

Bio-Identical Steroid Hormone Replacement

Selected Observations from 23 Years of Clinical and Laboratory Practice

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ABSTRACT: To maximize the safety and efficacy of human hormone replacement therapy, it is suggested that exact molecular copies of human hormones (“bio-identical” hormones) be administered in physiologic quantities and proportions, following physiologic timing and routes of administration. It is also suggested that physicians return to the practice of monitoring hormone therapy by precise laboratory measurement levels of the hormones administered. This paper also presents clinical and laboratory data concerning appropriate proportions of bio-identical estrogens, the physiologic and supraphysiologic nature of commonly employed doses, estrogen levels achieved by varying routes of administration, and the significant effects of iodine on estrogen metabolism and cobalt on estrogen excretion.

KEYWORDS: bio-identical hormones; estradiol; estrone; estriol; estrogens; menopause; hormone replacement therapy

The physician is only the servant of Nature, not her master. Therefore it behooves medicine to follow the will of nature.

—PARACELSUS

In contemporary medical therapeutics, “copy nature” is a dictum less often honored than ignored. The relatively recent outcomes of the Women’s Health Initiative¹ in the United States and the Million Women Study² in the UK have demonstrated once again that replacing human molecular substance with inexact molecular copies has undesirable consequences.

If human hormones are to be replaced during peri-menopause and postmenopausally, it is entirely logical to copy nature, replacing human hormones with exact molecular copies. It is also entirely logical to copy nature in every other parameter possible, including quantities of bio-identical hormones given, routes of administration, and timing of administration of bio-identical hormones.

Use of inexact molecular copies of human hormones has also led to inexcusable sloppiness of medical practice: For decades, women were given dosages of powerful steroid-hormone-mimetic substances with no follow-up testing at all to determine appropriate dosage. The use of nonhuman pseudohormones automatically precluded

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the normal practice of post-treatment testing, since (for example) there are no “normal” levels of equilin (the major molecular species in Premarin) or medroxyprogesterone (Provera) to be found in women of any age for use as guidelines to correct dosage of these substances. By contrast, dosing with thyroxine and/or tri-iodothyronine is almost always followed at intervals with serum testing of thyroid hormones to insure correct dosage and patient safety.

This paper will briefly review practice and research concerning:

- (1) types of estrogens used in bio-identical hormone replacement;
- (2) quantities (dose) of estrogens used; and
- (3) route of administration of estrogens.

This paper will also discuss two “problems” in bio-identical hormone replacement therapy and their correction with elements from nature:

- (4) incomplete metabolism of estrone and estradiol towards estriol; and
- (5) hyperexcretion of estrogens.

Although the focus of this paper is on practice and clinical research concerning bio-identical estrogens, in daily practice bio-identical estrogen replacement is routinely combined with bio-identical progesterone, testosterone, dehydroepiandrosterone, thyroid, and melatonin, mimicking physiologic quantities, timing, and route of administration as closely as possible.

SERUM ESTRIOL, ESTRADIOL, AND ESTRONE IN NONPREGNANT, PREMENOPAUSAL WOMEN

Exact molecular copies of human steroid hormones are increasingly referred to as “bio-identical” hormones, to distinguish them from inexact (and often patentable) molecular copies. While a small minority of physicians in the United States and a somewhat larger number in Europe and Japan have used one or more bio-identical steroids (usually estradiol, estriol, progesterone, testosterone) for the treatment of the symptoms of menopause and/or andropause for one or two decades or more, completely comprehensive bio-identical hormone therapy (including all female and male steroid metabolites, major and minor) has not been in use since the medieval period in China, where the earliest record of such therapeutic preparations (*chhui shih*) and their uses dates to 1025 AD.

Contemporary bio-identical steroid replacement uses only one or just a few of the many steroid hormones and their metabolites. For women, the bio-identical estrogen most often used in the United States and Europe is estradiol; in Japan, it is most often estriol. Bio-identical progesterone and testosterone are also often used for women.

In an effort to be a bit more comprehensive, and to better copy nature, a small but growing minority of American physicians and a handful throughout the world use a combination of bio-identical estrogens (along with progesterone, testosterone, and dehydroepiandrosterone). Bio-identical estrogen combinations most often used are either “triple estrogen” (estrone 10%, estradiol 10%, estriol, 80%) or “bi-estrogen” (estradiol 10–20% and estriol 80–90%). The use of these combinations in practice is supported by the following research data.

In an effort to confirm that triple estrogen as used since the early 1980s is reasonably close to “naturally occurring” estrogens in both proportions and quantities, our

TABLE 1. Serum estrogen levels and estrogen quotients^a

Subject no.	Day of cycle	Estriol (pg/mL)	Estradiol (pg/mL)	Estrone (pg/mL)	Estrogen quotient
1	10	233	52.5	21.2	3.2
2	10	329	43.4	14.4	3.2
3	10	1254	188.8	55.0	5.1
4	10	320	40.4	23.4	5.2
5	10	369	43.9	20.4	5.7
6	10	700	30.9	68.0	7.1
7	10	374	35.9	15.1	7.3
8	10	429	25.3	33.1	7.3
9	10	941	86.7	32.5	7.9
10	10	736	21.5	70.6	8.0
11	10	1616	61.2	127.4	8.6
12	10	726	61.7	52.5	6.4
13	10	826	22.6	39.1	13.4
14	10	1614	57.9	144.4	8.0
15	10	771	11.3	35.4	16.5
16	10	1700	30.7	58.6	19.0
17	11	59.5	15.1	35.9	11.7
18	11	2408	156.8	121.9	8.6
19	12	961	32.8	71.6	9.2
20	12	1161	71.2	27.3	11.8
21	12	1271	22.2	72.0	13.5
22	14	685	24.6	43.4	10.1
23	14	988	31.1	05.8	10.2
24	14	212	23.7	12.5	5.9
25	14	1412	183.4	54.7	5.9
26	14	1146	17.4	68.6	13.3
			Average:		8.9
			Standard deviation		3.9

^aFrom Robinson *et al.*³ (Estriol)/[(Estradiol) + (Estrone)].

laboratory (Meridian Valley Laboratory, Renton, WA) tested 26 women for estrone, estradiol, and estriol levels during the 10th to 14th days of their menstrual cycles. Participant criteria included good health, ages between 18 and 40, and not taking birth control, steroid, or steroid-mimetic medications. Results of these tests are shown in TABLE 1.

We also tested five other women meeting the same criteria stated above at varying points throughout their menstrual cycles. At all times tested, circulating estriol significantly exceeded the sum of circulating estrone and estradiol (FIGS. 1–5).

From these data, it is apparent that even in nonpregnant women, estriol is normally present in healthy, nonpregnant women in considerably larger quantities than either estrone or estradiol. Even though estriol has long been considered a “weak estrogen,” important only during pregnancy (much as DHEA was considered an “un-

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3/(E2+E1)
7	700	68	31	7.1
10	1616	127	61	8.6
14	685	43	25	10.1
17	944	52	31	11.4
24	897	40	22	14.5

EQ Average: 10.3

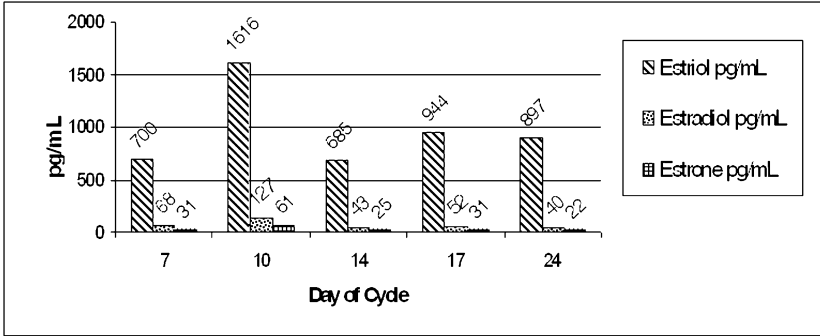


FIGURE 1. Serum estrogen concentrations on various days of the cycle: woman 1.

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3/(E2+E1)
7	689	36	17	13
12	961	72	33	9.2
21	1018	51	18	14.8

EQ Average: 12.3

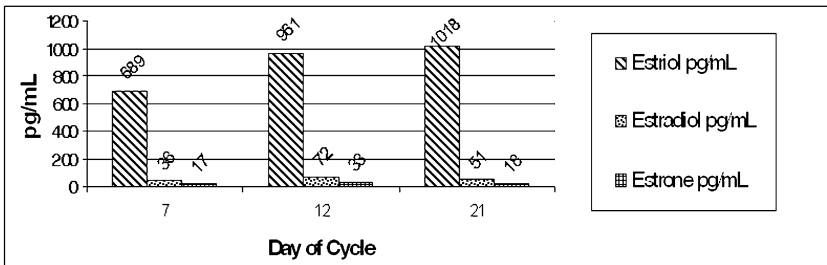


FIGURE 2. Serum estrogen concentrations on various days of the cycle: woman 2.

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3(E2+E1)
4	343	24	17	8.4
10	429	33	25	7.4
19	512	12	17	17.7

EQ Average: 11.1

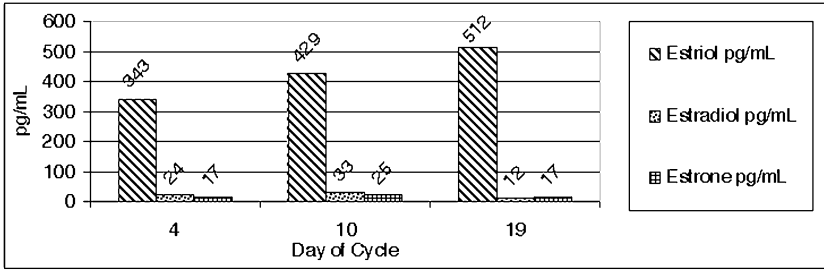


FIGURE 3. Serum estrogen concentrations on various days of the cycle: woman 3.

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3(E2+E1)
2	303	7	1	37.9
15	988	66	31	10.2
19	653	85	23	6

EQ Average: 18.0

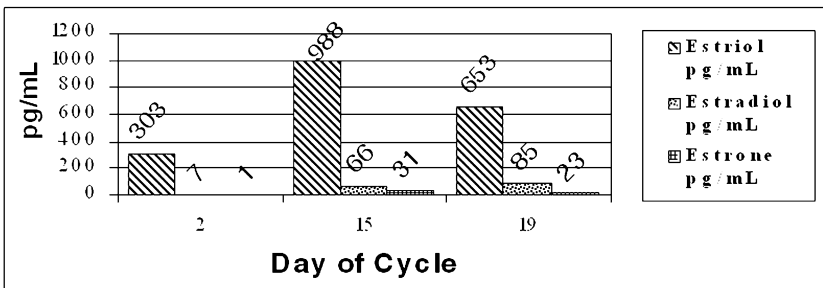


FIGURE 4. Serum estrogen concentrations on various days of the cycle: woman 4.

Day of Cycle	Estriol pg/mL	Estradiol pg/mL	Estrone pg/mL	Eq E3(E2+E1)
8	1104	68	11	14
10	736	71	22	7.9
26	786	17	10	29.1

EQ Average: 17.0

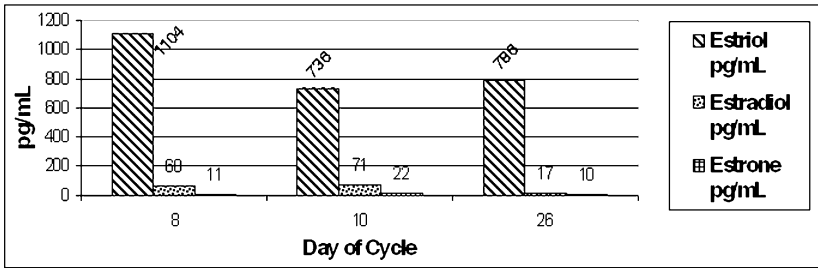


FIGURE 5. Serum estrogen concentrations on various days of the cycle: woman 5.

important steroid” for several decades), we conclude that nature must have a purpose for the presence of these relatively large proportions, even in healthy nonpregnant women.

Unless future controlled studies demonstrate unacceptable risk, we believe that estriol, estradiol, and estrone used in physiologic quantities and proportions, along with progesterone and testosterone, copying both nature’s timing and routes of administration as closely as possible are the safest form of (ovarian) steroid “hormone replacement therapy.”

ESTRADIOL: IMPORTANCE OF APPROPRIATE DOSE AND METABOLISM TO ESTRONE

Careful attention is also given to dose, with a deliberate effort made to copy nature by not exceeding physiologic quantities of any of the bio-identical hormones administered. Follow-up testing is always done to ascertain whether this goal has been achieved. Many practitioners deliberately target hormone levels slightly above the “normal” menopausal range, overlapping into the “low physiologic range” found in young, healthy, cycling women.

In the United States, when a bio-identical estrogen is recommended instead of an inexact molecular copy, the large majority of academic and affiliated practitioners have given estradiol alone. (Practitioners recommending “triple estrogen” or “bi-estrogen” are usually community-based.) Doses given by academic and affiliated practitioners have routinely been in the range of 1–2 milligrams per day, with no follow-up testing done to examine whether these doses compare to physiologic quantities. Unfortunately, a very widely read book by a Hollywood actress undergoing treatment for breast cancer also takes this approach. The actress writes of taking 2

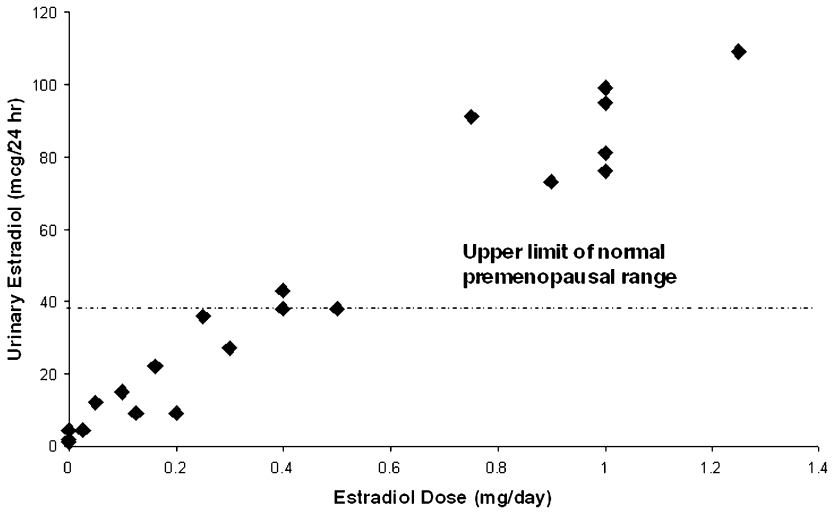


FIGURE 6. Urinary estradiol excretion after oral estradiol. (Reproduced from Friel *et al.*⁴ with permission.)

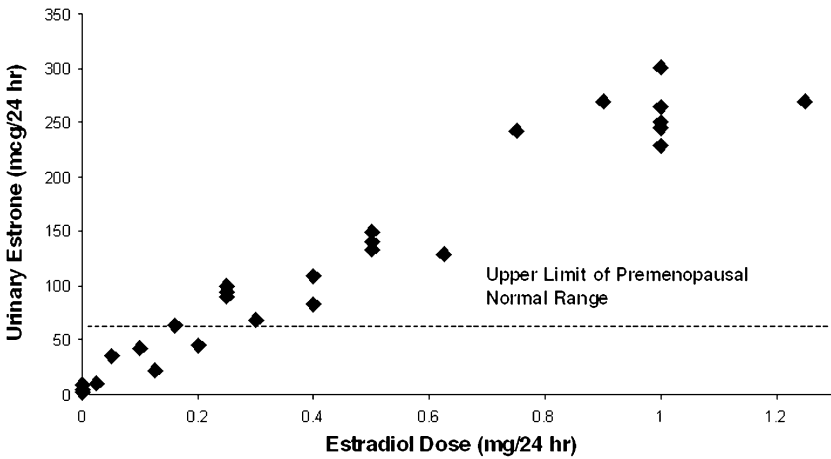


FIGURE 7. Urinary estrone output in postmenopausal women taking oral estradiol. (Reproduced from Friel *et al.*⁴ with permission.)

milligrams of estradiol daily, and reports no follow-up testing. The following data illustrates the hazards of this approach.

Twenty-four-hour urinary steroid hormone profiles, including the measurement of estrone, estradiol, and estriol, were conducted for 35 postmenopausal women receiving oral estradiol at doses from 0.025–2.0 mg/day. Urinary excretion of estradiol exceeded normal premenopausal values in women taking estradiol at doses greater than 0.5 mg/day (FIG. 6). Urinary estrone excretion exceeded normal premenopausal values in women taking estradiol doses of 0.25 mg/day or higher (FIG. 7).

These results show that frequently recommended oral doses of estradiol (1–2 mg/day) result in urinary excretion of estrone at values 5–10 times the upper limit of normal in premenopausal women. Based on these measurements, a prudent dose ceiling for oral estradiol replacement therapy appears to be 0.25 mg/day. Retrospective studies associating oral estradiol with increased risk of breast cancer may reflect over-dose conditions.

Under most circumstances serum and urinary estrogens correlate well. However, our laboratory measures serum levels of estrogens less frequently than urinary levels. TABLE 2 shows results for serum estrone measured in women at various phases of the menstrual cycle and pregnancy by another group, compared with serum estrone levels in women taking estradiol 1.0 milligrams daily orally. As FIGURE 7 demonstrates with urinary measurement, TABLE 2 shows that estradiol at 1.0 milligrams orally results in suprphysiologic serum levels, which are very likely unnecessarily hazardous.

Since the early 1980s, average daily “triple estrogen” doses have uniformly contained 0.25 milligrams estradiol, 0.25 milligrams estrone, and 2.0 milligrams estriol. Bi-estrogen doses have usually contained 0.25 milligrams of estradiol, and either 2.0 or 2.25 milligrams of estriol. Follow-up measurement of hormone levels in women given these doses routinely finds both blood and urine doses within the physiologic range noted above: slightly above menopausal, overlapping into the “low range” of these hormones as found in young, healthy, cycling women. (Exceptions are found among women who appear to be “estrogen hyperexcreters” as described in Cases 1, 2, and 3 below.)

TABLE 2. Estrone concentrations in pre- and postmenopausal women, in pregnancy, and with estradiol^a

Patient status	Serum estrone (pg/mL)
Postmenopausal	14–103
Follicular phase	37–138
Luteal phase	50–114
Peri-ovulatory	60–229
Estradiol 1.0 mg/day	159–997
First trimester of pregnancy	62–715
Second trimester of pregnancy	167–1862
Third trimester of pregnancy	1039–3210

^aFrom Stehman-Breen *et al.*⁵

INFLUENCE OF THE ROUTE OF ADMINISTRATION ON ESTROGEN BIOAVAILABILITY

Nature introduces estrogens and other ovarian steroids into the circulation via the pelvic plexus of veins, whence they are carried to the heart and circulated through the lungs, then back to the heart again, and thence to be carried to all parts of the body, including the liver, which is thought to be the major organ of steroid hormone metabolism and detoxification. It is fairly obvious that nature does not introduce ovarian steroids into the intestinal tract, where they might have been absorbed into the plexus of veins leading to the portal vein, and thence taken directly to the liver.

To more closely copy nature, the large majority of physicians prescribing bio-identical estrogens prescribe "transdermal" preparations, usually rubbed in to areas of "thin skin" (inner thighs, wrists) on a monthly cyclic basis. While this practice is closer to the "natural route" described above, it is not as close as possible. Intravaginal administration of the transdermal preparation is the closest possible approximation of the "natural route" of ovarian hormones, introducing them first into the pelvic venous plexus. Experience has shown that this is not just a theoretical consideration.

At Tahoma Clinic we ask women using bio-identical replacement therapy to monitor their urinary estrogen levels (representing "free" and "conjugated" but not "sex-hormone globulin bound" estrogens) at regular intervals to make certain that doses used are within the physiological target range. Over several years time, many women using transdermal estrogen preparations have progressively lower urinary estrogens. Sometimes these lower levels are reflected in symptoms, but sometimes (particularly in women who have used bio-identical hormone replacement for longer periods of time) there are no symptoms of these lower estrogen levels. When the route of administration is then switched to intravaginal, with no change in dosage, the urinary levels rise once again to the target range, and any symptoms of low estrogens disappear.

We have termed this phenomenon "dermal absorption fatigue." Because it occurs often, we have switched our routine recommendation for site of bio-identical hormone administration to the intra-vaginal route.

An example of "dermal absorption fatigue" is shown in FIGURE 8.

On the basis of this and other clinical observations, it appears that intravaginally or transdermally administered doses of estrogens might be absorbed, metabolized, or excreted somewhat differently than orally administered estrogens, even if doses are the same. The following data appear to demonstrate some of these differences.

Eighteen postmenopausal women were given the same 2.5-milligram quantity of bio-identical triple estrogen as part of hormone replacement therapy. Seven took it orally or sublingually, four rubbed it into the skin (routine transdermal administration), and seven used the intravaginal route of administration. Women using triple estrogen by the vaginal or labial route applied the cream on the night before the 24-hour urine collection, to avoid potential contamination of the urine specimen.

For the three different routes of administration the median values for urinary estrone and estradiol concentrations are shown in FIGURE 9, while FIGURE 10 shows the median values for urinary estriol concentrations.

One might wonder whether route of administration of estrogens would produce similar results in both serum and urine. As a very preliminary attempt to answer this question, two postmenopausal women receiving estriol (one woman taking 1 milli-

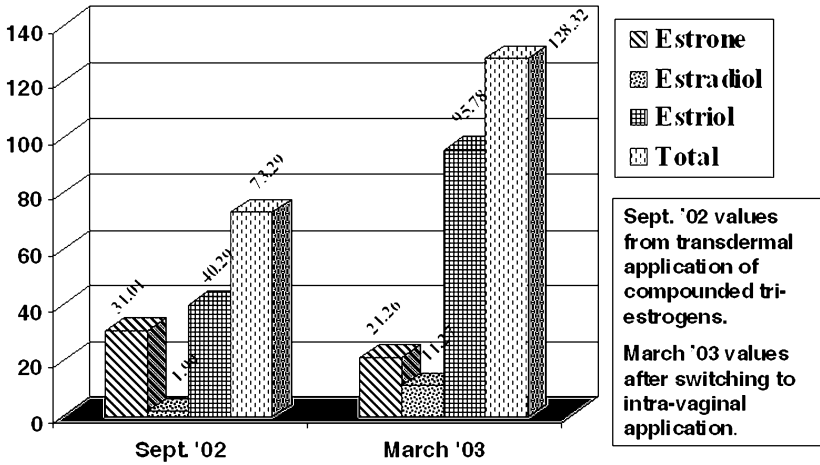


FIGURE 8. 24-hour urine comprehensive hormone levels.

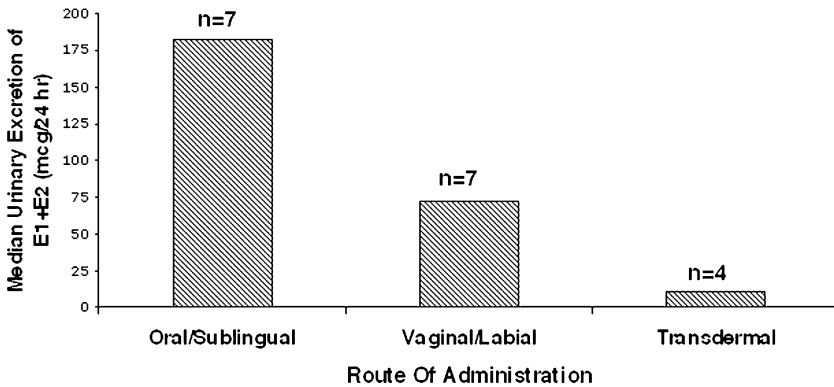


FIGURE 9. Estrone plus estradiol excretion in patients receiving 2.5-mg triple estrogen therapy daily.

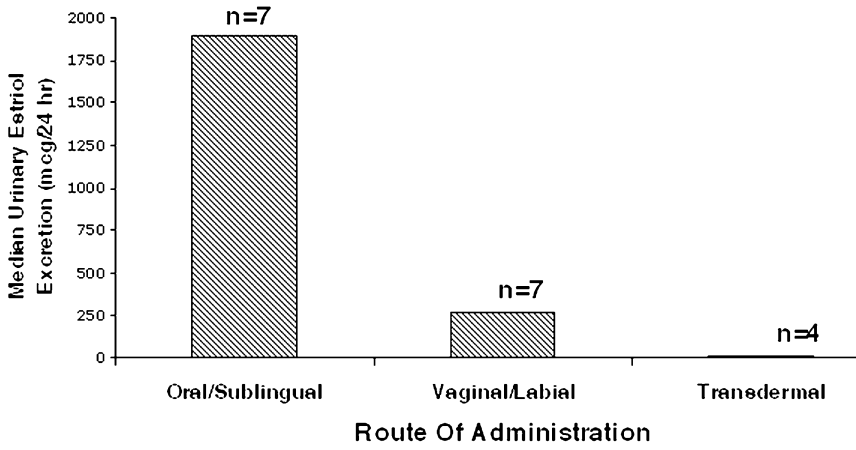


FIGURE 10. Estriol excretion in patients receiving 2.5-mg triple estrogen therapy daily.

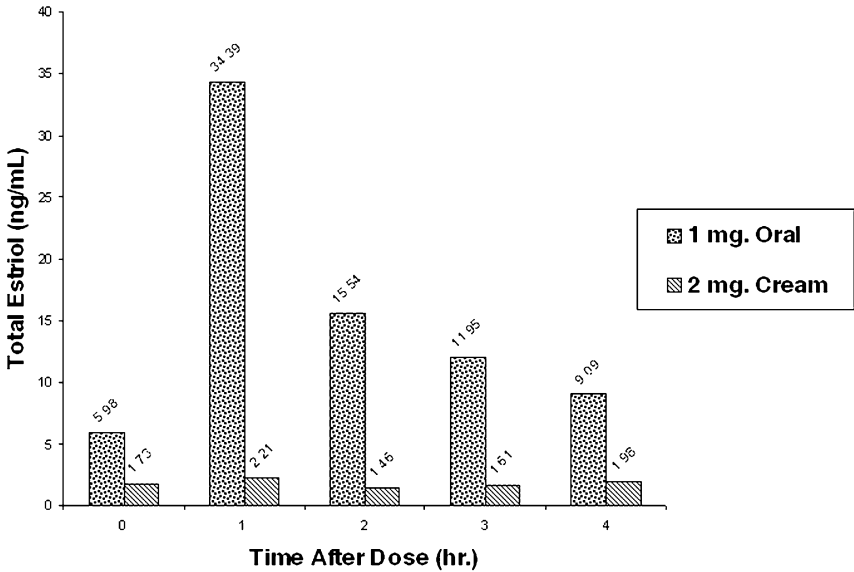


FIGURE 11. Serum estriol: 1-mg oral dose vs. 2 mg creme.

gram orally, the other 2 milligrams transdermally) were tested for total serum estriol immediately before administration of a dose, and at 1, 2, 3, and 4 hours post dose. The results are shown in FIGURE 11, which demonstrates that serum total estriol concentrations are in fact much higher in the woman who took 1 mg orally than in the woman who took 2 mg transdermally, in agreement with the urinary excretion data presented here.

Admittedly, the data presented in this section are very small. However, clinical experience over 23 years is in accordance with this laboratory data. It appears reasonable to hypothesize preliminarily (pending large-scale studies) that the route of bio-identical hormone administration closest to nature’s route is preferable over the long term.

BIO-IDENTICAL ESTROGEN TREATMENT FAILURE AND ESTROGEN HYPEREXCRETION: CORRECTION WITH PHYSIOLOGIC-DOSE COBALT

Practitioners who have prescribed bio-identical hormones for menopausal or postmenopausal women for any period of time have experienced occasional treatment failures. In this small percentage of women, despite carefully escalating doses of bio-identical estrogens (and other accompanying steroid hormones), hot flashes and other symptoms of menopause are not relieved, or are relieved only minimally.

In most cases these treatment failures occur in menopausal or postmenopausal women who have previously taken Premarin or other non-bio-identical “hormone” replacement. In frustration, most of these women may return to taking Premarin or other more risky pseudohormones, since “at least they take care of my symptoms.”

Over the years, it has become obvious that almost all treatment failures with bio-identical hormone replacement have a common biochemical “signature.” When given an “average effective treatment dose” of bio-identical estrogens, women who ex-

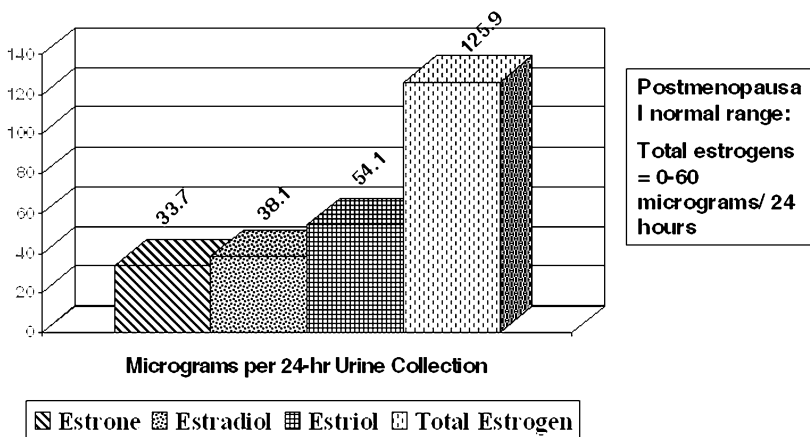


FIGURE 12. Typical normal response with complete symptom relief using triple estrogen: 2.5 mg on days 1–25 (progesterone 25 mg).

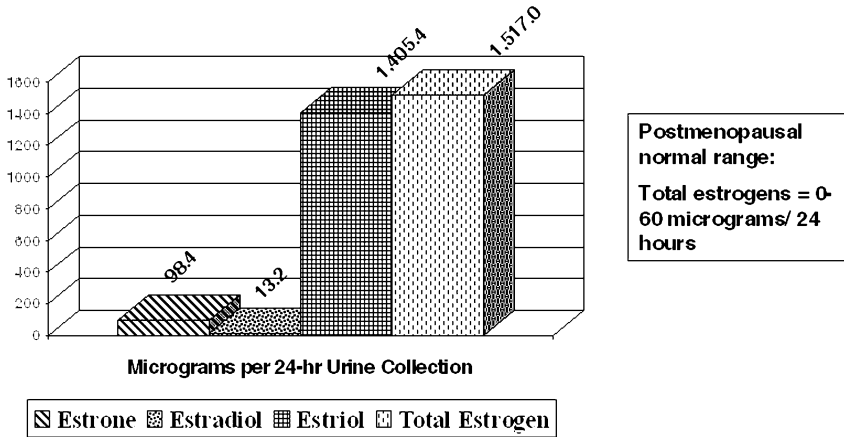


FIGURE 13. Example of hyperexcretion prior to cobalt supplementation while using triple estrogen: 2.5 mg on days 1–25 (progesterone 25 mg).

perience treatment failure hyperexcrete estrogens, as compared with women who respond to treatment. FIGURES 12 and 13 show typical estrogen excretion patterns in two women (a “responder” and a “treatment failure”) using the exact same dosage and route of administration of bio-identical estrogens.

Along with many other substances, estrogens are metabolized and “detoxified” by cytochrome P450 (and other) cytochrome enzymes. It seems logical to hypothesize that non-responders to bio-identical estrogen replacement may have upregulated cytochrome enzymes that may be gradually downregulated to normal function. A variety of minerals, both essential and toxic elements, are known to affect cytochrome function.

Because of its safety in quantities ordinarily found in dietary surveys, cobalt was chosen as a possibility for “downregulating” possibly overactive cytochrome P450 enzymes. The results in three typical cases follow.

Case 1

The patient, R.W., was a 49-year-old white woman with a prior history of chronic fatigue syndrome.^a In December 1997, she saw Dr. Lamson concerning menopausal symptoms, including moderately severe hot flashes, insomnia, and anxiety. She collected a 24-hour urine specimen, upon which a comprehensive steroid determination was performed, with results reported in January 1998. Estrogens were reported as: estrone: 12.30 mg/24 h; estradiol: 22.60 mg/24 h; estriol: 1.85 mg/24 h; and total estrogens: 36.75 mg/24 h.

^aThe data in this first case were collected by my clinic at the Tahoma Clinic, Davis Lamson, N.D., and his patient R.W.

The patient was started on triple estrogen [E1:E2:E3/10:10:80], 1.25 milligrams daily, with no ensuing symptom relief. The same estrogens were increased to 2.5 milligrams daily. Symptoms continued unabated.

While still using the 2.5-milligram daily dosage of estrogens, the patient collected another 24-hour urine specimen, upon which the same steroid determinations were performed. This time results were: **estrone:** 55.7 $\mu\text{g}/24\text{ h}$; **estradiol:** 53.6 $\mu\text{g}/24\text{ h}$; **estriol:** 808.8 $\mu\text{g}/24\text{ h}$; and **total estrogens:** 918.0 $\mu\text{g}/24\text{ h}$.

Along with her continuing triple estrogen therapy, R.W. then started cobalt supplementation, 400–500 micrograms daily. Two weeks later, she reported that her hot flashes and other menopausal symptoms ceased for the first time. However, she also reported that if she skipped a daily dose of cobalt, the hot flashes promptly returned, only to disappear with resumption of the cobalt.

Slightly over a month after starting the cobalt, she reported that on another “skipped dose” occasion, she had not only return of hot flashes, but also “spotting,” which continued at a low level for two weeks, even though the hot flashes ceased as before with resumption of cobalt.

As she continued cobalt (along with the triple estrogen at 2.5 milligrams daily, taken on a 25/28 day cyclic basis) she had no further hot flashes. She omitted occasional cobalt dosages without recurrence of hot flashes.

After 10 weeks of supplemental cobalt along with the continuing triple estrogen, her 24-hour steroid analysis yielded the following estrogen values: **estrone:** 11.3 $\mu\text{g}/24\text{ h}$; **estradiol:** 50.4 $\mu\text{g}/24\text{ h}$; **estriol:** 41.7 $\mu\text{g}/24\text{ h}$; and **total estrogens:** 103.4 $\mu\text{g}/24\text{ h}$.

As noted above, this estrogen total is within the anticipated range for postmenopausal women supplemented with 2.5 milligrams of triple estrogen daily.

Case 2

The patient, J.S., was a 63-year-old woman^b who had been on bio-identical hormone replacement therapy for approximately three years. She was still having night sweats and difficulty sleeping, as well as difficulty with memory and concentration. Twenty-four hour urinary estrogens were: **estrone:** 98.4 $\mu\text{g}/24\text{ h}$; **estradiol:** 13.2 $\mu\text{g}/24\text{ h}$; **estriol:** 1405.4 $\mu\text{g}/24\text{ h}$; and **total estrogens:** 1517.0 $\mu\text{g}/24\text{ h}$.

The patient continued to take triple estrogen 2.5 milligrams daily (cyclic basis), and was advised to start cobalt, 500 micrograms daily. Eleven weeks later, her estrogens were: **estrone:** 8.8 $\mu\text{g}/24\text{ h}$; **estradiol:** 95.6 $\mu\text{g}/24\text{ h}$; **estriol:** 32.2 $\mu\text{g}/24\text{ h}$; and **total estrogens:** 136.5 $\mu\text{g}/24\text{ h}$.

Her symptoms of menopause were relieved.

Case 3

The patient, J.K., was a 52-year-old woman with symptoms of hypothyroidism and menopause, the latter including night sweats, vaginal dryness, anxiety, irritability, and mood swings. Her last menstrual period was four months previously.

^bThe data for the patients in Cases 2 and 3 were collected by my former Tahoma Clinic colleague, Joni Olehausen, N.D., and her patients J.S. and J.K.

She was already taking bi-estrogen (estriol 1 milligram, estradiol 250 micrograms) twice daily on a cyclic basis with a progestin. Her sex hormones were evaluated with the 24-hour urine testing for sex steroids with the result below: **estrone:** 396.9 $\mu\text{g}/24\text{ h}$; **estradiol:** 101.3 $\mu\text{g}/24\text{ h}$; **estriol:** 1405.4 $\mu\text{g}/24\text{ h}$; and **total estrogens:** 1903.5 $\mu\text{g}/24\text{ h}$.

Menopausal symptoms continued. On a return visit, six months later, she was advised to start on cobalt, 500 micrograms daily, while continuing her bio-identical estrogens. Ten weeks later, her estrogen values were as follows: **estrone:** 212.8 $\mu\text{g}/24\text{ h}$; **estradiol:** 73.3 $\mu\text{g}/24\text{ h}$; **estriol:** 25.9 $\mu\text{g}/24\text{ h}$; and **total estrogens:** 311.9 $\mu\text{g}/24\text{ h}$.

Although the patient's total estrogens had not yet diminished to a more expected range, except for continuing difficulty in sleeping, her menopausal symptoms were improved. Unfortunately, she has not come for follow-up evaluation.

Although many individuals need only 500 micrograms of cobalt daily to help normalize symptoms of menopause and reduce apparent estrogen hyperexcretion, some have needed up to 1120 micrograms daily. In nearly all cases, cobalt supplementation has been discontinued without need for resumption once estrogen excretion has declined to normal.

In both Cases 2 and 3, although total estrogen excretion declined dramatically after the ingestion of cobalt, the relative proportion of estriol as a fraction of total excreted estrogens also declined dramatically. This is addressed in the next section.

APPARENT STIMULATION OF THE ESTRADIOL \rightarrow ESTRONE \rightarrow ESTRIOL \rightarrow PATHWAY BY IODINE AND IODIDE

While estrone and estradiol are both physiologic estrogens, they are generally conceded to be slightly pro-carcinogenic. Estriol has been long considered as either neutral or anti-carcinogenic. Accumulating research shows that in the presence of more pro-carcinogenic estrogens, estriol becomes anti-carcinogenic.

The most prominent proponent of the "estriol hypothesis" of anti-carcinogenesis, gynecologic oncologist, Henry Lemon, M.D., has argued that the relative proportions of estrone, estradiol, and estriol were at least as important as the absolute quantities of each hormone. He developed and named the Estrogen Quotient (EQ), the quantity of estriol divided by the sum of estrone and estradiol [$\text{EQ} = \text{E3} / (\text{E1} + \text{E2})$]. He argued that a higher estrogen quotient means lower cancer risk and a better chance of recovery from cancer should it occur.

The following is one of the best examples available of the iodine-estrogen interaction, specifically the effect of iodine and iodide in stimulating the estradiol \rightarrow estrone \rightarrow estriol pathway towards estriol, and thus a higher estrogen quotient (EQ). The following case history is taken directly from chart notes and laboratory tests compiled between 1980 and 1992.

Case 4

23 April 80: The 34-year-old patient's initial visit was for fibrocystic breast disease. Prior to this visit, she had detected three breast lumps; she stopped caffeine intake and the lumps disappeared. However, her breasts were still uncomfortable, so she sought medical attention. She reported that her menstrual periods are regular, but

lighter than before. Her last menstrual period was on 13 April. She took thyroid 5 years ago, and was now taking supplemental kelp. Her examination disclosed minimal but tender fibrocystic breast disease.

2 May 80: 24-hour urinary estrogens showed the following values: **estrone**: 19.3 $\mu\text{g}/24\text{ h}$; **estradiol**: 17.8 $\mu\text{g}/24\text{ h}$; **estriol**: 27.4 $\mu\text{g}/24\text{ h}$; and **estrogen quotient (EQ)**: 0.74.

She was asked to start on iodo-niacin tablet (135 milligrams iodide, 15 milligrams niacin; no longer available) once daily, along with other supplementation.

30 May 80: Her breast tenderness was much improved; patient instructed to continue iodo-niacin.

22 December 80: No further fibrocystic problems unless patient eats beef, and then her breasts become a little tender.

6 August 81: 24-hour urinary estrogens (same supplement program) were as follows: **estrone**: 44 $\mu\text{g}/24\text{ h}$; **estradiol**: 42 $\mu\text{g}/24\text{ h}$; **estriol**: 84 $\mu\text{g}/24\text{ h}$; and **EQ**: 0.97.

20 August 81: Fibrocystic disease remained abated. T3, T4, and TSH were checked as iodine was to be continued.

22 September 82: Fibrocystic disease remained improved. Patient can only use iodo-niacin 3 times weekly or her nose drips. Thyroid function tests to be checked to make sure there is no suppression; estrogens also to be re-checked.

25 September 82: 24-hour urinary estrogens were: **estrone**: 11 $\mu\text{g}/24\text{ h}$; **estradiol**: 9 $\mu\text{g}/24\text{ h}$; **estriol**: 29 $\mu\text{g}/24\text{ h}$; and **EQ**: 1.48

9 October 82: Thyroid function test results were normal; patient to continue program, including iodo-niacin 3 times weekly.

[Summer 1983: Patient subsequently reported stopping iodo-niacin at this time as her breasts were better.]

7 February 84: 24-hour urinary estrogens were: **estrone**: 32 $\mu\text{g}/24\text{ h}$; **estradiol**: 11 $\mu\text{g}/24\text{ h}$; **estriol**: 21 $\mu\text{g}/24\text{ h}$; and **EQ**: 0.5.

7 March 84: Patient has a small nodule in her left breast, probably fibrocystic, for which a mammogram is scheduled. Results of thyroid function test remain normal. Since iodo-niacin has become unavailable, Lugol's iodine solution is recommended at dose of 6 drops daily (~ 37.5 milligrams iodide and iodine).

15 October 84: 24-hour urinary estrogens were: **estrone**: 40 $\mu\text{g}/24\text{ h}$; **estradiol**: 4 $\mu\text{g}/24\text{ h}$; **estriol**: 44 $\mu\text{g}/24\text{ h}$; **EQ**: 1.0.

17 December 84: Mammogram "benign." Patient's breasts were much softer again since resumption of iodine per Lugol's solution.

25 March 87: 24-hour urinary estrogens were: **estrone**: 15 $\mu\text{g}/24\text{ h}$; **estradiol**: 2 $\mu\text{g}/24\text{ h}$; **estriol**: 76 $\mu\text{g}/24\text{ h}$; and **EQ**: 4.47.

5 May 87: Doing very well. No interim problem with fibrocystic breast symptoms. Therapy continued as is.

[“Sometime in 1988”: As patient's fibrocystic breast disease symptoms had been gone since 1984, she cut back the Lugol's iodine to 1 drop daily.]

11 September 89: 24-hour urinary estrogens: **estrone**: 19.2 $\mu\text{g}/24\text{ h}$; **estradiol**: 9.6 $\mu\text{g}/24\text{ h}$; **estriol**: 11.5 $\mu\text{g}/24\text{ h}$; and **EQ**: 0.4.

12 October 89: On the basis of these follow-up lab results with the lowered EQ the importance of resuming Lugol's iodine, 6 drops daily, was emphasized.⁵

9 January 91: Thyroid function tests normal. In 1990 patient switched from Lugol's iodine [6 drops daily] to SSKI, 6 drops daily; these contain iodide total of 108 milligrams). First appearance of “hot flashes” and other menopausal symptoms.

22 February 92: 24-hour urinary estrogens: **estrone**: 2 µg/24 h; **estradiol**: 1 µg/24 h; **estriol**: 9 µg/24 h; **EQ**: 3.0

22 April 92: No changes. Patient not interested in bio-identical hormones for symptoms of menopause.

Case 5

26 August 85: The patient, an asymptomatic postmenopausal woman, made an initial visit for pelvic examination and Pap smear. Because she had a family history of estrogen-related cancer, 24-hour urinary estrogen determination as recommended.

28 August 85: 24-hour urinary estrogens: **estrone**: 3 µg/24 hours; **estradiol**: 16 µg/24 hours; **estriol**: 1 µg/24 h; **EQ**: 0.05.

29 October 85: Results of Pap smear unremarkable, but because of very low estrogen quotient, Lugol's iodine, 8 drops daily (equivalent to 50 milligrams iodine and iodide daily), was recommended and her thyroid function was to be checked before next visit.

31 December 85: Results of 24-hour urinary estrogens: **estrone**: 8 µg/24 h; **estradiol**: 1 µg/24 hours; **estriol**: 14 µg/24 h; **estrogen quotient**: 1.55

Case 6

[day obscured] February 1993: The patient, a postmenopausal woman without symptoms of menopause, presented for a general health check, pelvic exam, and Pap smear. Because she has a family history of estrogen-related cancer, testing of 24-hour urinary estrogens was recommended.

2 March 93: Results of 24-hour urinary estrogens: **estrone**: 10 µg/24 h; **estradiol**: 5 µg/24 h; **estriol**: 15 µg/24 h; **EQ**: 1.0.

19 April 93: Follow-up visit concerned results of lab tests and Lugol's iodine, 8 drops daily, was recommended.

28 September 93: 24-hour urinary estrogens: **estrone**: 20 µg/24 h; **estradiol**: 13 µg/24 h; **estriol**: 46 µg/24 h; **EQ**: 1.39.

Case 7

The following case illustrates that large quantities of iodine are sometimes needed to change the estrogen quotient. Of course, thyroid function should be monitored.

31 January 84: The patient's initial visit was for fibrocystic breast disease. Her history showed that she had had one breast cyst drained and was taking 800 IU vitamin E daily, believing it helped a little. Mammogram in November 1983 was "negative." Breast exam disclosed 2+ fibrocystic changes bilaterally. Myers' iodine treatment for fibrocystic breast disease and a 24-hour urinary estrogen test was recommended.

22 March 84: 24-hour urinary estrogen levels were as follows: **estrone**: 13 µg/24 h; **estradiol**: 11 µg/24 h; **estriol**: 45 µg/24 h; **EQ**: 0.67.

1 May 84: The patient's breasts were better with Myers' treatment, but are improving more slowly than usual; there is sufficient improvement to switch to iodine, 1 tablet daily.

9 October 84: Breasts are generally better, but recent small tender lump was felt in right breast. Examination disclosed a small tender lump in the right breast, al-

though her overall fibrocystic problem is less than it as in January. Mammogram taken as a precaution and the patient was to continue iodo-niacin.

7 April 85: 24-hour urinary estrogens: **estrone:** 13 µg/24 h; **estradiol:** 2 µg/24 h; **estriol:** 10 µg/24 h; **EQ:** 0.67.

As the patient's EQ is no better, she was to increase iodo-niacin to 2 tablets, 3 times daily and to have her thyroid function monitored.

16 November 86: 24-hour urinary estrogens: **estrone:** 14 µg/24 h; **estradiol:** 3 µg/24 h; **estriol:** 33 µg/24 h; **EQ:** 1.94.

Results of thyroid function test were within normal limits.

DISCUSSION

Since 1982, I've reviewed several thousand 24-hour urinary steroid analysis reports (which include estrone, estradiol, and estriol), both from individuals I have worked with in my practice and from other practitioners who have had specimens sent to the Meridian Valley Laboratory. While a majority of women have a "favorable" estrogen quotient, a significant minority have relatively low levels of estriol, with the majority of these having higher estrone than estradiol levels. When estradiol alone is used as a supplement for symptoms of menopause, most women whose preliminary tests show low estriol fractions continue to have lower estriol fractions, with relatively greater increases in estrone and estradiol.

Japan has the highest average daily dietary iodine and iodide intake world-wide. It is likely not a coincidence that Japanese women following traditional Japanese diets have both the highest average serum estriol levels world-wide, and also the world's lowest rate of breast cancer. It would likely be prudent to copy nature in her 3000+-year Japanese dietary iodine experiment, and include at least "Japanese quantities" of iodine in our recommendations to women who want to reduce their risk of cancer, especially women with low estrogen quotients.

CONCLUSION

The above data have been gathered from 23 years of bio-identical hormone replacement therapy and clinical laboratory testing of this therapy, contained in a background of 35 years of medical practice using natural substances and homeopathy magnets. Certainly such data are not a substitute for large-scale, controlled studies; but they can possibly be used to provide some direction and clues for future research. Until such research studies are done, these few data appear to confirm the observations of Paracelsus and the many, many other less famous physicians who have noted that copying nature as closely as possible is the best and safest practice of medicine.

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