clinical factors may cause confusion in interpreting data relating $R_E$ status to prognosis, and their observations may also apply to $R_P$. In early studies numbers were small or receptor data from primary and secondary tumours were combined. In some, no allowance was made for patients receiving additional systemic or local treatment following mastectomy, in others, the status of the axillary nodes was not accurately known, staging being based on pectoral node biopsy, a technique which in our experience may give a false-negative rate of axillary node involvement as high as 20% (Howat & Harris, 1982).

The length of follow-up is short in many of the reports claiming prolonged RFS (Knight et al., 1977; Maynard et al., 1978; Pichon et al., 1980), and actual survival (Bishop et al., 1979; Croton et al., 1981) for receptor +ve patients. Our experience has emphasised the importance of prolonged follow-
up. At a median follow-up of 24 months our results were similar to those of Knight et al. (1977), Maynard et al. (1978) and Kinne et al. (1981). We observed an increase in RFS for REc +ve patients with lymph node involvement, but not for any other sub-group. The data suggested that only those with minimal axillary disease (1–3 nodes) benefited and it was thought that too few node –ve patients had recurred to show any difference attributable to the REc status and that patients with extensive nodal involvement (≥4) had recurred too rapidly for any beneficial effect of REc to become apparent. However, when the median follow-up reached 34 months the difference between REc +ve and REc –ve patients in the 1–3 node subgroup had disappeared. Hahnel and his colleagues (1979) made similar observations. An apparently advantageous effect of the REc in node +ve patients seen in the first 2 years after mastectomy disappeared so that at 5 years they too were unable to demonstrate a significant difference between the RFS of REc +ve and –ve patients in any subgroup. Von Maillot et al. (1982) obtained similar results for both REc +ve and RPc +ve patients when they were compared with receptor-negative cases. Benson et al. (1982) made similar observations on survival. At 5 years there was no benefit for REc +ve patients despite an earlier trend in their favour.

It is not surprising that the progesterone receptor did not influence the RFS in this study for its presence is closely linked to that of REc. Thus one might expect that the absence of any effect on RFS of the REc would be reflected in the results obtained with RPc.

As the data obtained in our study did not demonstrate any marked prognostic value for either REc or RPc status and as the presence of these receptors may merely reflect more easily assessed histological features, we conclude that the measurement of these receptors is of no value in identifying those patients at greatest risk of recurrence. Other factors such as tumour size and axillary node status remain pre-eminent as reliable guides to prognosis.

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