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# Serum Levels of Cortisol, Dehydroepiandrosterone, Dehydroepiandrosterone Sulphate, Estrone and Prolactin after Surgical Trauma in Postmenopausal Women

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## ABSTRACT

Changes in serum hormone concentrations induced by surgical trauma were studied by determination of cortisol, dehydroepiandrosterone (DHA), dehydroepiandrosterone sulphate (DHAS), estrone (E1) and prolactin in 25 postmenopausal women. Blood samples were collected before, during and after mastectomy (14 women) and cholecystectomy (11 women). A slight peroperative increase in DHA preceded a marked postoperative decrease whereas no significant changes were seen concerning DHAS. The posttraumatic increase in cortisol values was delayed in relation to that of DHA, reaching its maximum on the first postoperative day. There was a pronounced postoperative increase in estrone which was only slightly ($r = 0.3$) correlated to the concomitant changes in the serum levels of DHA and cortisol indicating that other factors than increased availability of precursor steroids might influence this change. Prolactin levels showed an about fourfold peroperative increase and were normalized on the first day after surgery. No significant differences in preoperative values were seen between the groups although generally more pronounced and retarded changes were seen after cholecystectomy than after mastectomy.

## INTRODUCTION

The stress of a surgical trauma will cause changes in the serum levels of pituitary (10,18) as well as adrenal hormones (10). In postmenopausal women the bulk of plasma estrogens originates from peripheral conversion of adrenal steroids (13,15). In the present study the serum concentrations of cortisol,

dehydroepiandrosterone (DHA), dehydroepiandrosterone sulphate (DHAS), estrone and prolactin were measured in postmenopausal women before, during and after a surgical trauma. The purpose of the study was to estimate stress-induced changes in serum concentrations of these hormones in postmenopausal women.

## MATERIAL AND METHODS

### Patients

This study was performed on 25 female patients. Fourteen were undergoing simple or modified radical mastectomy for primary breast carcinoma and 11 were undergoing cholecystectomy for gallstone disease. The mean age of the mastectomy group was 66 years (range 48-85) and of the cholecystectomy group 62 years (range 52-71).
All patients were postmenopausal according to history and to an FSH-concentration in the serum exceeding 3 ug/l (26). No women had undergone a surgical menopause. Two patients in the breast cancer group were treated with glucocorticoids at the time of surgery and were not included in the statistical calculations. They are reported on separately. The other patients were free from medications.

The drugs used for premedication and the methods for anesthesia were identical in the groups. The operations were all uncomplicated. On the day of surgery all patients were fasting with intravenous fluid therapy - 2000-2500 ml glucose electrolyte solutions. All mastectomy patients had peroral feeding on the first postoperative day while 7 of the cholecystectomy patients were fasting until the second postoperative day.
Venous blood samples were drawn at different times in relation to surgery as shown in Table I. Sample I was collected on the day of admission at about 10 a.m., sample II on the day of surgery preoperatively at about 8 a.m. and sample III half an hour after the start of surgery on the average at 12 a.m. (range 9 a.m.-4p.m.). Samples IV-VI were collected on the first, third and fifth postoperative day, respectively, at about 8 a.m. Sample VI was not originally included in the study and was later taken only in those 7 patients with breast cancer and 9 with gallstone disease, who were still hospitalized on the fifth postoperative day. The last sample (VII) was taken randomly during the day at the first postoperative visit to the out-patient clinic. This occurred in 2/3 of the cases 2-4 weeks after the operation and in all instances within 12 weeks. The serum was stored at $-20^{o}$ C until all samples for each patient were concomitantly analysed.

## Hormone analyses

Cortisol in serum (S-cortisol) was determined by a radioimmunoassay without prior extraction using a commercial kit from Diagnostic Products Corp., Los Angeles, Calif., U. S. A. The method uses an ($^{125}$I)cortisol tracer and free and bound antigen are separated by a double antibody-polyethylene glycol precipitation technique.

S-dehydroepiandrosterone (DHA) was determined after ether extraction by radioimmunoassay using anti-dehydroepiandrosterone-17-(carboxymethyl oxime) bovine serum albumin (Hypolab, S.A., Coinsins, Switzerland). This antibody crossreacts to 7.3% with 5-androstene-3β,17β-diol and to 4.1% with 5-pregnenolone. These steroids together will thus account for approximately 3.5% of the DHA values obtained ((calculated from serum steroid levels given in (1,3,4,22)).

S-dehydroepiandrosterone sulphate (DHAS) was measured by a modification (9) of the procedure of Metcalf (16). The method includes hydrolysis of DHAS by autoclaving diluted serum at pH 4.5 at 120$^{o}$ C, extraction with diethyl ether and radioimmunoassay as described for unconjugated DHA. Unconjugated DHA will account for approximately 1% and the sulphates of 5-androstene-3β, 17β-diol and 5-pregnenolone for less than 1% of the values (calculated from 1,5,22,23)).

S-estrone was measured after ether extraction by a radioimmunoassay (6) using anti-estrone-6-(carboxymethyl oxime) bovine serum albumin (generously supplied by Dr. Gordon Niswender, Colorado State University, Fort Collins, Colorado, U. S. A.).

S-prolactin was determined using a commercial kit from KABI AB, Stockholm, Sweden. Bound and free ($^{125}$I) prolactin were separated by precipitation with polyethylene glycol. The values are expressed as μg/l of human prolactin NIH V.L.S. 1.

Within and between assay variations were for cortisol 4.5 and 7.0%, for DHA 5.4 and 7.1%, for DHAS 8.1 and 12.1%, for estrone 4.5 and 6.2%, and for prolactin 7.2 and 14.6%, respectively.

## Statistical methods

All p-values refer to comparison with the first (I) serum sample using a two-tailed Wilcoxon matched-pairs signed-ranks test. The product moment correlation coefficient was used as a measure of correlation.

Time-course of serum levels

The mean steroid and prolactin levels for the 2 groups at different sampling times are given in Tables 1 and 2 in Figs. 1a-e. No significant differences were found between the 2 groups concerning the initial levels.

Cortisol. (Fig. 1a). The highest mean value for cortisol was noted on the first postoperative day when it was significantly ($p < 0.05$) higher than the initial values (sample I) in both groups of patients.

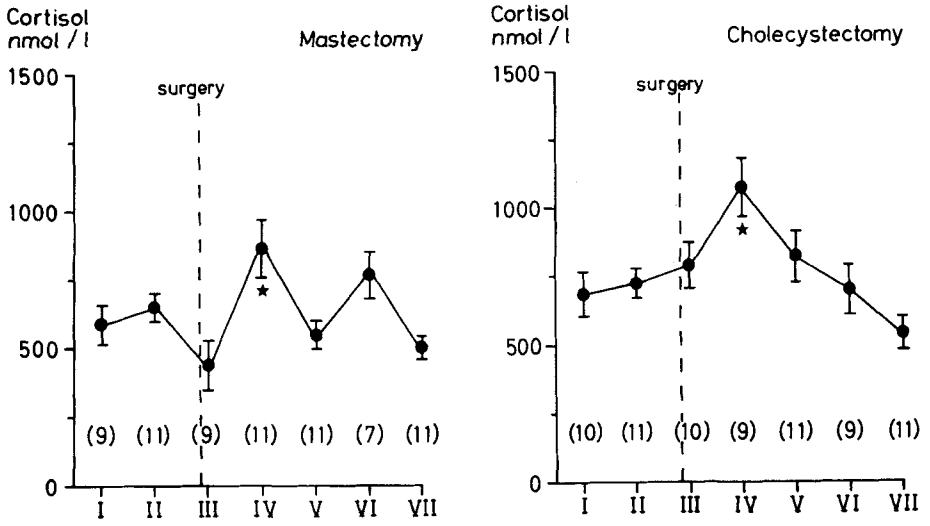


Fig. 1 a. Concentration of cortisol in the serum before, during and after surgery in the mastectomy and cholecystectomy group. The mean value, SEM and number of observations (within brackets) is shown for each measurement period. Significant differences related to the first value (I) are indicated as *($p < 0.05$).

DHA. (Fig. 1b). The highest mean DHA value was noted on the day of surgery, half an hour after the start of surgery, in both groups. This value was significantly ($p < 0.05$) higher than the initial value in the gallstone group only, while no significant increase was noted for the breast cancer group. In both groups the mean DHA values decreased postoperatively, being significantly lower than the initial values on day 3 after surgery in the breast cancer group ($p < 0.01$) and on day 5 in the gallstone group ($p < 0.01$).

Table 1. Breast cancer group. Mean values, standard deviations and number of observations (within brackets) for cortisol, DHA, DHAS, E1 and prolactin at different measurement periods in relation to mastectomy.

| | preoperative | | peroperative | postoperative | | | |
|---|---|---|---|---|---|---|---|
| | at admission | day of operation | ½ hour after start of surgery | day 1 | day 3 | day 5 | more than 2 weeks postop randomly during the day |
| Hormone | 10.30 a.m. | 08.00 a.m. | 9 a.m.-4 p.m. | 08.00 am. | 08.00 a.m. | 08.00 a.m. | |
| | I | II | III | IV | V | VI | VII |
| Cortisol nmol/l | 593±220 | 648±156 | 446±266 | 870±335 | 550±167 | 770±244 | 501±142 |
| | (9) | (11) | (9) | (11) | (11) | (7) | (11) |
| DHA nmol/l | 20±13 | 19±13 | 22±15 | 21±10 | 11±5 | 16±13 | 16±9 |
| | (12) | (11) | (10) | (12) | (11) | (7) | (12) |
| DHAS nmol/l | 2937±1644 | 2660±1460 | 2083±1163 | 2045±1260 | 1793±1113 | 1573±1283 | 2747±1007 |
| | (5) | (8) | (8) | (7) | (6) | (6) | (6) |
| EI pmol/l | 159±85 | 170±78 | 130±67 | 226±98 | 141±78 | 141±104 | 107±52 |
| | (12) | (11) | (10) | (12) | (12) | (7) | (12) |
| Prolactin µg/l | 4.42±2.82 | 6.44±3.43 | 25.44±11.54 | 6.78±5.86 | 6.67±3.30 | 8.03±3.60 | 7.54±5.14 |
| | (5) | (8) | (9) | (8) | (6) | (7) | (5) |

Table 2. Gallstone group. Mean values, standard deviations and number of observations (within brackets) for cortisol, DHA, DHAS, E1 and prolactin at different measurement periods in relation to cholecystectomy with the same denotations as in Table 1.

| | I | II | III | IV | V | VI | VII |
|---|---|---|---|---|---|---|---|
| Cortisol nmol/l | 687±245 | 732±172 | 794±266 | 1072±317 | 824±286 | 704±235 | 535±187 |
| | (10) | (11) | (10) | (9) | (11) | (9) | (11) |
| DHA nmol/l | 26±14 | 32±19 | 38±19 | 31±10 | 19±14 | 12±6 | 24±13 |
| | (11) | (11) | (10) | (10) | (11) | (9) | (11) |
| DHAS nmol/l | 2234±1267 | 2367±1009 | 1672±693 | 2403±1268 | 2059±1474 | 1451±906 | 2129±967 |
| | (7) | (9) | (9) | (8) | (10) | (9) | (9) |
| E1 pmol/l | 122±63 | 159±67 | 148±78 | 300±126 | 233±111 | 144±70 | 133±52 |
| | (11) | (11) | (10) | (10) | (11) | (9) | (11) |
| Prolactin µg/l | 5.21±3.17 | 4.93±2.77 | 35.52±12.99 | 6.01±2.82 | 9.67±4.88 | 9.54±7.60 | 8.65±7.56 |
| | (7) | (10) | (8) | (7) | (11) | (9) | (11) |

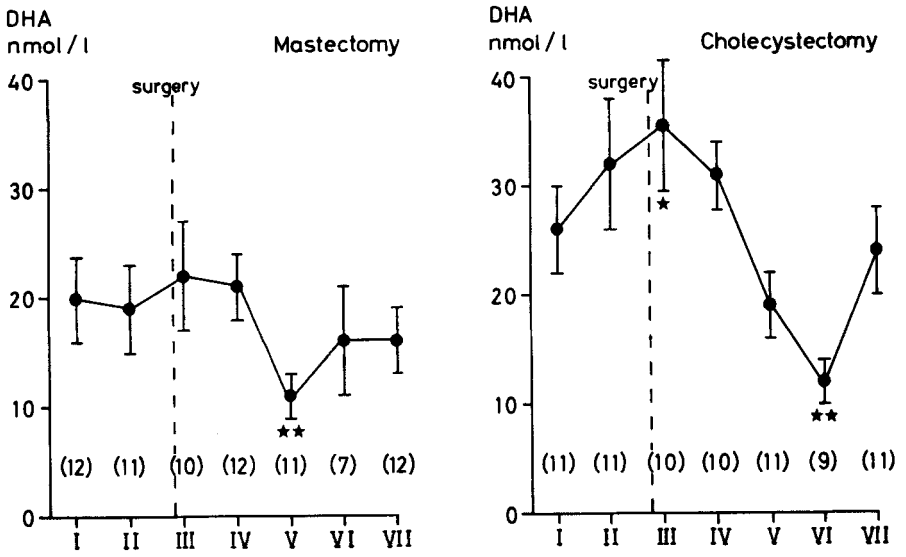


Fig. 1 b. Concentration of DHA in the serum before, during and after surgery in the mastectomy and cholecystectomy group. The mean value, SEM and number of observations (within brackets) is shown for each measurement period. Significant differences related to the first value (I) are indicated as *($p < 0.05$) and **($p < 0.01$).

DHAS. (Fig. 1c). Due to lack of serum, determination of DHAS was performed only on a limited number of patients. There were no significant changes in the serum levels of DHAS in any of the groups.

E1. (Fig. 1d). The highest mean estrone level was noted on the first postoperative day in the gallstone group ($p < 0.01$) as well as in the breast cancer group ($p < 0.05$). In the gallstone group the mean estrone level was still elevated 3 days after surgery ($p < 0.01$) but after that they returned to initial values. In the breast cancer group the estrone values decreased rapidly after the first postoperative day and became lower than the initial values in the last sample.

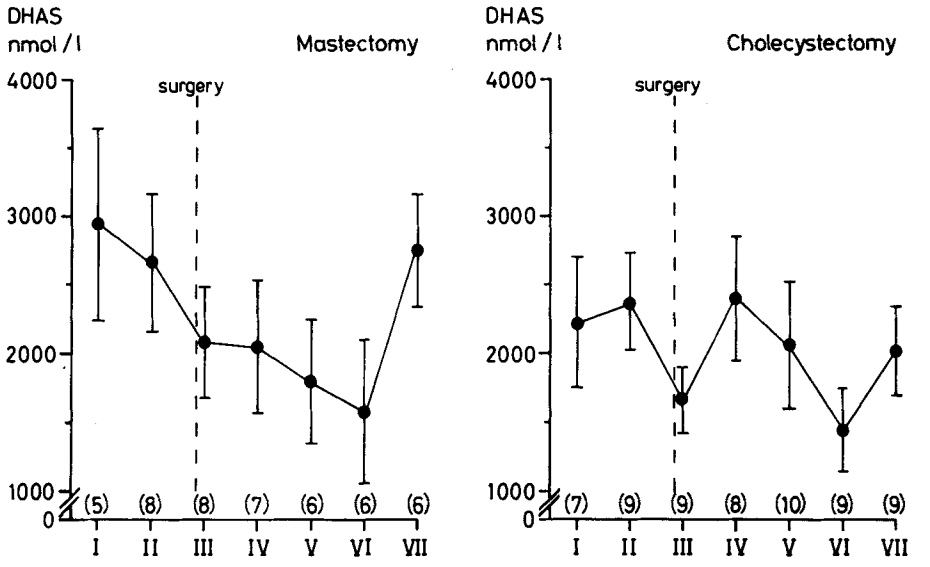


Fig. 1 c. Concentration of DHAS in the serum before, during and after surgery in the mastectomy and cholecystectomy group. The mean value, SEM and number of observations (within brackets) is shown for each measurement period.

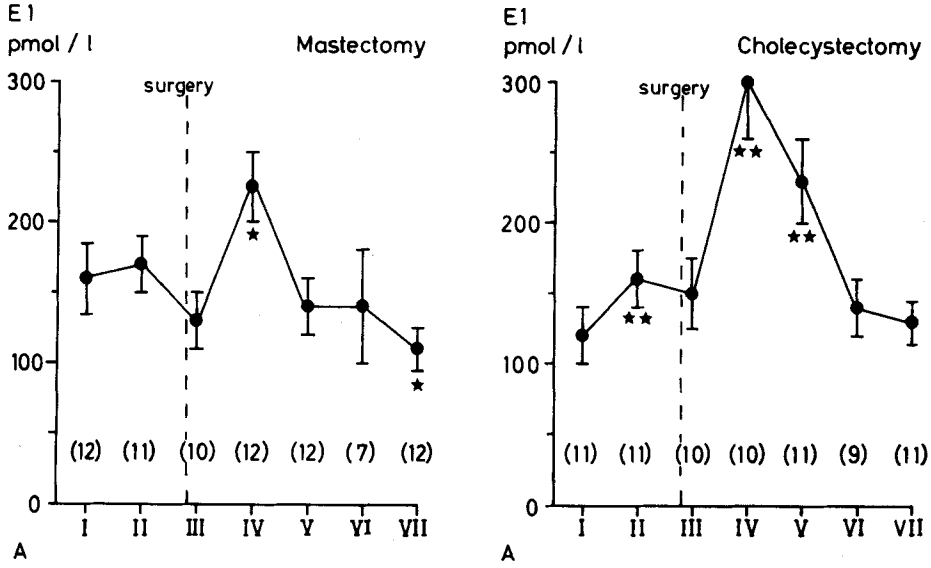


Fig. 1 d. Concentration of E1 in the serum before, during and after surgery in the mastectomy and cholecystectomy group. The mean value, SEM and number of observations (within brackets) is shown for each measurement period. Significant differences related to the first value (I) are indicated as *($p < 0.05$) and **($p < 0.01$).

Prolactin. (Fig. 1e). The concentration of serum prolactin was measured only on a limited number of patients due to the lack of serum, which in 5 patients gave cause for the use of sample II instead of sample I as a preoperative reference. The serum levels were markedly increased during surgery (sample III) in both groups ($p < 0.01$).

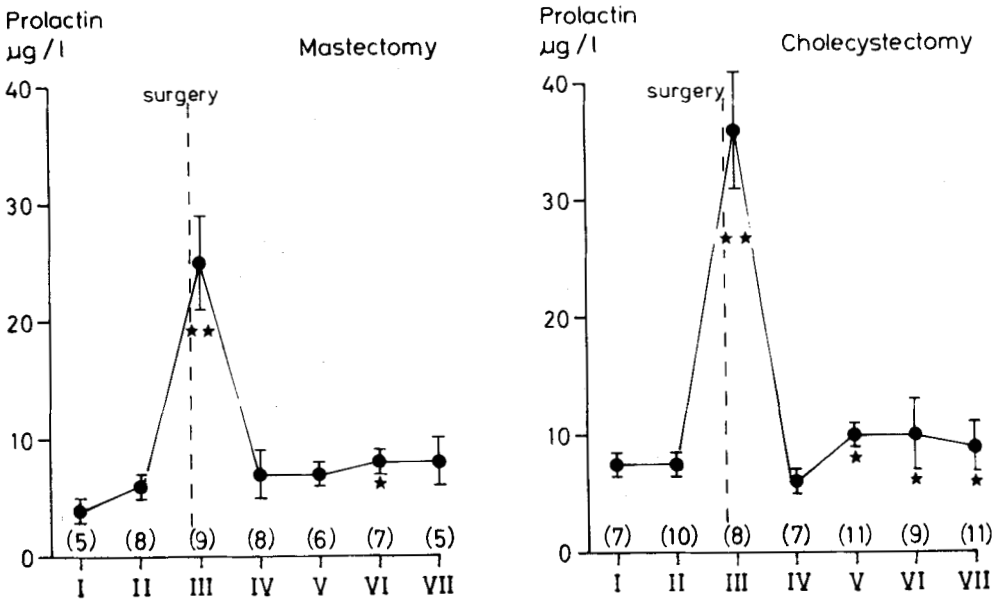


Fig. 1 e. Concentration of prolactin in the serum before, during and after surgery in the mastectomy and cholecystectomy group. The mean value, SEM and number of observations (within brackets) is shown for each measurement period. Significant differences related to the first value (I) are indicated as * ($p < 0.05$) and ** ($p < 0.01$).

DHA and estrone values from 2 women on glucocorticoid treatment were separately analysed. One of them received hydrocortisone 100 mg x 4 intravenously on the day of surgery and the first postoperative day and after that Prednisolone orally in doses declining from 5 mg x 4 (day 2) to 5 mg x 1 (day 5). She had uniformly low DHA values (2.5 -3.8 nmol/l). The estrone levels were below the sensitivity of the method at all measurement periods. The other woman was given hydrocortisone 100 mg x 2 intravenously on the day of surgery only and was the only one showing a definitely decreased E1 value from sampling period I to IV (240.5 to 111.0 pmol/l). Her DHA values decreased already in sample IV.

Correlations

When values from the two groups during the postoperative period (samples IV-VII) were combined and the changes from the first to the fourth sampling period were studied by a regression analysis, a signficant correlation was found between the changes in cortisol and DHA ($r = 0.83$). Poor correlation were however found between the changes in cortisol and estrone ($r = 0.38$) and in DHA and estrone ($r = 0.33$).

Uniformly lower correlations were found when the same calculations were repeated using the perioperative (sample III) DHA value instead of the first postoperative value (sample IV) or when the lowest value instead of the first one was used as a reference.

## DISCUSSION

It is well known that surgical trauma, as in the present study, causes increased cortisol levels, secondary to an increased pituitary secretion of ACTH. No changes in serum cortisol were found after 30 minutes of surgery neither in the present study nor in the investigation carried out by Charters et al. (10) but would probably have been shown with another sampling schedule including samples taken later than 30 minutes during surgery.

In view of the pattern observed for cortisol, the time-courses of another adrenocortical steroid, DHA, and its sulphate DHAS are interesting. Maximum values for DHA occurred earlier than the maximum in cortisol, i.e. 30 minutes after the start of surgery (sample III), and this increase, although not statistically significant was more pronounced in the gallstone group. Following the first postoperative day (sample IV), however, the time course of DHA in serum was similar to that of cortisol in both groups. DHAS was not significantly changed in any of the groups.

The initial discrepancies between the time courses of cortisol and DHA might be due to changes in the balance between unconjugated and conjugated DHA or indicate differences in the regulation of DHA and cortisol. A lot of evidence have been accumulated for the existence of an "adrenal androgen stimulating hormone" or "reticulotrophin" differing from ACTH, which selectively stimulates the adrenal DHA synthesis (14). The nature of this hormone (s) is not known. Its action seems to require a sufficient ACTH stimulation of the adrenal cortex. Prolactin, being increased during surgery (18) has been suggested as the adrenal androgen stimulating hormone (16,21). We found highly increased prolactin levels during surgery and this increase was more pronounced in the gallstone group. The role of prolactin has, however,

been seriously questioned in this respect (14). Other protein hormones such as hGH, FSH, LH and TSH have also been proposed as possible adrenal androgen stimulating hormones. Increased levels of these hormones during surgery have been reported (2,10), but they seem to be even less possible than prolactin in an adrenal stimulating role (14).

Charters et al. (10) found maximum cortisol values after 2 - 3 hours of surgery. It is very likely that maximum DHA values also occur at this time, since DHA follows closely to cortisol in ACTH stimulation tests (7,21). At the first postoperative day Charters et al. (10) noticed still significantly elevated cortisol values. In the present study cortisol but not DHA, was significantly elevated on this day. One explanation for this discrepancy may be the shorter biological half-life for DHA, i.e. 1 - 2 hours, compared with 3 hours for cortisol (7,12,19). From the first postoperative day the time courses for cortisol and DHA were rather similar indicating a common regulator of the 2 steroids at this time, i.e. ACTH.

Significantly decreased DHA values were noted on the third day after surgery (sample V) in the breast cancer group and on the fifth day (sample VI) in the gallstone group. A tendency towards lower DHAS values was also noted in these samples. One may speculate over a negative rebound effect of the previously increased cortisol levels upon the adrenal androgen biosynthesis. Decreased values for DHAS as well as for another adrenocortical androgen, androstenedione, following mastectomy have previously been reported by Wang et al. (24,25).

Maximum estrone levels were observed on the first postoperative day concomitantly with the maximum cortisol values. Already in 1959 Brown (8) showed that administration of ACTH caused an increase in urinary estrogens in oophorectomized women. It is well known (17,20) that ACTH stimulation increases estrone production in postmenopausal women. Thus, the maximum estrone levels on the first postoperative day may be due to an ACTH induced increase in the production of adrenal estrone precursors, notably androstenedione. However, it should be pointed out that ACTH has been reported to cause changes in the balance between unconjugated and sulphoconjugated steroids (11), notably by increasing sulphatase activity.

The low degree of correlation between the increase of the presumed precursor DHA and estrone might be due to a change in the conversion rate as a function of the precursor concentration as suggested by Vermeulen and Verdonck (22).

One woman on continuous glucocorticoid treatment showed no changes at all in her serum levels of DHA and estrone. Another woman who got glucocorticoid injections only on the day of surgery showed a definite decrease of the serum levels of DHA, and estrone on her first postoperative day; a result strongly pointing to the important role the adrenals are playing for the formation of estrone in postmenopausal women.

The more pronounced changes in the serum hormone levels observed in the gallstone group (Tables 1 + 2, Figs. 1) could be due to the greater surgical trauma experienced by these patients. The reason, however, for the observed rise of estrone already in sample II in the gallstone group remains obscure. The presence of a preoperative stress as an explanation is not supported by any other hormonal changes. Besides the previously known influence of stress and surgical trauma on the pituitary - adrenal axis, the present results also indicate effects upon the steroid balance which are not related to the action of ACTH upon the adrenocortical de novo steroid biosynthesis.

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