J Cancer Res Clin Oncol 98, 173–183 (1980)

Journal of
Cancer Research
and
Clinical Oncology

Multiple Steroid Hormone Receptors in Normal and Abnormal Human Endometrium*

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Summary. The cytoplasmic concentrations of ER, AR, PR, and GR were determined in 124 specimens of normal and abnormal endometrium and other uterine human tissues by the DCC technique. In the endometrial carcinoma group, we observed that pretreatment with MAP leads to low cellularity, higher amount of AR, lower amounts of detectable ER, GR, and PR: the last receptor was almost always absent. A positive correlation between ER presence and tumor grade of differentiation was found in endometrial tumors from hormone-untreated patients. With the value of 142 fmol/mg DNA as the cut off point between high and low binding capacity, the frequency of the single receptors within the hormone-untreated cancer group ranged from 61% to 88%; ER and PR were simultaneously present in 55% of cases (they are tightly correlated in the different biopsies with respect to frequency and amount); ER-AR-PR were present in 45% and all the four receptors in 40% of cases. Slightly higher values were found in normal endometrium collected from hormone-untreated patients.

Key words: Steroid hormone receptors – Human endometrium – Endometrial carcinoma

Data on the presence of cytoplasmic ER and PR in normal and pathologic human tissues are becoming more and more frequent in literature. In the beginning, search was focused on normal endometrium (Haukkamaa et al. 1971; Ramanath Rao et al. 1971; Notides et al. 1972; Evans et al. 1973; Trams et al. 1973; Verma et al. 1973;

* This work was supported by a grant from Ministero della Pubblica Istruzione, Rome and "Donazione Testoni", Bologna, Italy

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Abbreviations. ER = 17β-estradiol receptor; AR = 5α-dihydrotestosterone receptor; PR = progesterone receptor; GR = glucocorticoid receptors; α-DHT = 5α-dihydrotestosterone; β-DHT = 5β-dihydrotestosterone; MAP = medroxyprogesterone acetate; P = progesterone; F = cortisol; T = testosterone; E = 17β-estradiol; DES = diethylstilbestrol; TEBG = testosterone-estradiol binding globulin; CBG = corticosteroid binding globulin; DCC = dextran-coated charcoal; R 1881 = methyltrienolone; Kd = dissociation constant

0171-5216/80/0098/0173/$2.20

Table 1. Clinical and histological data concerning all the biopsies examined

		Biopsy	Patients no.[a]		Postmenopausal patients (no.)	Age (yr)
Endometrium	Normal	Proliferative	13 (1[b])		1	44.79 ± 1.10
		Secretory	11		1	
		Hyperplastic	10 (1[b] + 1[c])		3	51.30 ± 1.89
		Atrophic	4 (1[b] + 1[c])		3	
	Benign	Polyp	1 (1[c])		1	54.25 ± 2.53
		Adenoma	4 (1[c])		1	
	Malignant	Primary carcinoma	33	(19 grade I)	16	60.43 ± 1.04
				(13 grade II)	10	
				(1 grade III)	0	
		Primary carcinoma	33[c]	(18 grade I)	15	
				(13 grade II)	13	
				(2 grade III)	2	
		Metastatic carcinoma	2		2	
		Mesodermic mixed tumor	2		2	
		Sarcoma	3		2	
	Myometrium	Normal	3 (1[b])		2	
		Fibroma	2		1	
	Cervix	Normal	1 (1[b])		0	
		Carcinoma	2 (1[b] + 1[c])		1	

[a] In parentheses the number of patients who underwent hormone therapy before biopsy collection
[b] From patients who received continuously estro-progestins p.o. before biopsy collection
[c] From patients who received i.m. 1 g MAP/day during the week prior to surgery (Bonte 1972)

Crocker et al. 1974; Young and Cleary 1974; Pollow et al. 1975, 1977; Daxenbichler et al. 1977; Janne et al. 1977; Martin et al. 1979; Prodi et al. 1979) and only more recently data on an adequate number of cases of endometrial carcinoma (Haukkamaa et al. 1971; Terenius 1973; Evans et al. 1973; Crocker et al. 1974; Pollow et al. 1975, 1976, 1977; Gustafsson et al. 1977; Janne et al. 1977; Martin et al. 1979; Prodi et al. 1979) have became available. Moreover, data on direct or inverse correlations between ER (Terenius et al. 1971; Evans et al. 1973; Pollow et al. 1975, 1977; Janne et al. 1977; Friberg et al. 1978) and PR (Pollow et al. 1975, 1976, 1977; Young et al. 1976; Janne et al. 1977; Martin et al. 1979) presence and tumor grade of differentiation have been reported as well as data on the absence of any relationship (Haukkamaa et al. 1971; Gustafsson et al. 1977). In endometrial carcinoma, very limited data (Friberg et al. 1978; Prodi et al. 1979) are available on the binding of α-DHT, while the frequency of GR in the same tissues is given in only one paper (Prodi et al. 1979) which reports some of the cases of the present study.

Material and Methods

The human uterine tissues from diagnostic curettage and hysterectomy for malignant lesions or other pathologies, were collected between March 1976 and April 1979. Non-neoplastic specimens were assessed as proliferative, secretory, hyperplastic, or atrophic endometrium by histological criteria whereas

Table 2. Details on the method employed in determining steroid hormone receptors

		ER	AR	PR	GR
Minimal amount of tissue:		100 mg for each receptor determination			
Buffer[a]:		10 m*M* Tris- 1 m*M* EDTA- 250 m*M* sucrose (pH 8.0) at 0 – +4 °C			
Cytosol isolation:		ultracentrifugation at 105000 g for 1 h at 0 – +4 °C			
Cytosol protein concentration:		0.5 – 3.0 mg/ml			
Aliquot of cytosol used for incubations:		0.2 ml			
Tracer[b]	Series (+) 0.18 – 2.70 n*M*:	[^{3}H] E	α- [^{3}H] DHT + 333-fold molar excess radioinert β – DHT[c]	[^{3}H] P + 333-fold molar excess radioinert F	[^{3}H] F
	Series (–) the same + 333-fold molar excess radioinert:	DES[d]	α-DHT + β-DHT[c]	P + F	Aldosterone[e]
Incubation	Temperature (°C):	30	0	0	0
	Time (min):	30	60	60	60
Further incubation with DCC (0.25% charcoal and 0.025% dextran-T 70) for (min):		10	15	5	0.5
Binding parameters[f] to be assessed for receptor presence:		1) Specificity, by further trials with strong competitors[g] 2) Affinity (Kd in the order of 10^{-9} *M*) 3) Amount higher than 142 fmol/mg DNA[h]			

[a] For comparisons with other buffers quoted in literature see: Galli et al. (1978); Grilli et al. (1978); Prodi et al. (1979)
[b] Purchased from The Radiochemical Centre, Amersham, England. Specific acticities (Ci/m*M*): 115, 48, 101, 85, respectively. Purity: over 98%
[c] Which is capable of discriminating between TEBG and AR (Lippman et al. 1976b; Galli et al. 1978; Prodi et al. 1979)
[d] Which binds to receptor but does not bind to TEBG
[e] Which binds to GR (Teulings and van Gilse 1977; Prodi et al. 1979) but does not bind to CBG (Chen et al. 1961; Prodi et al. 1979)
[f] Calculated according to Scatchard (1949)
[g] See: Galli et al. (1978); Grilli et al. (1978); Prodi et al. (1979). No difference was found between normal and pathological tissue cytosols
[h] See Table 3

only the supericial part of the vegetating tumors was taken after surgery for receptor analysis: a frozen section of the adjacent tissue was prepared and examined by the pathologist to exclude contaminations by normal tissue which were virtually absent in all the cases included in our series. No patients received chemo- or radiotherapy before surgery and only a part of them underwent hormone treatment, as reported in Table 1, which also shows the most important details. In each patient, the plasma levels of T, E, P, α-DHT, F, FSH, and LH were assayed before surgery.

Tissue aliquots from biopsies were immediately placed in saline at 0 to +4 °C and transferred to the laboratory, where they were processed immediately or kept at −25 °C for a maximum of 1 month.

In determining cytoplasmic receptors concentration, we used a DCC method (Grilli et al. 1977; Galli et al. 1978; Prodi et al. 1979) which employs natural hormones as tracers and is capable of detecting receptor amounts lower than 1 fmol per mg protein (De Giovanni et al. 1978). As regards PR dosage, we underline that (Grilli et al. 1978): (I) the employment of [^{3}H] MAP (58 Ci/m*M*), purchased from New England Nuclear, Dreieich, FRG, in the absence of an excess of cold cortisol gave, in endometrial and mammary carcinomas, results quite comparable to those obtained when [^{3}H] P was used; (2) the tracer [^{3}H] R 1881 (55.5 Ci/m*M*), a kind gift from Dr. Raynaud, Roussel-Uclaf, Romainville, France, was shown to be unsatisfactory in AR estimation since it also binds to PR; (3) the method did allow isotopic exchange.

The criteria to establish receptor presence are briefly shown in Table 2: more details on method, chemicals, radiochemicals, and competition trials performed to further confirm the binding specificity are given in previous papers (Galli et al. 1978; Grilli et al. 1978; Prodi et al. 1979).

Statistical evaluation was performed by Student's t-test and Fisher's factorial χ^2-test and simple regression analysis using a CDC CY76 computer.

Results and Discussion

As regards E, P, FSH, and LH plasma levels, the only differences found were related to menopausal status, except for E, T, and F plasma concentrations which were lower ($P<0.05$) in premenopausal patients with endometrial carcinoma (E 27.79 ± 5.16 pg/ml; T 0.32 ± 0.05 ng/ml; F 95.75 ± 18.48 ng/ml) than in premenopausal patients free of tumor (E 96.40 ± 21.34; T 0.51 ± 0.05; F 190.00 ± 18.18). This data is in contrast with that of Reed et al. (1978) who found no differences in T and F plasma levels between patients with and without neoplastic disease.

No relationship between hormone plasma levels (which were in the lower normal limits) and related receptor amounts was observed: this seems to indicate that DCC method is capable of detecting both filled and unfilled cytoplasmic receptors.

The criteria used in choosing the cut off point between high and low binding capacity, based on the comparison of cellularity (expressed as DNA yield per g of tissue) between endometrial and mammary neoplasms (Nicoletti et al., submitted), are given in Table 3.

In receptor evaluation, biopsies taken from MAP-pretreated women have been considered separately since this hormone treatment led to lower cellularity ($P<0.01$, Table 4). When the negative cases were also included, it appeared that the same pretreatment further led to higher AR amount (fmol per mg DNA or protein), lower ER and GR amounts (fmol per mg protein) and, above all, lower concentration of PR, which was almost always absent: this agrees with previous data (Janne et al. 1977; Martin et al. 1979). The disappearance of cytoplasmic PR in endometrial specimens from MAP-pretreated tumor-bearing patients could be due to receptor occupation with non-labeled MAP from high-dosage treatment, receptor shifting into nucleus and/or to a direct toxicity affecting receptor resynthesis. We also wish to underline that MAP-pretreatment led to slight decrease in E and F plasma concentrations.

Table 3. Basis of the cut off point between high and low binding capacity in endometrial tumors

Biopsy	No. of cases	Tissue DNA yield[a] (mg/g)	Minimal significant amount of receptor (fmol/mg DNA)
Hormone-untreated breast neoplasms[b]	153	0.956 ± 0.071	47[c]
Hormone-untreated endometrial neoplasms	43	2.891 ± 0.218	142[d]

[a] Mean ± S.E.
[b] Our series (Nicoletti et al. submitted)
[c] Corresponding to at least 3 fmol per mg protein (Horwitz et al. 1975)
[d] Obtained multiplying 47 by 3.02 (ratio: endometrium/breast DNA yield)

Table 4. Preoperative MAP-administration to endometrial carcinoma-bearing patients: effect on cellularity and steroid hormone receptors occurrence

Biopsy	Tissue DNA yield[a] (mg/g)	Receptor			
		ER^+	AR^+	PR^+	GR^+
MAP-untreated carcinoma	3.02 ± 0.26[c]	22/33 = 67%	22/33 = 67%	20/33 = 61%	22/25 = 88%
MAP-pretreated carcinoma[b]	2.14 ± 0.18[c]	21/33 = 64%	24/32 = 75%	5/33 = 15%[c]	24/26 = 92%

[a] Mean ± S.E.
[b] Patients who received i. m. 1 g MAP/day during the week prior to surgery
[c] $p < 0.01$

Table 5 shows the steroid receptor frequency and amount in the main biopsy groups. We wish to emphasize that the ratios of receptor amount (fmol per mg DNA) between proliferative and secretory endometrium were: 2.75, 2.78, 0.92, and 3.00 for ER, AR, PR, and GR, respectively. The data on ER agrees with previous findings showing a higher ER amount in proliferative phase than in secretory phase (Evans et al. 1973; Trams et al. 1973) whereas PR amount was shown to be the highest around the time of ovulation by Pollow et al. (1977). Furthermore, steroid hormone receptors were also present in endosarcoma.

As far as ER is concerned, there was a trend to a direct correlation between ER presence and tumor grading ($P = 0.12$) since ER^+ cases were: 15 of 19 in grade I, 7 of 13 in grade II, and 0 of 1 in grade III endometrial carcinoma. Such a correlation became fully significant ($P < 0.05$) when the two mesodermic mixed tumors (both grade III, ER^- and PR^-) where included. This data is in agreement with those of Terenius et al. (1971), Evans et al. (1973), and Janne et al. (1977), but does not agree with other reports where negative correlations (Pollow et al. 1975, 1977) or absence of correlation (Crocker et al. 1974) are reported. ER frequency in normal endometrium was lower in biopsies from premenopausal patients than in specimens collected from postmenopausal women ($P < 0.05$). Furthermore, ER

Table 5. Multiple steroid receptors occurrence and amount[a] in the main groups of normal and pathologic human endometrial tissues from hormone-untreated patients

Biopsy	Receptor	Occurrence	Amount	
			fmol/mg protein	fmol/mg DNA
Proliferative	ER[b]	8/11 = 73%	206 ± 87	3,300 ± 1,620
	AR	7/10 = 70%	174 + 40	2,450 ± 940
	PR	8/11 = 73%	271 ± 89	3,820 ± 1,670
	GR	7/7 = 100%	501 ± 159	2,970 ± 1,220
Secretory	ER	8/11 = 73%	185 ± 35	1,200 ± 330
	AR	6/7 = 86%	156 ± 14	880 ± 230
	PR	6/9 = 67%	579 ± 191	4,130 ± 1,690
	GR	4/4 = 100%	312 ± 111	990 ± 220
Hyperplastic	ER[b]	7/7 = 100%	346 ± 202	810 ± 200
	AR	5/5 = 100%	93 ± 23	450 ± 130
	PR	6/7 = 86%	183 ± 32	1,180 ± 330
	GR	6/6 = 100%	361 ± 93	1,880 ± 540
Adenoma	ER	3/3 = 100%	100 ± 53	480 ± 20
	AR	3/3 = 100%	81 ± 16	560 ± 200
	PR	3/3 = 100%	116 ± 46	610 ± 90
	GR	3/3 = 100%	839 ± 462	5,970 ± 3,430
MAP-untreated carcinoma	ER	22/33 = 67%	146 ± 28	1,300 ± 270
	AR	22/33 = 67%	68 ± 11	680 ± 110
	PR	20/33 = 61%	139 ± 37	1,100 ± 220
	GR	22/25 = 88%	384 ± 60	4,550 ± 1,190
MAP-pretreated carcinoma[c]	ER	21/33 = 64%	67 ± 12	890 ± 130
	AR	24/32 = 75%	62 ± 13	940 ± 220
	PR	5/33 = 15%	18 ± 1	520 ± 160
	GR	24/26 = 92%	328 ± 82	6,100 ± 1,270
Sarcoma	ER	2/3 = 67%	(68 – 182)	(690 – 2,020)
	AR	2/3 = 67%	(135 – 147)	(1,500 – 1,790)
	PR	2/3 = 67%	(156 – 167)	(1,590 – 2,020)
	GR	2/2 = 100%	(461 – 534)	(6,100 – 6,460)

[a] Mean of positive cases ± S.E. (or range)
[b] Not evaluated in one case
[c] From patients who received 1 g MAP/day i. m. during the week prior to surgery

amount (fmol per mg DNA or protein) was higher in normal tissue than in neoplastic biopsies ($P < 0.05$). No significant difference in ER amount between benign and malignant tumors has been observed.

Concerning the PR occurrence in biopsies from untreated patients, no significant difference between normal tissue (74%) and endometrial carcinoma (61%) was noted (Table 6), while there was a trend to significant difference ($0.1 > P > 0.05$) between benign (100%) and malignant (58%) diseases. Furthermore, there was no correlation between grading and PR, in agreement with some reports (Haukkamaa et al. 1971; Gustafsson et al. 1977) and in contrast with other findings (Pollow et al. 1975, 1977; Young et al. 1976; Janne et al. 1977; Martin et al. 1979). PR frequency in neoplastic tissues decreased in postmenopausal women

Table 6. Percentage of steroid hormone receptors occurrence in human endometrial carcinoma and normal (proliferative, secretory, and hyperplastic) endometrium from hormone-untreated patients

No. of receptors	Receptor	Carcinoma	Normal
At least 1	ER	22/33 = 67%	23/29 = 81%
	AR	22/33 = 67%	18/22 = 82%
	PR	20/33 = 61%	20/27 = 74%
	GR	22/25 = 88%	17/17 = 100%
At least 2	ER–PR	18/33 = 55%	17/25 = 68%
	ER–AR	16/33 = 48%[a]	17/22 = 77%[a]
	ER–GR	14/25 = 56%	11/15 = 73%
	PR–AR	17/33 = 52%	15/22 = 68%
	PR–GR	14/25 = 56%	11/17 = 65%
	AR–GR	16/25 = 64%	12/15 = 80%
At least 3	ER–AR–PR	15/33 = 45%[b]	15/22 = 68%[b]
	ER–PR–GR	12/25 = 48%	9/15 = 60%
	PR–AR–GR	12/25 = 48%	9/15 = 60%
	ER–AR–GR	10/25 = 40%[a]	11/15 = 73%[a]
All 4 receptors	ER–AR–PR–GR	10/25 = 40%[b]	9/15 = 60%[b]

[a] $p < 0.05$
[b] $0.10 > p > 0.05$

($P < 0.05$). In disagreement with previous data (Young et al. 1976), we found no relationship between patient age and PR amount: such a correlation was also proven not to exist when other receptors' amounts were considered. Finally, PR amount (fmol per mg DNA or protein) was higher in normal tissue than in neoplastic tissue ($P < 0.01$).

As regards AR occurence, we have found no variation among the different groups: AR frequency observed in endometrial carcinoma (67% and 75% in hormone-treated and hormone-untreated women, respectively) was much higher than that reported by Friberg et al. (1978) (8%) with a similar number of cases, using agar gel electrophoresis. A higher AR amount (fmol per mg protein) was present in normal tissues than in neoplastic biopsies: this significant difference ($P < 0.01$) was mainly due to the menopausal status. We also observed that the AR amount (fmol per mg protein) was lower in the hyperplastic group than in the secretory group ($P < 0.05$) (Table 5).

There was, also, no significant difference among patient groups when GR frequency was considered since this receptor was almost always present. GR amount (fmol per mg protein) was higher in benign tumors than in both malignant and normal tissues ($P < 0.05$). We are unaware of other studies of this parameter in human endometrial specimens.

As regards the receptors occurence in the miscellaneous human uterine specimens, whose results are not given in Table 5, we found that (1) ER and PR were present also in atrophic endometrium in contrast to a previous finding (Haukkamaa et al. 1971); (2) ER and PR were present both in myometrium or fibroma, in agreement with previous data (Farber et al. 1972; Rubin et al. 1972), and in normal or neoplastic cervix, in accordance with other reports (Terenius et al. 1971; Rubin

et al. 1972); (3) the receptors pattern in omental metastasis from a grade III endometrial carcinoma was identical to that of the primary tumor; (4) patient pretreatment with MAP led to PR loss in biopsies of both endometrial benign lesions and cervical carcinoma, as well as in specimens of endometrial cancer (Table 4).

When considering the amounts (fmol per mg DNA) of the different receptors, direct correlations have been obtained between ER and AR ($P<0.05$), between ER and PR ($P<0.01$) and between AR und GR ($P<0.05$), both in normal and neoplastic tissue. Also, significant relationships ($P<0.01$) were found in the occurrence of the same receptor patterns when the bioptic specimens of proliferative, secretory, hyperplastic, and carcinomatous endometrium from hormone-untreated patients were considered as a whole. In particular, we found that 60% of cases were ER^+PR^+, 10% ER^+PR^-, 25% ER^-PR^-, and 5% ER^-PR^+. The strong correlation ($P<0.001$) between ER and PR presence was even observable when endometrial carcinomas were further subdivided according to grading. Horwitz et al. (1975) have never found a single case of breast cancer ER^-PR^+. On the contrary, always in breast cancer, ER^-PR^+ cases have been reported by: Terenius (1973) (one); Bloom et al. (1977) (two); Horwitz and McGuire (1977) (four); Leclercq et al. (1977) (four malignant and further three benign); Pichon and Milgrom (1977) (one); Ramanath Rao and Meyer (1977) (three); McGuire to be publ. (twelve). In our series on breast cancer (Nicoletti et al. submitted) we found ER^-PR^+ in: one fibroadenoma, one normal breast tissue, two ductal and one lobular carcinomas. Furthermore, five ER^-PR^+ cases were also observed is the series of uterine tissue reported here, i.e. one secretory endometrium, one fibroma, two grade II (one from hormone-treated patient) and one grade III endometrial carcinomas. Since it is generally believed that PR presence in target organs is the expression of ER presence and function (Horwitz et al. 1975), these discrepancies (ER^-PR^+) tend to decrease the importance of only one receptor, PR, in predicting the response of breast cancer (Horwitz et al. 1975) and endometrial cancer (Pollow et al. 1976; Young et al. 1976) to hormone treatment. This is further confirmed by clinical data which report that about 80% of breast cancers (Bloom et al. 1977; Horwitz and McGuire 1977; Leclerq et al. 1977; McGuire to be publ.) and endometrial cancers (Martin et al. 1979) respond to hormone mangement only if they are ER^+PR^+. ER^-PR^+ cases show lower, but still significant, response (50%) to this treatment while the response rates for ER^+PR^- and ER^-PR^- cases are 27% and 10%, respectively (McGuire, to be publ.).

Finally, Table 6 reports multiple steroid receptors occurrence in normal and neoplastic groups: in the latter group at least one of the receptors was present in 66%-88% of cases; ER-PR in 55%; ER-AR-PR in 45%, and all four receptors in 40% of the cases. In normal endometrium slightly higher frequencies were noted in the following receptor combinations: ER-AR-PR, ER-AR-PR-GR, and these differencies were near significance ($0.1>P>0.05$).

The whole receptors pattern in tumor biopsies could play an important role in predicting the response to hormone therapy, following what has already been stated in breast cancer (Lippmann et al. 1976a) and also considering that the percentage of random tumor-bearing patients who respond to hormone management is 40%, which is just the identical percentage we found to be $ER^+AR^+PR^+GR^+$.

Table 7. Summary of the main series reporting estrogen and progesterone receptors in human endometrial carcinoma from hormone-untreated patients

Author	Method	Definition of positive receptor value (fmol)	Positive rate of the receptors	
			ER^+	PR^+
Terenius et al. (1971)	Tissue slices	n.g.	7/9 = 77.8%[a]	
Young et al. (1976)	DCC	50 per mg protein		16/23 = 69.6%
Gustafsson et al. (1977)	isoelectric focusing	1 per mg protein		9/11 = 81.8%
Janne et al. (1977)	DCC + sucrose gradient	n.g.	37/37 = 100%	31/37 = 83.8%[b, c]
Pollow et al. (1977)	n. s.	30 per mg protein	30/30 = 100%	24/30 = 80.0%
Martin et al. (1979)	DCC + sucrose gradient	10 per mg protein	54/54 = 100%	32/54 = 59.3%[b]
Present study	DCC	142 per mg DNA	22/33 = 66.7%[a]	20/33 = 60.6%[c]

[a] $p < 0.01$ when compared to the remaining series

[b, c] $p < 0.05$

n.g. = not given; n.s. = not specified if: DCC, isoelectric focusing, agar-gel electrophoresis, sucrose density gradient, gel filtration, or DEAE-Sephadex chromatography

Following this line, we emphasize that there is a sufficient agreement among the various series on ER and PR occurrence in endometrial carcinoma (Table 7) since the slight discrepancies could be easily explained both by the methods employed for receptor quantitation and by differences in the definition for positive receptor value. Furthermore, an increase both in the collection of clinical data related to receptor occurrence (we have not yet data since the follow-up of patients – all stage I or II – is up to now insufficient and at least 3 more years of observation are required) and in findings which will emerge from a routine use of cell (Satyaswaroop et al. 1978) and organ (Iacobelli et al. 1978) culture, will be of great interest.

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Received January 14, 1980/Accepted July 29, 1980