Cancer Chemother. Pharmacol. 2, 115–120 (1979)

Cancer
Chemotherapy and
Pharmacology

Multiple Steroid Receptors in Human Breast Cancer

III. Relationships Between Steroid Receptors and the State of Differentiation and the Activity of Carcinomas Throughout the Pathologic Features

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Summary. *Histopathologic features (tumor cell density, histological type, and histoprognostic grade) were analyzed in 314 breast cancers investigated for estrogen (E) and progestin (P) receptors (R). The presence of PR is associated with the presence of ER. A relationship was found between the acinoductal differentiation of the lesions and the presence of SR: the more differentiated the carcinoma, the higher the frequency of ER. HPG III carcinomas have the lowest frequency of positive ER and HPG I tumors the opposite: the likelihood of the presence of SRs is inversely correlated with HPG. No statistically significant relationship existed between tumor cell density (TCD) and the presence of ER or ER content. Similar findings were observed for the stromal reaction. The results are discussed with respect to the biological significance of SR and histopathologic features: SR presence could be correlated with (1) a differentiated state of the tumors and (2) a slow rate of cellular replication.*

Introduction

Long after the pioneering work demonstrating the beneficial effects of ablative endocrine surgery on mammary carcinomas [1], biochemical studies have shown the presence of steroid receptors in some breast cancer [14, 15, 16]. Both findings have led to the concept of a hormone-dependent nature of breast cancer [15, 29, 31], where the growth of the tumor depends on the presence of the steroid hormone, the steroid receptor (SR), and an intact biochemical pathway [9, 13, 17, 30]. It was suggested that the presence of estrogen (E) and progestin (P) receptors (R) could improve the selection of hormone-responsive tumors [14, 21, 28, 31]. There is little information on the biological and pathological significance of SR in breast cancer cells [8]. Most studies are devoted to either the mechanism of action of steroid hormones [2, 14, 21, 22, 29] or the clinical relationships of SR to endocrine therapy [27, 28, 31, 38]. One study suggested that the absence of ER in mammary tumors correlates with rapid rates of cellular replication [32]. We have previously reported the distribution of ER and PR in a large population of breast cancers and demonstrated the necessity for considering certain pathologic features of the tumor in the expression of SR values [24, 25, 26], specifically tumor cell density. This paper deals with the histopathologic features of 314 breast cancers analyzed for ER and PR content. This study was undertaken to determine whether SR correlates with the degree of differentiation of the tumor or with other pathologic features associated with the aggressive nature of the tumor, such as histoprognostic grade, cellularity, and histological type.

The abbreviations used are SR, steroid receptor; ER, estrogen receptor; PR, progestin receptor; TCD, tumor cell density; HPG, histoprognostic grade; HT, histological type.

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Materials and Methods

Within the last three years, 314 primary and metastatic breast cancers have been routinely investigated for SR content and histopathology in our laboratory. Of these, 36 special histological types of carcinoma were not allocated to any histoprognostic grade. The age, endocrine status, history of disease, and clinical staging were recorded for each patient.

After surgery, the tumors were divided into two representative parts: one for histopathological examination and the other for SR analysis. The ratio was 1 : 5. The simultaneous assay of ER and PR has been described in detail elsewhere [25].

Pathologic features were examined by one of the authors (J. J.). After fixing of the specimen overnight, routine slides were prepared from paraffin blocks and stained (trichrome : hematein-eosin-safranin). The cellularity of the tumor was estimated by comparing the density of the cancer cells with that of the stroma. We established an

0344-5704/79/0002/0115/$ 01.20

arbitrary classification of the carcinomas according to the TCD on a scale of I to III. TCD I includes cases where the tumor epithelial component is low relative to the stromal component. In TCD III the stromal component is reduced to some fibrous lines. TCD II is intermediate with regard to the cellularity.

Histoprognostic grading was performed according to Scarff and Bloom [3, 4, 36]. This reproducible technic concerns the degree of differentiation, nuclear pleomorphism, and mitotic activity of a tumor. Because of their own prognostic value, special histological types were not graded [36].

Histological types (HT) were examined within two different populations according to the morphological aspects and the degree of differentiation [6]: the most commonly found HT are the well-differentiated (tubular), atypical, and polymorphic carcinomas, the last being considered with respect to its degree of differentiation (more or less than 50% differentitation). Special HT include lobular in situ, infiltrating intraductal in situ, colloid, and medullary carcinomas with a lymphocytic reaction. The stromal reaction was classified as fibrohyalin, lymphocytic, or fibrinoid.

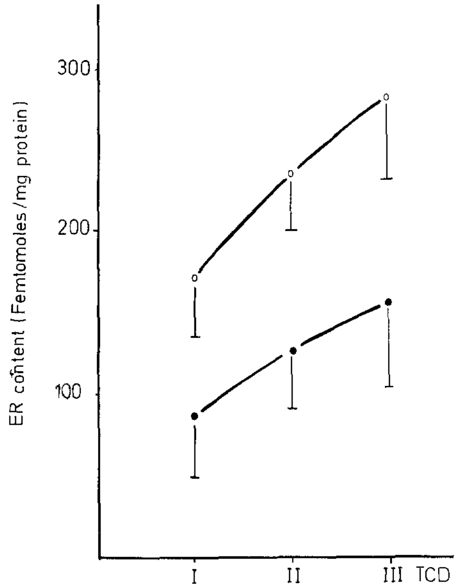

Fig. 1. Relationship between TCD and ER content (mean ± SD) in 314 cases of breast carcinoma. Patients were divided into a group under 50 years of age (●—●) and one over 50 (○—○)

Results

Breast Cancer Population. To determine whether our 314 breast cancer patients were representative of a general population, we compared the distribution of HT of breast cancer with that of a more extensive series established during the last 10 years at the G. Roussy Institut (F) [6]. The same terminology was used for pathologic features [7, 36]. The distribution of histological types presented in Table 1 shows no significant difference between the two populations.

Cellularity in Tumors. To determine the importance of the TCD for the interpretation of steroid receptor concentrations in tumor samples [10, 24] we examined the ER content and TCD in 278 cases of positive ER breast cancers. Patients were grouped by menopausal status, assuming premenopausal to mean less than 50 years of age and postmenopausal over 50. The correlation between menopausal status, ER content, and TCD is shown in Fig. 1. Postmenopausal patients have a higher ER content than premenopausal patients in all TCD groups. Although within each menopausal group the mean ER content increases as a function of TCD, these differences are not statistically significant, due to the wide range of ER values.

Histoprognostic Grades. The HPG of 278 breast cancers have been correlated with the presence and level of both ER and PR. HPG does not correlate with menopausal status. About 70% of patients within each grade were postmenopausel (Table 2). A significant inverse correlation ($P < 0.001$) was found between the fre-

Table 1. Distribution of HT of breast carcinomas. Comparison of the 314 cases of this study (I.P.C.) with a 10-year series established at the G. Roussy Institute (I.G.R.) (over 2,000 cases)

Histological type	I.G.R. %	I.P.C. %
Isolated cells	3.6	1.5
Intraductal	2.3	3.9
Well-differentiated	9.3	9.3
Polymorphic	44.2	57.9
Atypical	34.7	32.7
Lobular infiltrating	3.9	3.9
Medullary	1.2	3.2
Colloid	0.6	1.0

Table 2. Relationships between HPG and presence of SRs in breast cancers. The presence (+) and absence (–) of SRs are expressed as percentages of each population

Histoprognostic grade	I		II		III	
Age (years)	< 50	> 50	< 50	> 50	< 50	> 50
Sample (n)	13	31	32	93	35	74
Receptor populations in breast cancer						
Total ER+	75%	88%	66%	70%	48%	46%
PR+	73%	74%	56%	47%	45%	35%
ER+ PR+	71%	72%	50%	41%	40%	32%
ER+ PR–	4%	16%	16%	29%	8%	14%
ER– PR+	2%	2%	6%	6%	5%	3%
ER– PR–	23%	10%	28%	24%	47%	51%

quency of positive receptors and HPG. The HPG I lesions were more likely to be SR-positive than were HPG III specimens. HPG II tumors were intermediate in SR content. Thus, the higher the grade, the lower the frequency of receptor. The level of significance is lower in the premenopausal patients ($P < 0.05$), probably because there were fewer patients in each group. Thus, the menopausal status of the patient does not appear to influence the relationship between ER and HPG. The same relationship is observed for PR and HPG which is not unexpected since there is a significant correlation between PR and the presence of ER. Similarly, when the presence of both receptors is considered with respect to grade, the same relationship holds. Thus, tumors with a higher HPG have a lower percentage of receptor positivity, perhaps indicating a lower percentage of endocrine-dependent tumors.

Table 3 shows that ER content in tumors increases with advancing age of patients. However, HPG could not be correlated with the concentration of ER in the tumor.

Histological Types. To examine a possible relationship between SR and the degree of differentiation of breast cancer, SR content was investigated in relation to HT in 311 lesions (Table 4). The ER content could not be statistically related to the HT of tumors. As previously described, this is due to the wide range of SR values and to the relatively small number of cases of differentiated carcinoma. However, it should be noted that the mean ER content decreases as the degree of differentiation increases. This is particularly evident between the well-differentiated and the atypical adenocarcinomas.

The most commonly found HTs were correlated with the presence of SR (Tables 4 and 5). It is apparent that the presence of receptors is related to the degree of differentiation of the acinoductal system ($P < 0.05$). The most highly differentiated HTs (well-differentiated and polymorphic, over 50% differentiated types) were associated with a higher frequency of SR than the less highly differentiated types ($P < 0.03$). Thus it appears that these tumors can be grouped into class I (well-differentiated types and polymorphic types with over 50% differentiation) and class II tumors (the less highly differentiated: polymorphic with less than 50% differentiation and atypical breast cancers).

Because of their small populations and their own prognostic values, lesions with an unusual HT have been examined separately. Twelve of thirteen lobular infiltrating (92%) and six of seven intraductal (86%) carcinomas were found to be ER-positive. For these HTs, PR was associated with ER in 50% and 57% of cases, respectively. The six cases of medullary carcinoma were equally distributed between positive for both ER and PR

Table 3. Relationship between HPG and ER content (fmol/mg protein)

Histoprognostic grade	I		II		III	
Age (years)	< 50	> 50	< 50	> 50	< 50	> 50
Sample (n)	13	31	32	93	35	74
ER presence (%)	75%	88%	66%	70%	48%	46%
ER content	75 ± 53	295 ± 272	71 ± 68	230 ± 310	113 ± 144	248 ± 350

Table 4. Relationships between HT and SR presence and content (fmol/mg protein; mean ± SD) in mammary carcinomas

Histological type	Well-differentiated		Polymorphic				Atypical	
			Differentiation < 50%		Differentiation > 50%			
Age (years)	<50	>50	<50	>50	<50	>50	<50	>50
Sample (n)	8	18	4	33	37	87	31	60
ER presence (%)	75%	78%	75%	85%	57%	71%	58%	58%
PR presence (%)	75%	78%	75%	70%	51%	58%	45%	46%
ER content	60 ± 38	134 ± 125	63 ± 24	235 ± 246	166 ± 192	252 ± 310	$n = 18$[a] 241 ± 310 $n = 15$ 118 ± 115	221 ± 350

[a] ER content is given for total group ($n = 18$) and then ($n = 15$) after withdrawal of the three specimens with the highest ER concentrations (ER > 1,000 fmol/mg protein)

Table 5. Distribution of steroid receptors by HT of mammary carcinoma

Histological type	Well-differentiated		Polymorphic				Atypical	
			Differentiation < 50%		Differentiation > 50%			
Age (years)	<50	>50	<50	>50	<50	>50	<50	>50
Sample (n)	8	18	4	33	37	87	31	60
Receptor populations in breast cancer:								
ER + PR +	5	11	2	21	14	45	11	22
ER + PR −	1	3	1	7	7	17	7	13
ER − PR +	1	3	1	2	5	6	3	6
ER − PR −	1	1	−	3	11	19	10	19

Table 6. Estrogen receptor content and presence according to the type of stroma of mammary carcinomas

Type of stroma	Patients below 50 years of age			Patients above 50 years of age		
	Samples (n)	ER presence	ER content[a]	Samples (n)	ER presence	ER content[a]
Fibrinoid	17	59%	115 ± 145	48	69%	130 ± 132
Fibrohyalin	31	51%	145 ± 211	96	80%	260 ± 396
Lymphocytic reaction	30	73%	110 ± 145	64	73%	221 ± 288

[a] fmol/mg protein: mean ± SD

(3/6) and negative for both ER and PR (3/6). The three cases of colloid (mucinous) lesions were all positive for ER and negative for PR. From the histopathological point of view, the lobular infiltrating and ductal carcinomas have retained the differentiation characteristics of the mammary gland. This is not the case for the medullary tumors.

The results indicate that whatever the HT, the presence of SR is linked to the degree of differentiation of the carcinoma.

Stromal Reaction. The stromal reaction was correlated with ER in 311 breast cancers. The results presented in Table 6 show that neither the presence nor the content of ER could be statistically related to the stroma reaction of the tumor. However, there is a difference ($P < 0.1$) in the frequency of ER between the fibrinoid and the lymphocytic reactions.

A statistically significant relationship between the intensity of the lymphatic reaction and the absence of ER has been described by Rosen et al. [33]. Our own findings are not in agreement with this observation. Since we have previously demonstrated that a high inflammatory cell infiltration could cause the loss of SR during storage of samples and/or in the SR determination [25], a technical feature could be the reason for this discrepancy.

Comparison of the stroma reaction and the age of patients in ER-positive tumors reveals a significant relationship ($P < 0.05$) between the distribution of lymphocytic and fibrohyalin stroma reactions according to the age of patients (data not shown). The lymphocytic reaction is found with a higher frequency in premenopausal than in postmenopausal patients. This is in agreement with the current concept that the immune system is more effective in younger than in older patients [2].

Discussion

Since the initial studies relating the presence of SR in tumors responsive to endocrine therapy [10, 20, 22], SR determination has been extensively used as a guide for endocrine therapy, so that the patients with SR-negative tumors can be spared the trauma of surgery that would not be beneficial [27, 28, 31]. It is only recently that a prognostic role has been suggested for SR, because the absence of ER in tumors was found to be associated with a higher frequency of early recurrences than has been seen in ER-positive carcinomas [19].

With respect to endocrine therapy, histological and pathologic features have not been frequently utilized for therapeutic guidance. No correlations were found between the histopathological type of tumors and response to adrenalectomy or oophorectomy [8]. Nevertheless, it is of interest that the medullary carcinomas revealed a 57% response to endocrine surgery and that we found that 50% of these tumors had both ERs and PRs [8]. In contrast, HPG and histopathology of the tumors are useful tools for the diagnosis and the prognosis of malignant lesions [6]. Several reports on relatively small numbers of specimens have failed to show any relationship between the ER content and the morphological features of a primary carcinoma [11, 12, 16, 21, 30, 33, 34, 37, 38].

To determine whether SR could be related to the state of differentiation and/or the rate of cellular replication of cancer cells, we related SR presence with TCD, HPG, and HT of 314 carcinomas.

Previous work [24, 25, 26] and the results reported here allow several conclusions about steroid receptors in breast cancer. Both incidence and absolute receptor level increase with the age of patients; a significant difference is observed between the patients below and those above 50 years of age, which is the age corresponding to the occurrence of the menopause in this population. Since the higher rates of incidence of breast cancer are found in women from 50–70 years of age, the majority of patients were postmenopausal. We have shown that the presence of PR is closely linked with the presence of ER. Most of the correlations found for PR are probably due to this relationship. According to the degree of dedifferentiation, both ER and PR contents vary widely from sample to sample. PR being linked to ER, PR content depends only upon the functional capacity of the SR system, the hormonal status, and the evolutionary phase of the disease. ER content, in contrast, increases with advancing age. No 'normal baseline values' could be established for either type of receptor. The well-differentiated and polymorphic tumors with more than 50% differentiation show a higher frequency of SR presence than the less highly differentiated tumors. The same relationship between SR presence and the status of differentiation is revealed in breast cancers with unusual HT, the likelihood of positive ER tumors being much higher in lobular infiltrating and intraductal carcinoma than in the medullary lesions. This last point has been previously suggested by Rosen et al. [33]. These findings, confirmed by the high incidence ER-positive tumors in the HPG I group, led us to the conclusion that the acinoductal differentiation in a tumor is associated with the presence of the steroid receptor system. It is interesting to note that well-differentiated tumors tended to be ER-positive more frequently but to have a lower absolute ER content than the undifferentiated tumors. The less highly differentiated tumors had a low frequency of ER positivity but a higher mean ER level. In addition, in this group there was a lower frequency of PR and a higher number of ER-positive, PR-negative tumors. This lower incience of PR and dissociation of ER and PR in the undifferentiated tumors is unexplained, but it may reflect a greater number of endocrine-independent cells in this group. Since a sequential clonal selection of breast cancer cells has been proposed as an irreversible mechanism for progression from the natural hormone dependence to endocrine autonomy [18], perhaps SR assays in addition to histopathological examinations would improve our ability to pinpoint the evolutionary phase of an individual tumor.

In comparing the HPG and presence of SR in 278 mammary carcinomas, we found an inverse correlation between HPG and SR. Low HPG is accompanied by a high frequency of ER. This result confirms a relationship between SR and the degree of differentiation of tumors. Furthermore, since nuclear pleomorphism and mitotic activity are important in the HPG, these data suggest that tumors with SR are associated with a low rate of cellular division. This is in agreement with the works of Meyer et al. [32], who showed that primary breast tumors with rapid rates of cellular replication, as represented by a high thymidine labeling index (TLI), present a low incidence of ER. We present data that support a prognostic role for SR. The association of HPG I with SR confirms the good prognostic value of SR-containing tumors. A poorer prognosis for HPG III tumors [3, 4], where SRs are often absent, supports the same idea.

From a therapeutic standpoint this could be of importance, since chemotherapy exerts its cytotoxic activity throughout the mechanism involved in cellular replication, thus leading to cell death [23]. The association of HPG III tumors with the abscence of SR but with a rapid rate of cell division could explain the observations that these tumors are most likely to respond to chemotherapy [5]. In contrast, one could speculate that patients bearing a breast tumor in which both ER and PR are associated with HPG I and differentiated carcinomas might fail to benefit from chemotherapy or radiotherapy.

As in previous work [24, 26], we have found that the ER content is not related to TCD. This suggests, in agreement with McGuire et al. [20], that there could be several populations of cancer cells in a tumor. The SR determination would indicate whether some of them have retained hormone dependence. This has led us to the conclusion that in SR-positive cases perhaps a combination of chemotherapy and hormonal treatment is indicated to treat both hormone-dependent and -independent cells.

In this paper, we report findings that could be used to improve the choice of the components of this combination. Since SR are associated with a slow rate of tumor growth, perhaps chemotherapy in addition to an active hormonotherapy would yield the best results in highly SR-positive tumors. The opposite situation might exist for less strongly SR-positive tumors with active cellular division, where an intense chemotherapy might be more efficient.

Acknowledgements: We gratefully acknowledge the cooperation of our collaborating surgeons and physicians: J. M. Spitalier, Y. Aime,

H. Brandone, L. Piana, and H. Serment. The authors wish to thank Mr. J. Ingrand and the Service d'Iconographie (I.P.C.) for their editorial assitance.

PHR is a fellow of the Ligue Nationale Française de Lutte contre le Cancer. This work was supported by INSERM, CRAT 76-1-491-C.

References

1. Beatson, G. T.: On the treatment of inoperable cases of carcinoma of the mamma: Suggestion for a new method of treatment with illustrative cases. Lancet **1896 II,** 104–107
2. Berg, W.: Inflammation and prognosis in breast cancer. A search for host resistance. Cancer **12,** 714–720 (1959)
3. Bloom, H. J. G.: Prognosis in carcinoma of the breast. Br. J. Cancer **4,** 259–288 (1950)
4. Bloom, H. J. G., Richardson, W. W.: Histological grading of prognosis in breast cancer. A study of 1409 cases, of which 359 have been followed 15 years. Br. J. Cancer **31,** 359–371 (1957)
5. Bonadonna, G., Rossi, A., Valagussa, P., Banfi, A., Veronesi, U.: The CMF program for operable breast cancer with positive axillary nodes. Cancer **39,** 2904–2915 (1977)
6. Contesso, G., Rouesse, J., Caem, J. L.: Facteurs anatomo-pathologiques du prognostic des cancers du sein. Ann. Anat. Pathol. (Paris) **18,** 373–388 (1973)
7. Fisher, E. R., Gregorio, R. M., Fisher, B.: The pathology of invasive breast cancer. Cancer **36,** 1–85 (1975)
8. Fracchia, A. A.: Indications for castration and adrenalectomy for advanced breast cancer. Cancer **28,** 1699–1701 (1971)
9. Gerschenson, L. E., Conne, E., Murai, J. T.: Regulation of the cell cycle by diethyl-stilbestrol and progesterone in cultured endometrial cells. Endocrinology **100,** 1468–1471 (1977)
10. Hahnel, R., Twaddle, E.: Estradiol binding by human breast carcinoma cytosols: The influence of commonly used reference parameters on the results. Eur. J. Cancer **14,** 125–131 (1978)
11. Hahnel, R., Vivian, A. B.: Biochemical and clinical experience with the estimation of estrogen receptors in human breast carcinoma. In: Estrogen receptors in human breast cancer. McGuire, W. L., Carbone, P. P., Vollmer, E. P. (eds.), pp. 205–235. New York: Raven Press 1975
12. Heuson, J. C., Longeval, E., Mattheiem, W. H., Deboel, M. C., Sylvester, R. J., Leclercq, G.: Significance of quantitative assessment of estrogen receptors for endocrine therapy in advanced breast cancer. Cancer **39,** 1971–1977 (1977)
13. Horwitz, K. B., McGuire, W. L.: Predicting response to endocrine therapy in human breast cancer: A hypothesis. Sciences **189,** 726–727 (1975)
14. Jensen, E. V., Suzuki, T., Kawashima, T., Stumpf, W. E., Jungblut, P. W., Desombre, E. R.: A two-step mechanism for the interaction of estradiol with rat uterus. Proc. Natl. Acad. Sci. USA **59,** 632–638 (1968)
15. Jensen, E. V., Block, G. E., Smith, S., Desombre, E. R.: Hormonal dependency of breast cancer. Recent Results Cancer Res. **42,** 55–62 (1973)
16. Jensen, E. V., Smith, S., Desombre, E. R.: Hormone dependency in breast cancer. J. Steroid. Biochem. **7,** 911–917 (1976)
17. Kiang, D. T., Kennedy, B. J.: Factors affecting estrogen receptors in breast cancer. Cancer **40,** 1571–1576 (1977)
18. Kim, U., Depowski, M. J.: Progression from hormone dependence to autonomy in mammary tumors as an in vivo manifestation of sequential clonal selection. Cancer Res. **35,** 2068–2077 (1975)
19. Knight, W. A., Livingston, R. B., Gregory, E. J., McGuire, W. L.: Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer. Cancer Res. **37,** 4669–4671 (1977)
20. Korenman, S. G.: Estrogen receptor assay in human breast cancer. J. Natl. Cancer Inst. **55,** 543–545 (1975)
21. Leclercq, G., Heuson, J. C., Mattheiem, W. H.: Estrogen receptors in human breast cancer. Eur. J. Cancer 7 55–673 (1973)
22. Lippman, M. E., Osborne, C. K., Knazeck, R., Young, N.: In vitro model system for the study of hormone-dependent human breast cancer. N. Engl. J. Med. **296,** 154–159 (1977)
23. Livingston, R. B., Hart, J. S.: The clinical applications of cell kinetics in cancer therapy. Annu. Rev. Pharmacol. Toxicol. **17,** 529–543 (1977)
24. Martin, P. M., Rolland, P. H., Jacquemier, J., Rolland, A. M., Toga, M.: Estradiol receptors (ER) in human breast cancer: Necessity of correlation with anatomopathologic examinations. Reviews on Endocrine Rel. Cancer (In press, 1978)
25. Martin, P. M., Rolland, P. H., Jacquemier, J., Rolland, A. M., Toga, M.: Multiple steroid receptor in human breast cancer. I. Technological features. Biomedicine **28,** 278–287 (1978)
26. Martin, P. M., Rolland, P. H., Jacquemier, J., Rolland, A. M., Toga, M.: Multiple steroid receptors in human breast cancer. II. Estrogen and progestin receptors in 672 primary tumors. Cancer Chemother. Pharmacol. (In press, 1978)
27. McGuire, W. L., Chamness, G. C.: Studies on the estrogen receptor in breast cancer. In: Receptors for reproductive hormones. O'Malley, B. W., Means, A. R. (eds.), pp. 113–116. Plenum Press 1973
28. McGuire, W. L., Chamness, G. C., Costlow, M. E., Sheperd, R. E.: Hormone dependence in breast cancer. Metabolism **23,** 75–100 (1974)
29. McGuire, W. L., Horwitz, K. B., Chamness, G. C., Zava, D. T.: A physiological role for estrogen and progesterone in breast cancer. J. Steroid Biochem. **7,** 875–882 (1976)
30. McGuire, W. L., Horwitz, K. B., Pearson, O. H., Segaloff, A.: Current status of estrogen and progesterone receptors in breast cancer. Cancer **39,** 2934–2947 (1977)
31. McGuire, W. L., Raynaud, J. P., Baulieu, E. E.: Progesterone receptors in normal and neoplastic tissues. In: Progress in cancer research and therapy, Vol. 4. New York: Raven Press 1977
32. Meyer, J. S., Rao, B. R., Stevens, S. C., White, W. L.: Low incidence of estrogen receptor in breast cancer with rapid rates of cellular replication. Cancer **40,** 2290–2298 (1977)
33. Rosen, P. P., Menendez-Botet, C. J., Nisselbaum, J. S., Urban, J. A., Mike, V., Fracchia, A. A., Schwartz, M.: Pathological review of breast lesions analyzed for estrogen receptor protein. Cancer Res. **35,** 3187–3194 (1975)
34. Saez, S., Mayer, M.: Facteurs hormonaux de prévision d'hormonodépendance du cancer du sein. Bull. Cancer (Paris) **64,** 557–566 (1977)
35. Sakai, F., Saez, S.: Existence of receptors bound to endogenous estradiol in breast cancers of premenopausal and postmenopausal women. Steroids **27,** 99–110 (1976)
36. Scarff, R. W., Torloni, H.: An histological typing of breast tumors. In: Coll. International Histological Classification of Tumors, No. 2, pp. 204–408. Geneva: WHO 1968
37. Walt, A. J., Singhakaowinta, A., Brooks, S. C., Cortez, A.: The surgical implications of estrophile protein estimations in carcinoma of the breast. Surgery **80,** 506–512 (1976)
38. Wittliff, J. L., Hilf, R., Brooks, W. F., Savlov, E. D., Hall, T. C., Orlando, R. A.: Specific estrogen-binding capacity of the cytoplasmic receptor in normal and neoplastic breast tissues of human. Cancer Res. **32,** 1983–1991 (1971)

Received May 1978/Accepted October 11, 1978