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Human Chorionic Gonadotropin-Like Substance in Plasma of Normal Nonpregnant Subjects and Women with Breast Cancer*

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ABSTRACT. To understand ectopic hormone secretion in cancer we compared the plasma concentrations of the hCG-like substance in normal nonpregnant subjects and in women with breast cancer. In 45 normal men the plasma concentrations did not vary with age (median, 5 pg/ml; range, <3–169) whereas in 45 normal women they increased after menopause (median, 48 pg/ml; range, <5–569, n = 20, $P < 0.0001$). In 56 women with breast cancer the plasma concentrations of the hCG-like substance after menopause were much higher than in normal women (median, 202 pg/ml; range, 14–1561; n = 35; $P < 0.001$), with no abnormally high pituitary gonadotropin values and no relationship with the tumor burden (same median after mastectomy, 198 pg/ml; n = 21). This hCG-like substance was glycosylated and similar to standard hCG according to molecular size, ionic strength, and immunoreactivity.

Our data are compatible with the following conclusions: 1) the plasma concentration of the hCG-like substance is normally very low but dependent on gonadal function in women. Its source might be the pituitary gland or peripheral tissues. 2) Its concentration is much increased in postmenopausal women with breast carcinoma. This increase is found with normal pituitary gonadotropin values and is independent of the tumor burden, suggesting it is of extrapituitary and nontumoral origin. (*J Clin Endocrinol Metab* **58**: 1171, 1984)

ECTOPIC secretion of polypeptide hormones is a frequent and perhaps universal concomitant of neoplasia (1). Direct secretion by tumors has been demonstrated repeatedly; the plasma concentrations of the ectopic hormones are then most often very high and fall when the tumor is removed (2–14). However, the concentrations of polypeptide hormones which are commonly found in the plasma of such patients are most often only moderately increased and there is no clear-cut relationship between tumor burden and circulating hormone levels (15–17). Moreover, in patients operated for lung carcinoma, ectopic ACTH has been found both in the tumor and in nonmalignant tissue distant from the tumor (11, 18). These observations suggest that whereas tumors can secrete ectopic hormones, they may not be the sole or even the main source of this secretion (18).

The significance of ectopic hormone secretion is not well understood either. Such secretion has been viewed as an accident resulting from disordered cell replication and genetic derepression. However, it is not a random event (19) and it can be very reproducible: all lung carcinomas, for instance, contain big ACTH (18). This is difficult to explain by disordered cell replication and chance. In this respect, the recent demonstration that similar polypeptide hormones are normally found in very different tissues raises the possibility that most cells have a constant low level of expression of many peptides and that the concept of ectopic hormone secretion needs to be reevaluated (20, 21).

We found that normal nonpregnant subjects secrete a hCG-like substance (22, 23). Such a substance is also present in many normal tissues (24–28). These findings suggested to us that the ectopic hormone secretion in cancer might simply be a quantitative deviation from normal (22). The purpose of the present work was to explore this hypothesis by comparing the plasma concentrations of the hCG-like substance in normal nonpregnant subjects and in patients with cancer. In order to study possible regulation of this substance by sex steroid hormones in cancer and its relationship with tumor size, we chose to investigate pre- and postmenopausal women with breast cancer, before and after mastectomy.

Subjects and Methods

Subjects

1. Normal subjects (n = 90) were medical students or blood donors of the Belgian Red Cross. None were taking hormones.

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All postmenopausal women were at least 1 yr after their last menses.

2. Women (n = 42) with a localized operable breast cancer were classified according to the International T-N-M classification (29): T for the diameter of the tumor (T_1, less than 2 cm; T_2, 2 to 5 cm; T_3, 5 cm or more) and N_+ for the presence of positive axillary lymph nodes at surgery. Blood from these women for measurement of the hCG-like substance was obtained within the month preceeding the mastectomy. None were taking hormones. They had never received chemotherapy.

3. Women (n = 14) with generalized breast cancer [or M for metastatic (29)]: the evidence of spread being recent. These women had never received hormonotherapy or chemotherapy.

4. Women (n = 21) cured of breast cancer by mastectomy. These women had been treated by total mastectomy on an average of 3.6 yr before the present study (median, 3.3; range, 0.25–16 yr) and had no evidence of residual tumor.

Staging procedures included history, physical examination, complete blood count, chest x-ray film, bone scan and skeletal survey, liver scan and liver function studies.

Purification of plasma hCG

All steps of the procedure were carried out at 4 C as previously described (23). A tracer amount of labeled hCG was added to the plasma ([^{125}I]hCG; SA, ~200 μC/μg; ~1500 cpm/20 ml, *i.e.* <1 pg/ml) in order to calculate the recovery at the end of the purification. An identical amount of labeled hCG was stored apart at this time for the measurement of ^{125}I decay. The tracer was freshly iodinated, eluting as a single peak on Sephadex G-100.

Chromatography on diethylaminoethyl (DEAE)-Sephadex A-50. Plasma (mean vol: 24 ml; SD, 2.0) was dialyzed extensively against distilled water and lyophilized. It was applied then to a column of DEAE-Sephadex A-50 (2.6 × 20 cm) and eluted with a linear gradient between 0.02 and 0.2 M NaCl in 0.04 M Tris-phosphate buffer, pH 8.0. This step was repeated on a smaller column (1.4 × 15 cm) in order to obtain further purification of hCG from human LH (hLH). The eluates were monitored for radioactivity due to ^{125}I-labeled hCG and, in order to eliminate most of the hLH, the hCG peak was collected from the midpoint of its ascending limb.

Gel filtration on Sephadex G-100. The fractions of the hCG peak were pooled, dialyzed, and lyophilized. The final preparation was applied to a column of Sephadex G-100 (1.6 × 86.5 cm) and eluted with 0.01 M sodium phosphate buffer, pH 7.4. The eluates were monitored again for radioactivity, and the tail of the peak was discarded; this further decreased the contamination of hCG by hLH. The elution peaks of dextran blue, standard hCG, hLH, and free α-subunit (hCG-α) were determined in separate experiments. The fractions under the hCG peak were pooled, dialyzed, lyophilized, and finally dissolved in 1 ml 0.05 M phosphate buffer, pH 7.5. The recovery of hCG from plasma was estimated by measuring the radioactivity in the final extract and ^{125}I-decay. The mean recovery of ^{125}I-labeled hCG added to plasma before extraction was 25% (range, 10–42). The recoveries of plasma hLH and hCG-α were measured by RIA. The recovery of hLH averaged 1.2% (range, 0–4.5); that of hCG-α was negligible. The recovery of plasma proteins, measured by the biuret method, was less than 0.1%.

RIAs of hCG, hLH, human FSH (hFSH), and hCG-α

The RIA for hCG was performed by the double antibody technique, as previously described (22, 23). It had a sensitivity of 25 pg/tube and, taking into account the volumes extracted and the recoveries, a sensitivity of up to 3 pg/ml original plasma. With regard to specificity, hLH was the main source of possible cross-reacting material after the purification. The cross-reaction of hLH in the RIA was less than 2%. Human TSH and hFSH did not cross-react and were removed by the purification procedures; hCG-α cross-reacted slightly (0.75%) and was also eliminated by the purification.

hCG was measured in 500–750 μl final extract; hLH was measured separately in 100 μl final extract. The measurement of hCG was corrected for losses and for possible contamination by residual hLH according to the dose-response curves of standard hCG and standard hLH in the RIA carried out with labeled hCG and the antibody to hCG. The comparison of these two dose-response curves allowed determination of the contribution of an amount of hLH equivalent to residual hLH in the RIA of hCG (23).

The RIAs for hLH, hFSH, and hCG-α were performed on the initial plasma and in the final extract, as previously described (22, 23). The immunological potencies of the standards were: 1 mg hCG = 6800 IU MRC 61/6, 1 mg hLH = 4200 IU MRC 68/40, and 1 mg FSH = 3260 IU MRC 69/104.

The results were expressed as the mean ± SD or as the median with the range.

Recovery of ^{125}I-hCG and standard hCG in the purification procedure

To determine whether ^{125}I-hCG can serve as a tracer for hCG in plasma the following study was carried out: ^{125}I-hCG (18, 250 cpm) and standard hCG (82 ng) in 25 ml 0.01 M sodium phosphate buffer, pH 7.4, containing 5% BSA were dialyzed, lyophilized, and processed exactly as a plasma sample. The SA of hCG at the end of the purification procedure was compared to that of the initial standard.

Chromatography on Concanavalin A-Sepharose 4 B

A pool of plasma from postmenopausal women with breast cancer was purified as described above. The resulting preparation was applied to a column of Concanavalin A (0.9 × 8 cm) and eluted first with 20 ml 0.01 M sodium phosphate buffer, pH 7.4, containing 0.9% sodium chloride and 1% BSA; it then was eluted with 20 ml 0.2 M methyl α-D-glucopyranoside (MαGP), and finally with 50 ml 1.25 M MαGP (30).

Immunological characterization

To further characterize the hCG-like substance a pool of plasma from 25 postmenopausal women cured of breast cancer by mastectomy (volume, 593 ml) was extensively purified by chromatography on DEAE-Sephadex A-50 and by gel filtration on Sephadex G-100. The final extract was then dissolved in 1

ml 0.05 M phosphate buffer, pH 7.5 for RIAs. hCG was measured in 100-, 150-, 200-, and 350-μl aliquots by the double antibody technique, using an antiserum against hCG-β (0.3% cross-reaction with hLH; Belgian Radiochemical Centre, Brussels, Belgium), ^{125}I-labeled hCG-β, and a purified hCG standard (31). hCG and hLH were also measured in 50-μl aliquots as described above, by the usual RIA.

Statistical analysis

The Kruskal Wallis H test was used to compare the plasma concentrations of the hCG-like substance in the various populations and the Spearman rank test was used to determine whether or not a correlation existed between the hCG values and other parameters (32).

Results

I. Recovery of ^{125}I-hCG and standard hCG in the purification procedure

^{125}I-hCG and standard hCG migrated together through the whole purification procedure. Indeed, as shown in Fig. 1, their elution profiles on Sephadex G-100 at the end of the purification were still very similar to each other. Furthermore, the SA of hCG after this last step (234 cpm/ng) was practically identical to that of hCG at the beginning of the study (222 cpm/ng). Therefore the recovery of hCG in the final residue was the same when calculated from ^{125}I radioactivity (*i.e.* 14.9%) or from the measurement of hCG by RIA (*i.e.* 14.1%). ^{125}I-hCG could thus serve as a tracer for following hCG at each step of the purification procedure and for measuring its recovery in the final preparation.

II. Normal men

In 45 normal men the plasma concentration of the hCG-like substance ranged from less than 3 to 169 pg/ml (mean, 21.3; median, 5). As shown in Fig. 2 there was no correlation with the age of the subjects, which ranged from 22–62 yr [mean, 37.5 ± 14.1 (SD)]. There was also no correlation with the hLH concentrations [1.36 ± 0.87 (SD) ng/ml] nor with the hFSH concentrations (0.63 ± 0.54 ng/ml).

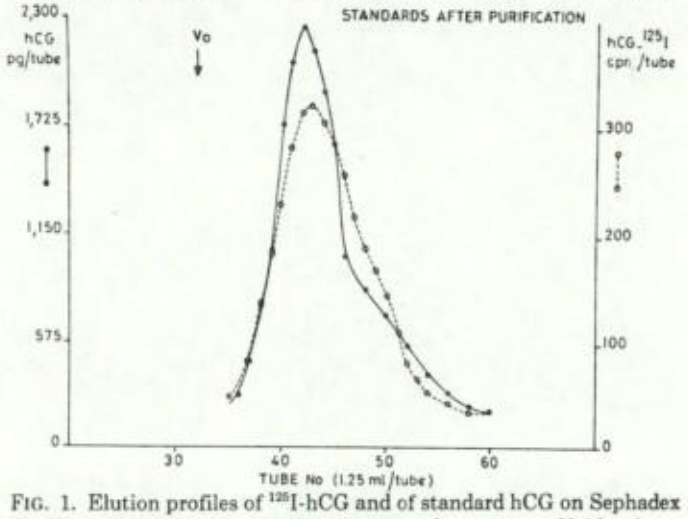

FIG. 1. Elution profiles of ^{125}I-hCG and of standard hCG on Sephadex G-100 at the end of the purification procedure. *Arrow*, Void volume (V_0) as determined by blue dextran elution.

III. Normal women

In 25 premenopausal women (Fig. 3) the plasma concentrations of the hCG-like substance ranged from less than 4 to 45 pg/ml (mean, 5.6; median, <5), but were most often undetectable in the younger women and appeared therefore to be lower than in the men ($P < 0.05$). There was no correlation with age (32.4 ± 10.0 yr) although two women older than 40 yr had definitely

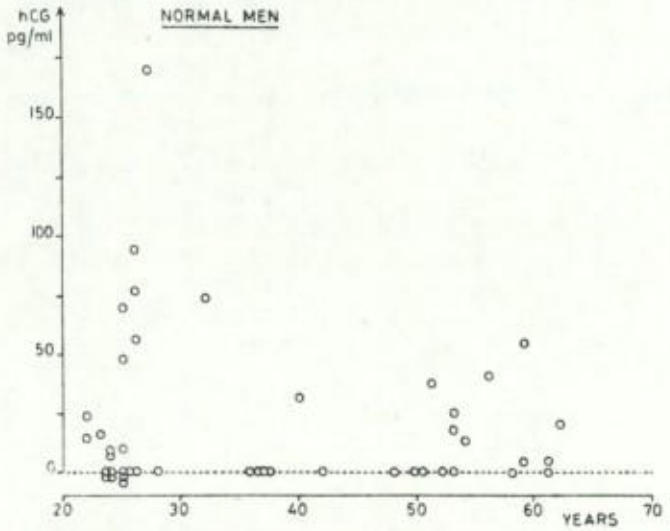

FIG. 2. The plasma hCG-like substance in normal men according to age. There was no relationship between plasma concentrations and age.

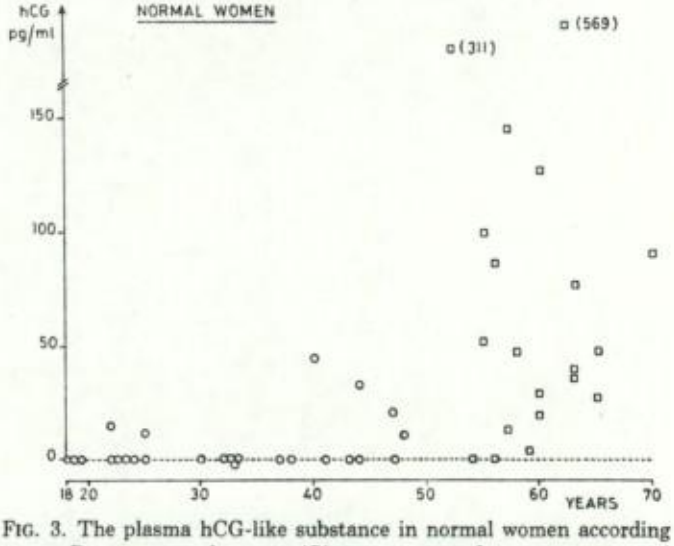

FIG. 3. The plasma hCG-like substance in normal women according to age. Premenopausal women (○) were compared to postmenopausal women (□). The plasma concentrations increased after menopause.

higher values. Also, there was no correlation with hLH concentrations (1.25 ± 0.70 ng/ml) or with hFSH concentrations (2.4 ± 1.05 ng/ml).

In 20 postmenopausal women (Fig. 3) plasma concentrations of the hCG-like substance rose very significantly ($P = 0.000015$), indicating a distinct population. They ranged from less than 5 to 569 pg/ml (mean, 91; median, 48), and also were very significantly higher than in the normal men ($P = 0.0005$). Again, they did not correlate with age (60 ± 4.47 yr), hLH concentrations (11.7 ± 4.34 ng/ml; $P = 0.19$), or with hFSH concentrations (28.3 ± 9.52 ng/ml). However, the latter two correlated with each other ($P < 0.001$).

IV. Women with breast cancer

In 21 premenopausal women (Fig. 4) plasma concentrations of the hCG-like substance ranged from less than 4 to 224 pg/ml (mean, 25.3; median, <6). Most values were low but three women had plasma concentrations definitely above the normal range. There was no correlation with age (44.7 ± 6.8 yr), with hLH concentrations (1.44 ± 1.05 ng/ml), or with hFSH concentrations (2.5 ± 2.25 ng/ml). In addition there was no relationship with the size or the stage of the tumor (Fig. 5).

In 35 postmenopausal women (Fig. 4), plasma concentrations of the hCG-like substance rose considerably ($P < 0.00001$) indicating again a quite distinct population. They ranged from 14–1561 pg/ml (mean, 313; median, 202) and were thus also much higher than in the normal postmenopausal women ($P < 0.001$). These plasma concentrations in the postmenopausal women did not further increase with age (62.9 ± 9.76 yr) (Fig. 4). There was no concomitant hypersecretion of the pituitary gonadotropins: indeed the concentrations of hLH (13.2 ± 5.44 ng/ml) and of hFSH (25 ± 12.0 ng/ml) were similar to those in the normal postmenopausal women. As expected, the hLH and hFSH values correlated with each other ($P < 0.01$). On the other hand, there was no relationship between the hCG-like substance and the size of the tumor, the status of the axillary lymph nodes, or the presence of distant metastases (Fig. 5). In this regard, it is remarkable that the plasma concentrations of the hCG-like substance in the women with the largest tumors (T_3) plus positive axillary lymph nodes and in the women with generalized tumors (median, 185 pg/ml; range, 20–1340; n, 14) were not significantly different from those of the women with smaller tumors (T_1, T_2) and negative axillary lymph nodes (median, 295 pg/ml; range, 14–1561; n = 10).

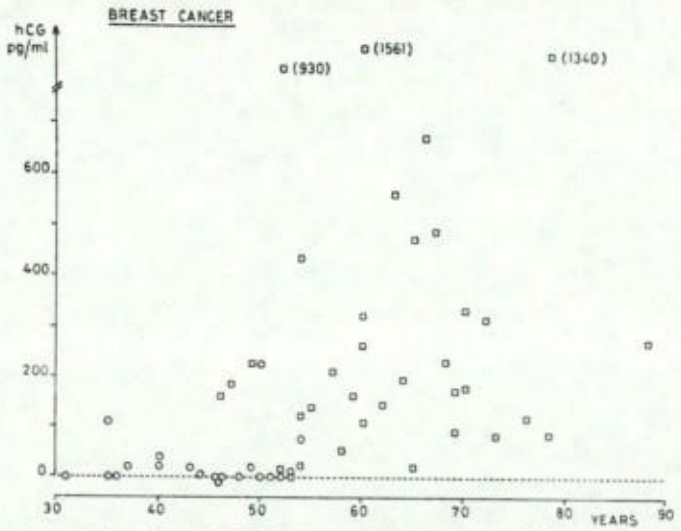

FIG. 4. The plasma hCG-like substance in women with breast cancer according to age. In most premenopausal women (○) the plasma concentrations were low but in the postmenopausal women (□) they were higher than in normal postmenopausal women.

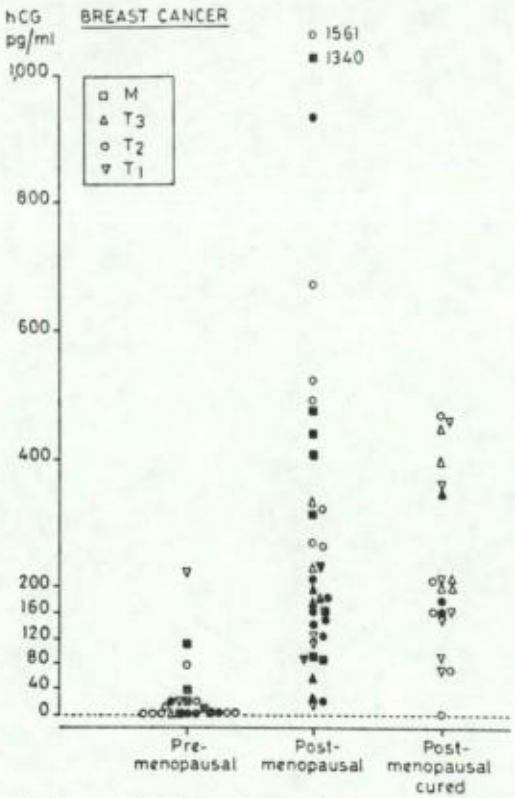

FIG. 5. The plasma hCG-like substance in breast cancer in relation to the size and the stage of the tumor. The plasma concentrations were independent of the size of the tumor (T_1, <2 cm; T_2, 2–5 cm; T_3, ≥5 cm), from the presence of positive axillary lymph nodes (*closed symbols*) and from the presence of distant metastases (M). Furthermore, they were not significantly lower after surgical cure (*column on the right*).

V. Women cured of breast cancer by mastectomy

In view of the higher plasma concentrations of hCG-like substance in postmenopausal women with breast carcinoma the hCG-like substance was measured in 21 postmenopausal women (65.5 ± 10.5 yr) who had been

operated for a localized tumor and were free of disease for an average of 3.6 years (see *Subjects and Methods*). Although these women had no clinical evidence of any residual disease, their plasma concentrations of the hCG-like substance ranged from less than 8 to 463 pg/ml (mean, 220; median, 198) and were not significantly different from those of postmenopausal women with a large progressing tumor (Fig. 5). The median was thus again 4 times higher than in the normal postmenopausal women ($P = 0.002$). As in the women with a progressing tumor, there was a borderline correlation with hLH concentrations ($P = 0.055$); however, the hLH concentrations were normal (11.3 ± 4.35 ng/ml) as were the hFSH concentrations (30 ± 10.5 ng/ml), the two correlating with each other ($P = 0.02$). On the other hand, there was no relationship between the hCG-like values and the size of the tumor or the status of the axillary lymph nodes at the time of the mastectomy (Fig. 5).

VI. Analysis of the hCG-like substance in the plasma of postmenopausal women with a breast cancer or cured of breast cancer by mastectomy

A pool of plasma from postmenopausal women with breast cancer was extracted (22), purified by chromatography on DEAE-Sephadex A-50, and then analyzed in three different ways:

1. Gel filtration on Sephadex G-100 (Fig. 6). In this system, the elution peak of immunologic hCG was identical to that of the standard hormone (tube 41). Its elution profile was comparable to that of the labeled hCG added initially to the plasma and distinct from that of hLH. The latter eluted before standard hLH as previously described (22).

2. Migration on DEAE-Sephadex A-50 (Fig. 7). In this system, the elution peak and the elution profile of immunologic hCG were again remarkably comparable to those of the labeled hCG added initially to the plasma and distinct from those of hLH. (As described in *Subjects and Methods*, for purpose of purification the peak of hCG was always collected from the midpoint of its ascending limb.)

3. Retention by Concanavalin A and elution with MαGP. After two purifications on DEAE A-50 plus one additional purification on Sephadex G-100, the preparation was applied to a column of Concanavalin A. As shown in Fig. 8, the hCG-like substance was retained and eluted in a fashion which is characteristic of a glycoprotein (30).

4. In addition, a pool of plasma from postmenopausal women cured of breast cancer was purified for immunological characterization (Fig. 9). The slopes of the dose response curves (least squares estimation after logit transformation) were very similar for standard hCG (−0.50) and for the aliquots from the final extract (−0.53) in the RIA carried out with an antiserum to hCG-β and

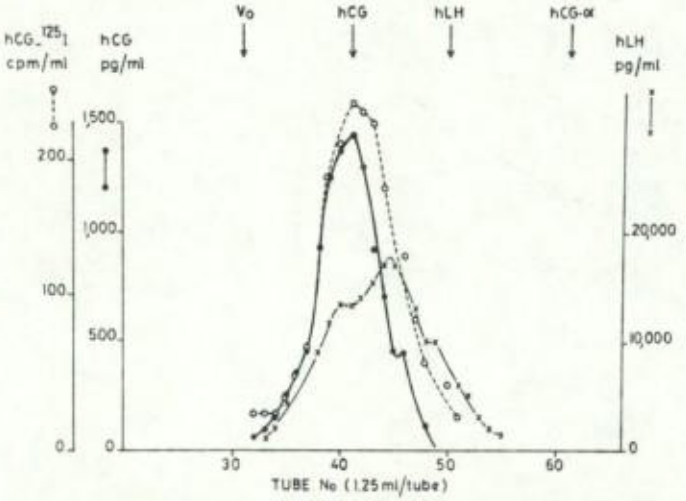

FIG. 6. Chromatography on Sephadex G-100 of the final extract from a pool of plasma from 10 postmenopausal women with breast cancer. *Arrows*, Void volume (V_0) and the elution peaks of the standards. As shown, the elution profile of the hCG-like substance (hCG, picogram per ml) was comparable to that of labeled hCG (hCG-^{125}I, counts per min/ml) and distinct from that of immunologic hLH (hLH, picogram per ml). The latter eluted ahead of standard hLH indicating that it is a larger molecule.

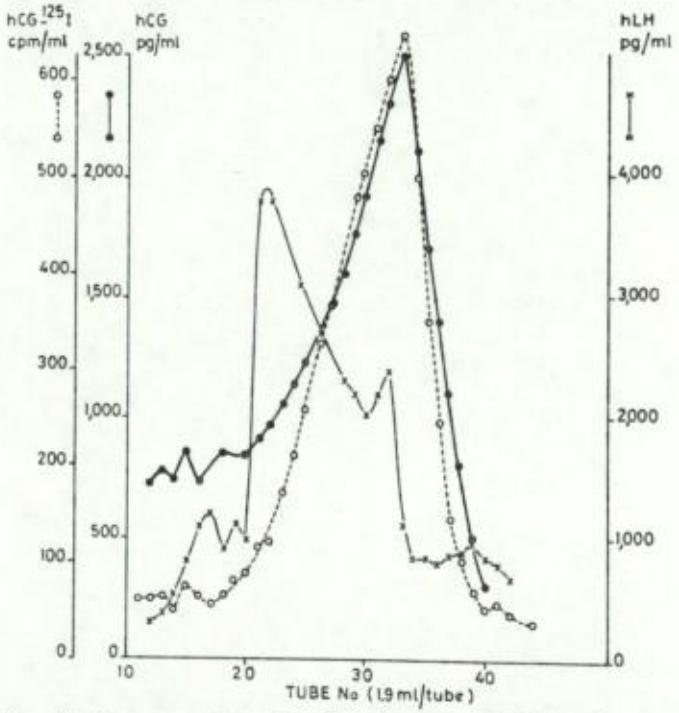

FIG. 7. Chromatography on DEAE-Sephadex A-50 of the final extract from a pool of plasma from seven postmenopausal women with breast cancer. The elution profile of the hCG-like substance (hCG, picograms per ml) was comparable to that of labeled hCG (hCG-^{125}I, counts per min/ml) and distinct from that of immunologic hLH (hLH, picograms per ml).

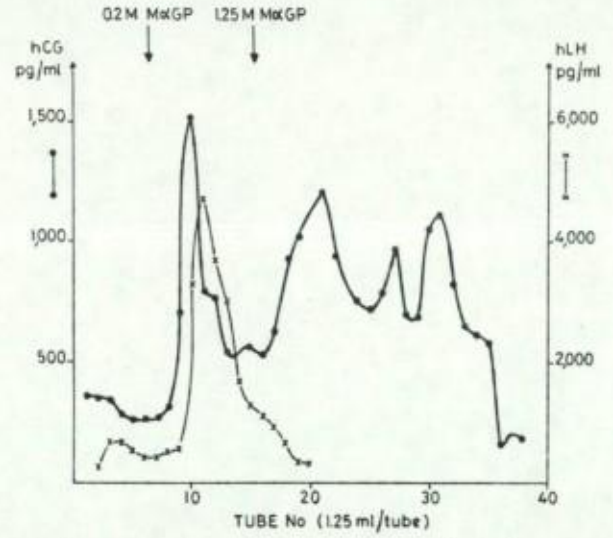

FIG. 8. Chromatography on Concanavalin A of the final extract from a pool of plasma from six postmenopausal women with breast cancer. Both the hCG-like substance (hCG, picograms per ml) and immunologic hLH (hLH, picograms per ml) were retained by Concanavalin A and eluted with MαGP (0.2 M and 1.25 M solutions, successively, as indicated by *arrows*).

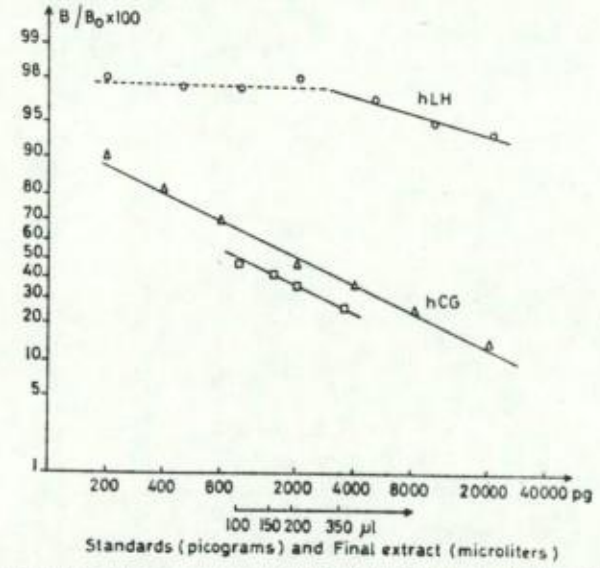

FIG. 9. Dose-response curves of standard hCG (△), standard hLH (○), and the hCG-like substance in aliquots of the final extract (□) in the RIA carried out with an antiserum to hCG-β and ^{125}I-labeled hCG-β. Note the parallelism of the slopes of standard hCG and of the hCG-like substance whereas the slope of hLH is quite different.

^{125}I-labeled hCG-β; on the other hand, these slopes were quite distinct from that of hLH. The concentration of the hCG-like substance in the initial plasma, using this RIA, was found to be 241 pg/ml, similar to that obtained with our usual RIA in 50-μl aliquots of the final extract, *i.e.* 250 pg/ml. These concentrations were also similar to the mean previously obtained in 21 women studied individually, 220 pg/ml (see above, *V*). The total amount of hLH in the final extract was 37.5 ng (recovery, 0.55%); it was less than twice the corresponding amount of hCG: 21.4 ng (recovery, 15%) and could not therefore significantly interfere with the measurement of the latter.

Discussion

hCG has the same biological activity as LH and a very similar structure, differing mainly by the 30 additional C-terminal residues of its β-subunit (hCG-β) and by carbohydrate differences (10). However, it is a distinct placental gonadotropin. The hCG-like substance found in the plasma of normal nonpregnant subjects (22) and of the women with breast carcinoma was similar to standard hCG according to several different criteria: 1) molecular size (identical filtration on Sephadex G-100), 2) ionic strength (identical elution from DEAE-Sephadex A-50), 3) immunoreactivity [distinct recognition by antiserums specific for hCG as shown by distinct elution profiles of the hCG-like substance and of hLH on Sephadex G-100 and on DEAE-Sephadex A-50, as also shown by distinct dose-response curves in RIAs for hCG (22) and hCG-β which distinguish hCG from hLH with great specificity]. In addition, it is glycosylated (retention on a Concanavalin A-Sepharose 4B and elution with MαGP). This material is comparable therefore to that which has been found by other authors in the urine of normal postmenopausal women (26, 28). However, in spite of the variety of the evidence, its exact structure will remain uncertain until its complete amino-acid sequence and its precise carbohydrate composition have been determined (28).

The regulation of the hCG-like substance in normal nonpregnant subjects is unknown. In this regard, our data indicate that, everything being equal, the concentrations of the hCG-like substance in the plasma of normal nonpregnant subjects are not directly dependent on age; in men, in premenopausal women, and in postmenopausal women, there was no relationship between plasma concentrations and age. On the other hand, the plasma concentrations of the hCG-like substance in normal women increased substantially after menopause. The concentration of the hCG-like substance appears therefore to be regulated, like those of the pituitary gonadotropins, by sex steroid hormones. Furthermore, estrogens may be more potent than androgens in inhibiting its production since the hCG-like substance was practically always undetectable in the plasma of premenopausal women until the age of 40 yr whereas appreciable concentrations were found often in men of any age.

Serum concentrations of hCG or hCG-β exceeding 1 ng/ml have been measured in patients with a variety of tumors, especially gonadal and gastrointestinal tumors (1, 8–10, 12, 33–36), in whom they may reach levels from 50 to several thousand nanograms per ml. Such serum

hCG or hcG-β elevations have been described in 7–50% of patients with breast cancer (9, 10, 34–40). In the majority of these patients the serum concentrations did not exceed 3 or 4 ng/ml (14, 35, 37, 38). In the present study, after extraction and extensive purification, we found increased plasma concentrations in patients with breast cancer. However, the highest plasma concentrations (above 1 ng/ml) formed the extreme of a continuum of increased values which started within the normal range. In addition, higher than normal values were almost exclusively found in the postmenopausal patients, and in the latter, the correlation between the hCG-like and the hLH concentrations indicated a similar dependence on sex steroid status. The secretion of the hCG-like substance in our patients with breast cancer appears thus to be regulated as in normal women but with clear-cut augmentation after the menopause.

The source of the hCG-like substance in normal nonpregnant subjects is not known. It might be normal nonendocrine tissue(s) and/or the pituitary gland; the two hypotheses do not exclude each other. Indeed, material with hCG-like immunoactivity has been extracted from normal human testis (24, 41), liver, colon, pituitary gland, lung, kidney, and other tissues (25–28, 42). Most interestingly, normal fibroblast lines and fetal kidney have been shown to secrete a hCG-like substance *in vitro* (19, 43, 44). On the other hand, in previous work we showed that after potent stimulation by the GnRH no significant amounts of the hCG-like substance were acutely released from the pituitary gland, whereas the mean hLH plasma concentration increased over 8-fold (23). This finding indicates that the plasma concentrations of the hCG-like substance are not modulated by GnRH in a fashion similar to hLH; it also constitutes an argument for an extrapituitary origin. The question then arises as to the main source of the hCG-like substance in the patients with breast cancer. Although it has been shown repeatedly, both *in vivo* (8–10, 12, 14, 36) and *in vitro* (2–7), that tumors can secrete ectopic hormones, including hCG or its free β-subunit, there are several arguments against the tumor being the main source of the hCG-like substance in our patients. There was no relationship between the plasma concentrations of the hCG-like substance and the stage of the tumor [*i.e.* its size, its lymph node involvement, or the presence of distant metastases (45)]. Furthermore, the plasma concentrations were not significantly lower in patients whose tumor had been removed by surgery. With regard to the pituitary gland, the finding that the plasma concentrations of the hCG-like substance were much higher in the postmenopausal women with breast cancer than in normal postmenopausal women whereas those of hLH were similar suggests again, but under conditions of prolonged stimulation, that the secretions of these two proteins vary independently from each other. Although a difference in peripheral metabolism cannot be excluded, it constitutes another argument for an extrapituitary origin of the hCG-like substance. Consequently, in addition to the tumor and to the pituitary gland, a significant contribution by nonmalignant nonendocrine, perhaps undifferentiated, cells must be considered. Such a source would explain why high plasma concentrations of the hCG-like substance can be found occasionally in healthy postmenopausal women (33) or in patients with nonmalignant diseases (35), especially of the breast (39), of the lung (40), and most importantly, in inflammatory bowel diseases, some of which are associated with neoplastic transformation (10, 33).

The secretion of a hCG-like substance by nonendocrine nonmalignant cells can be viewed as a primitive paracrine secretion persisting through evolution (21): indeed, hCG-β appears to be a very ancient (46) and much preserved protein, encoded by at least eight genes (47, 48). It also can be viewed as a fetal or trophoblastic function persisting after birth and reflect rapid cell turnover (10). In addition, as a trophoblastic function, the secretion of the hCG-like substance could be associated with the local production of estrogens, a well known concomitant of ectopic hCG secretion, to which the mammary cells are especially sensitive (49, 50).

Some tumors might thus grow in a milieu of increased paracrine secretions by nonmalignant cells and variably contribute to these secretions. The use of the ectopic hormones as markers of tumor progression will then depend on the relative secretion by the malignant and the nonmalignant cells, as was already proposed by Yalow (18) for big ACTH in bronchogenic carcinoma; this would explain the poor relationship which is most often found between the tumor burden and circulating hormone levels (15–17).

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