

Treatment of Advanced Postmenopausal Breast Cancer with an Aromatase Inhibitor, 4-Hydroxyandrostenedione: Phase II Report¹

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ABSTRACT

4-Hydroxyandrostenedione (4-OHA), a potent new aromatase inhibitor, was given i.m. (500–1000 mg) to 58 patients with advanced postmenopausal breast cancer. Of 52 assessable patients 14 responded (27%), in 10 (19%) the disease stabilized, and in 28 (54%) the disease progressed. Sterile abscesses occurred at the injection site in 6 patients and painful lumps were found in a further 3 patients. Two patients developed allergic-type reactions and 4 developed lethargy, suspected to be treatment induced. Plasma estradiol levels were suppressed from a mean of 7.2 ± 0.8 (SE) pg/ml before treatment to 2.6 ± 0.2 , 2.7 ± 0.2 , and 2.8 ± 0.3 pg/ml after 1, 2, and >4 months, respectively, of treatment and remained suppressed in patients whose disease relapsed. No significant fall in estrone levels was seen. Similarly, dehydroepiandrosterone sulfate, sex hormone binding globulin, and gonadotrophin levels were unaltered after 6 months of treatment. Plasma 4-OHA levels were measured in a radioimmunoassay for androstenedione after chromatographic separation of 4-OHA from androstenedione. Drug concentrations ranged from 0.7 to 23.2 (7.8 ± 1.1) ng/ml after 2 months on treatment.

4-OHA is an effective drug in the management of postmenopausal patients with breast cancer and does not produce notable systemic side effects.

INTRODUCTION

Estrogen deprivation is thought to be a major mechanism of the endocrine treatment of breast cancer. Approximately 30% of postmenopausal patients with advanced breast cancer respond to current modes of endocrine therapy. The source of estrogen in these patients is from conversion of circulating androgens by the estrogen synthetase enzyme complex, aromatase, in peripheral tissues (1). Our approach is to deprive tumors of estrogen with compounds which selectively inhibit this enzyme. Since our first report in 1973 we have identified a number of aromatase inhibitors of which 4-OHA³ (The material used in this study was supplied by Ciba-Geigy, Basle, Switzerland; 4-OHA; CGP 32349.) is the most potent inhibitor of human placental aromatase (2, 3) (K_i 0.15 μ M). 4-OHA treatment inhibits peripheral aromatization in rhesus monkeys (4), suppresses ovarian estrogen secretion in rats (3), and causes regression comparable to ovariectomy of carcinogen-induced mammary tumors in these animals (5).

Our preliminary communication on the first use of this drug in humans documented response in 4 of 11 postmenopausal women with advanced breast cancer (6). We report here a larger Phase II study confirming the biological activity of 4-OHA in advanced postmenopausal breast cancer, and toxicity findings are discussed. The endocrine effects and plasma drug levels of 4-OHA are also described.

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³ The abbreviations used are: 4-OHA, 4-hydroxyandrostenedione; ER, estrogen receptor; LH, leuteinizing hormone; FSH, follicle stimulating hormone; DHAS, dehydroepiandrosterone sulfate; SHBG, sex hormone binding globulin; AG, aminoglutethimide; 17 β OHSDH, 17 β -hydroxysteroid dehydrogenase.

PATIENTS AND METHODS

Patient Selection. All patients selected were postmenopausal or surgically ovariectomized women who had been shown to have primary breast cancer and assessable (by International Union Against Cancer criteria) progressive metastatic disease (7). Patients were included irrespective of the ER status of their primary or metastatic tumors. "ER positive" tumors were designated to be those which bound more than 15 fmol estradiol per mg cytosol protein as measured by a previously described method (8). No patient had received endocrine or chemotherapy within 4 weeks of the start of treatment. Exclusion criteria included a second primary tumor; significant renal (blood urea nitrogen, >12 mM), hepatic (bilirubin, >17 μ M), or cardiac disease; rapidly progressive life threatening metastases; a life expectancy of <6 weeks; adverse psychological factors or refusal to give written informed consent. Informed consent was obtained from all patients, and the study was approved by the Royal Marsden Hospital Ethics Committee; the Office for Protection from Research Risks, NIH; and Human Volunteers Research Committee, University of Maryland School of Medicine, Baltimore, MD. Patients were free to withdraw from the trial at any time.

Clinical Protocol. All patients were fully staged by previously published methods (9) at the beginning of treatment and again at 2, 6, and 12 months and 6 monthly intervals thereafter. They were seen on an outpatient basis weekly for the first 8 weeks and then once a month. Investigations included a history, full clinical examination by at least 2 physicians with bidimensional measurement of all lesions, full blood count, urea, electrolytes, calcium, phosphate, liver function tests, γ -glutamyl transferase on each visit and chest X-ray, bone scan, limited skeletal survey, liver ultrasound, and photography every 2 months. Response to treatment was measured according to the standard criteria of the International Union Against Cancer (7). In the case of bidimensional lesions response was defined as either disappearance of all lesions or a decrease by 50% or more in the sum of the products of the diameters of individual lesions with no lesion increasing in size. In each case no new lesions should have appeared. Progression was defined as either the appearance of new lesions or an increase of 25% or more in the sum of the products of the diameters of individual lesions or if an increase of less than 25% made additional treatment necessary. In situations such as infiltration of the breast, liver involvement, or mediastinal lymphadenopathy objective regression was classified as a 50% or greater decrease in that measurement which was regarded as being in excess of that usual for the site under consideration.

Initially patients received 4-OHA at a dose of 500 mg once weekly in alternate buttocks by i.m. injection. The dose chosen was approximately 0.2% of the acute 10% lethal dose obtained in mice during preclinical toxicity studies. Later in 11 patients, mainly nonresponders, the dose was increased to 1000 mg (500 mg in each buttock weekly). The drug, supplied as a sterile microcrystalline powder and stored at 4°C, was suspended in physiological saline (500 mg/4 ml) immediately prior to administration. Injection sites were varied to avoid local side effects. Where these became severe, treatment was decreased in frequency or stopped. In the event of disease progression, treatment was immediately discontinued, the patient was restaged (as above), and alternative treatment was considered. Patients who died or whose treatment was discontinued before 4 weeks of treatment were excluded from analysis. Patients on treatment for less than 8 weeks were not assessable.

Toxicity and side effects were assessed by routine blood tests, clinical examination when visiting the hospital, and a standard questionnaire

completed each week by the patient and a district nurse. Particular attention was paid to the development of local toxicity and to symptoms or signs suggestive of hormonal side effects.

Hormone Measurement. Estradiol, estrone, LH, FSH, and DHAS were measured by radioimmunoassay according to previously described methods with minor modifications (6, 10–12). Cross-reaction of 4-OHA in the estradiol assay was $<1 \times 10^{-6}\%$ and was avoided in the estrone assay by the chromatography of ether extracts on Lipidex 5000 (Packard) using chloroform:hexane:methanol (50:50:1) as eluent. SHBG binding capacity was measured by the two-tier column method as described previously (13).

Blood was taken from patients before therapy was instituted and during treatment, shortly before each injection of 4-OHA, and at a similar time of day for each patient. Plasma was stored at -20°C until analysis. All samples from the same patient were analyzed in the same assay batch.

Drug Measurement. Ether extracts of plasma were subjected to chromatography on Lipidex 5000 in trimethylpentane:isopropyl alcohol (1:5) which separated androstenedione from 4-OHA. The levels of 4-OHA were then measured, utilizing its 25% cross-reaction in a previously described androstenedione assay (14). Full details of this methodology are to be published elsewhere.

RESULTS

Response to Therapy. Six of the 58 patients entered into the trial were not assessable because 4-OHA was administered for less than 3 weeks. Table 1 gives the pretreatment characteristics of all the patients entered. Most patients were heavily pretreated, 29 (50%) having received at least 2 previous endocrine therapies. Only 8 patients had not received any previous endocrine therapy.

Overall evaluation of 52 assessable patients (Table 2) revealed that 14 (27%) had objective complete (4 patients) or partial (10 patients) responses to treatment. In 10 (19%) patients the disease stabilized for at least 8 weeks on therapy and in 28 (54%) patients the disease progressed. Of the 22 ER positive patients, 6 responded to 4-OHA, 3 had static disease, and in 13 the disease progressed. Of the 3 patients with ER negative tumors 1 responded and 2 had progressive disease. Twenty-four patients had previously responded to endocrine therapy,

Table 1 Pretreatment characteristics of patients treated with 4-hydroxyandrostenedione

The majority of 58 treated patients had soft tissue disease either locally or as skin metastases or lymph nodes. In association with these bone metastases were the most common distant site of involvement. Fifty % of the patients had had two or more endocrine therapies.

No. of patients entered	58
Age (yr)*	
Median	64
Range	37–84
ER status	
Positive	24
Negative	3
Unknown	31
Pretreatment sites of disease (no.)	
Local disease	31
Skin, other than chest wall	20
Lymph nodes	26
Bone	35
Bone pain	8
Lung parenchyma	8
Pleural effusion	3
Liver	11
Central nervous system	2
No. of patients who had 2 or more previous endocrine therapies	29 (50%)
Objective response to prior endocrine therapy	27 (47%)

Table 2 Response to 4-hydroxyandrostenedione according to estrogen receptor status and previous response to endocrine therapy

Fourteen patients responded to 4-OHA. Only one responder was known to have an ER negative tumor. Four patients who had failed to respond to other therapies (tamoxifen in all cases) responded to 4-OHA.

	Response to 4-OHA				
	CR*	PR	NC	PD	NA
Overall response	4	10	10	28	6
	14				
ER status					
Positive	1	5	3	13	2
Negative	0	1	0	2	0
Unknown	3	4	7	13	4
Previous response to endocrine therapy					
Responders	2	5	3	14	3
Nonresponders	2	2	3	9	0
No previous therapy or response not assessable	0	3	4	5	3

* CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NA, not assessable.

Table 3 Response to 4-hydroxyandrostenedione according to sites of disease

Soft tissue sites were the commonest to respond to therapy. Although bone pain was relieved in 63% only a minority of patients showed a healing of bone metastases sufficient to qualify as a partial response.

Site of disease	No. having disease	No. responding to 4-OHA
Local disease	31	11 (35%)
Skin other than chest wall	20	5 (25%)
Lymph nodes	26	8 (31%)
Bone	35	4 (11%)
Bone pain	8	5 (63%)
Lung parenchyma	8	1 (13%)
Pleural effusion	3	0
Liver	11	0
Central nervous system	2	0

and 7 of these responded to 4-OHA, while in 3 the disease stabilized. There was no difference ($P = 0.4$) in disease free interval (*i.e.*, the time from primary diagnosis to first relapse) between responders and nonresponders. Response by site of disease is shown in Table 3. The responses seemed to occur most often in soft tissue and lymph nodes affected by breast cancer, with only 1 response in a visceral site. There were no responses in liver metastases ($n = 11$). Only 4 of 35 (11%) patients' skeletal metastases responded although bone pain was alleviated in 5 of 8 patients with this symptom. Of the 14 patients who responded to 4-OHA, 4 have since relapsed at 3, 4, 4, and 13 months. Ten patients remain in remission for periods between 2 and 18 months. Mean duration of response and response to subsequent therapy cannot yet be adequately evaluated.

Toxicity. Sterile abscesses occurred at the injection site in 6 patients (in 4 only after the dose had been increased to 1000 mg) and moderately painful lumps occurred in a further 3 patients. The severity of the abscesses caused treatment to be discontinued in 2 patients and the frequency of injections was decreased in 2 others. Four patients experienced transient, mild lethargy which appeared to be treatment related. One patient who had been on treatment for 6 months developed an anaphylactoid reaction immediately after an injection. Perioral edema which resolved within 24–48 h occurred in 1 patient. No other systemic toxicity was noted.

Endocrine Effects. Plasma estradiol levels were suppressed from 7.2 ± 0.8 (SE) pg/ml before treatment to 2.6 ± 0.2 pg/ml after 1 month of treatment. There was no further change in estradiol levels after 2 or ≥ 4 months of treatment (Fig. 1). There was no significant difference between responders and

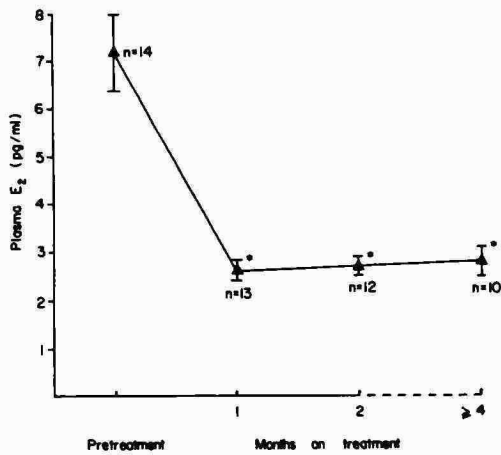


Fig. 1. Mean plasma levels of estradiol (E_2) in patients before and during treatment with 4-OHA (500 mg i.m. weekly). Bars, SE. * $P < 0.001$ versus pretreatment.

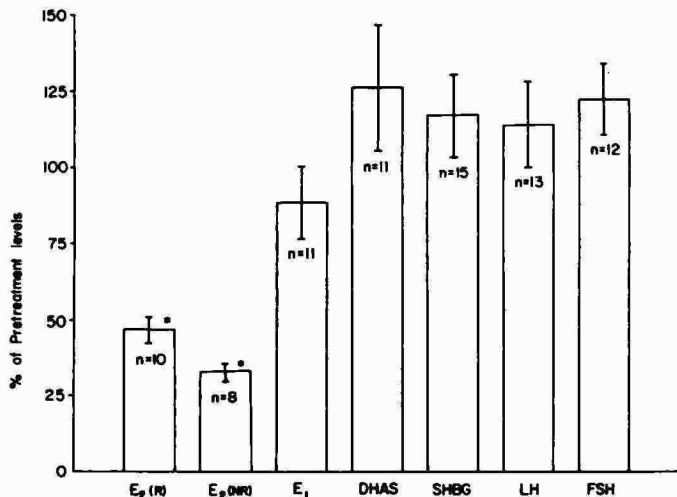


Fig. 2. Endocrine effects of chronic 4-OHA (500 mg i.m. weekly; >1 month) in patients. E_2 , estradiol; E_1 , estrone; (R), responders; (NR), nonresponders. * $P < 0.001$ versus pretreatment.

nonresponders in the suppression of estradiol levels ($P > 0.1$) (Fig. 2).

Plasma levels of estrone, DHAS, SHBG binding capacity, LH, and FSH after at least 1 month of treatment are shown in Fig. 2. Mean pretreatment levels were; estrone, 26.5 ± 4.2 pg/ml; DHAS, 0.82 ± 0.19 μ g/ml; SHBG, 12.2 ± 1.6 ng testosterone/ml; LH, 47.6 ± 6.2 IU/liter; and FSH, 49.8 ± 4.3 IU/liter. There was no significant fall or rise in any of these hormones (paired t tests). The mean estrone level fell to 88.2% of baseline values but this fall was not statistically significantly different from pretreatment levels ($P > 0.1$).

Drug Levels. Drug concentrations in plasma taken from 22 patients after 2 months of therapy and 1 week after their previous injection, ranged from 0.7 to 23.2 (7.8 ± 1.1) ng/ml.

DISCUSSION

Approximately 30–40% of postmenopausal patients with advanced breast cancer respond to hormonal manipulation if selected randomly without regard to the ER status of their tumors (15). AG is an example of an agent in current clinical use (16, 17). It is thought to exert its antitumor effect by suppressing circulating estrogens through its inhibitory action on the enzyme complex aromatase (18). However, it also inhib-

its earlier steps in the steroid biosynthetic pathway (19), depleting corticosteroids, and requiring their replacement (20). In addition, AG causes substantial drowsiness in approximately 40% of patients and a morbilliform, maculopapular skin rash in approximately one-third of patients (16). Our study addressed the question of whether a more powerful and selective aromatase inhibitor than AG could produce improved response rates without adverse side effects.

The observed overall response rate of 27% is similar to other major forms of endocrine treatment although there was a bias in favor of ER positive tumors in our study (ER positive, 22; ER negative, 3; unknown, 27) which might have favored higher response rates (21). However, most patients had advanced metastatic disease (average, 2.5 metastatic sites per patient) and one-half had already received several endocrine therapies prior to receiving 4-OHA. A number of these patients had been resistant to their previous therapy which would reduce the likelihood of their response to subsequent endocrine treatment (15). In addition the optimum dose, route of administration, and dose scheduling have not yet been determined. A comparison of 4-OHA to other forms of endocrine therapy is now needed to define its exact role in breast cancer management.

As regards toxicity, the most frequent side effect was development of local sterile abscesses and moderately painful lumps at the injection sites. The incidence of painful lump decreased as the technique of administration was modified. A slow rate of injection through a narrow bore needle together with careful selection of the injection site, tended to alleviate this problem. This is in keeping with the experience of other investigators using parenteral medroxyprogesterone acetate, another steroid used in patients with advanced breast cancer (22). Local tolerability is not a problem with the lower dosage regimens now being investigated. Lethargy is a common symptom in patients with malignant disease and its occurrence in four of our patients is difficult to evaluate. The two allergic-type reactions noted both occurred in patients with known previous drug allergies. The possibility that the cause of these was an excipient used in the formulation is being investigated.

We have reported previously (6) that plasma estradiol levels were suppressed by greater than 50% by a single 500-mg i.m. injection of 4-OHA and that this suppression was maintained for at least 1 week. In the present study this marked suppression was confirmed and it was demonstrated that there is no escape from suppression as treatment is continued. Since similar suppression of estradiol was seen in responders and nonresponders it is likely that any lack of tumor response is due to differences in estrogen dependence in the tumors and not to ineffective suppression of estradiol.

The failure of 4-OHA to suppress estrone was an unexpected finding since both estradiol and estrone are formed from the conversion of androgenic precursors (testosterone and androstenedione, respectively) and the two estrogens are interconvertible by 17β OHSDH. 4-OHA inhibits conversion of both androgen precursors to their respective estrogens with equal efficiency in human placental microsomes. Aminoglutethimide which is an aromatase inhibitor by virtue of its interaction with cytochrome P-450 (18) reduces plasma estradiol and estrone in a parallel manner (23). The lack of estrone suppression in this study is unlikely to be due to cross-reaction of 4-OHA in the assay since the column chromatography system used prior to the estrone assay was designed specifically to avoid this potential problem. 4-Hydroxyestrone is a minor metabolite of 4-OHA *in vitro* (24) and is converted very rapidly to 4-methoxyestrone (25) which does not coelute with estrone from the Lipidex columns and is therefore unlikely to interfere in the

analysis. The validity of the result is supported by previous observations in rats where suppression of estradiol synthesis by 4-OHA was markedly greater than that of estrone (3, 26). This nonparallel suppression of the estrogens by 4-OHA might be expected to occur if the drug caused inhibition of 17β HSDH. Although the drug appears to interact with that enzyme [4-hydroxytestosterone is a metabolite of 4-OHA in rhesus monkeys (27)], the inhibition of 17β HSDH by 4-OHA *in vitro* is about 100-fold less effective than that of aromatase (28). Although the explanation for the result remains unknown, these results indicate that inhibition of estradiol but not estrone synthesis is important for successful endocrine treatment of postmenopausal breast cancer.

Plasma DHAS levels are a relatively stable marker of adrenal activity and are closely related to urinary free cortisol levels (20). Since 4-OHA therapy did not affect DHAS it is unlikely that it has a significant effect on adrenal function.

Gonadotrophin levels were unaffected by 4-OHA treatment in patients although in ovariectomized rats levels of LH and FSH were suppressed after administration of 4-OHA (26) which was probably due to the slight androgenic activity of the compound (3). Higher doses of 4-OHA in patients may suppress gonadotrophins; however, peripheral aromatase is not under gonadotrophin control in postmenopausal women. These results indicate that at the dose used in this study this is unlikely to be a significant mechanism of action in these patients. Lack of significant androgenic activity is confirmed by our observation that therapy does not alter SHBG binding capacity.

Measurable 4-OHA plasma concentrations 1 week after the previous injection suggest that a depot of drug is formed at the injection site. Slow release of the compound from this site together with its rapid metabolism and clearance rate (27) may account for the low levels found. We have previously reported (29) that 4-OHA is both a competitive, reversible inhibitor of aromatase as well as a slower irreversible suicide inhibitor. This latter effect together with the depot formed at the injection site may account for the sustained suppression of estradiol despite low drug levels.

In conclusion, 4-OHA, a potent new aromatase inhibitor, is capable of markedly reducing plasma estradiol levels and producing tumor regression in postmenopausal patients with advanced breast cancer. This is the first direct evidence that selective inhibition of estradiol synthesis is important in the endocrine treatment of postmenopausal breast cancer. A major advantage of its use over other forms of endocrine therapy is the apparent absence of significant systemic toxicity. Optimum dose, route of administration, and dose scheduling are now being investigated.

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REFERENCES

- Grodin, H. M., Siiteri, P. K., and MacDonald, P. C. Source of estrogen production in postmenopausal women. *J. Clin. Endocrinol. Metab.*, **36**: 207-214, 1973.
- Brodie, A. M. H., Schwarzel, W. C., and Brodie, H. J. Studies on the mechanisms of estrogen biosynthesis in the rat ovary. *J. Steroid Biochem.*, **7**: 787-793, 1976.
- Brodie, A. M. H., Schwarzel, W. C., Shaikh, A. A., and Brodie, H. J. The effect of an aromatase inhibitor 4-hydroxy-4-androstene-3,17-dione, on estrogen-dependent processes in reproduction and breast cancer. *Endocrinology*, **100**: 1684-1695, 1977.
- Brodie, A. M. H., and Longcope, C. Inhibition of peripheral aromatization by aromatase inhibitors, 4-hydroxy- and 4-acetoxyandrostenedione. *Endocrinology*, **106**: 19-21, 1980.
- Brodie, A. M. H., Garrett, W. M., Hendrikson, J. R., and Tsai-Morris, C. H. Effects of aromatase inhibitor 4-hydroxyandrostenedione and other compounds in the DMBA-induced breast carcinoma model. *Cancer Res.*, **42**: 3360s-3364s, 1982.
- Coombes, R. C., Goss, P. E., Dowsett, M., Gazet, J.-C., and Brodie, A. M. H. 4-Hydroxyandrostenedione in treatment of postmenopausal patients with advanced breast cancer. *Lancet*, **2**: 1237-1239, 1984.
- Hayward, J. L., Carbone, P. P., Heuson, J.-C., Kumaoka, S., Segaloff, A., and Rubens, R. D. Assessment of response to therapy in advanced breast cancer. *Cancer (Phila.)*, **39**: 1289-1294, 1977.
- McGuire, W. L., and De La Garza, M. Improved sensitivity in the measurement of estrogen receptor in human breast cancer. *J. Clin. Endocrinol. Metab.*, **37**: 986-989, 1973.
- Coombes, R. C., Powles, T. J., Gazet, J.-C., *et al.* Assessment of biochemical tests to screen for metastases in patients with breast cancer. *Lancet*, **1**: 296-298, 1980.
- Harris, A. L., Dowsett, M., Jeffcoate, S. L., and Smith, I. E. Aminoglutethimide dose and hormone suppression in advanced breast cancer. *Eur. J. Cancer. Clin. Oncol.*, **19**: 493-498, 1983.
- Ferguson, K. M., Hayes, M., and Jeffcoate, S. L. A standardized multicentre procedure for plasma gonadotrophin radioimmunoassay. *Ann. Clin. Biochem.*, **19**: 358-361, 1982.
- Harris, A. L., Dowsett, M., Jeffcoate, S. L., McKinna, J. A., Morgan, M., and Smith, I. E. Endocrine and therapeutic effects of aminoglutethimide in postmenopausal patients with breast cancer. *J. Clin. Endocrinol. Metab.*, **55**: 718-722, 1982.
- Dowsett, M., Attree, S. L., Virdee, S. S., and Jeffcoate, S. L. Oestrogen related changes in sex hormone binding globulin levels during normal and gonadotrophin-stimulated menstrual cycles. *Clin. Endocrinol.*, in press, 1986.
- Dowsett, M., Harris, A. L., Smith, I. E., and Jeffcoate, S. L. Endocrine changes associated with relapse in advanced breast cancer patients on aminoglutethimide therapy. *J. Clin. Endocrinol. Metab.*, **58**: 99-104, 1984.
- Kennedy, B. J. Hormone therapy for advanced breast cancer. *Cancer (Phila.)*, **18**: 1551-1557, 1965.
- Wells, S. A., Santen, R. J., Lipton, A., *et al.* Medical adrenalectomy with aminoglutethimide. Clinical studies in postmenopausal patients with metastatic breast carcinoma. *Ann. Surg.*, **187**: 475-484, 1978.
- Smith, I. E., Fitzharris, B. M., McKinna, J. A., *et al.* Aminoglutethimide in treatment of metastatic breast carcinoma. *Lancet*, **2**: 646-649, 1978.
- Chakraborty, J., Hopkins, R., and Parke, D. V. Biological oxygenation of drugs and steroids in the placenta. *Biochem. J.*, **130**: 19P-20P, 1972.
- Camacho, A. M., Cash, R., Brough, A. J., and Wilroy, R. S. Inhibition of adrenal steroidogenesis by aminoglutethimide and the mechanism of action. *J. Am. Med. Assoc.*, **202**: 20-26, 1967.
- Santen, R. J., Wells, S. A., Runic, S., *et al.* Adrenal suppression with aminoglutethimide. I. Differential effects of aminoglutethimide on glucocorticoid metabolism as a rationale for use of hydrocortisone. *J. Clin. Endocrinol. Metab.*, **45**: 469-479, 1977.
- McGuire, W. L., Carbone, P. P., Sears, M. E., and Escher, G. C. Estrogen receptors in human breast cancer: an overview. In: W. L. McGuire, P. P. Carbone, and E. R. P. Vollmer, (eds.), *Estrogen Receptors in Human Breast Cancer*, pp. 17-30. New York: Raven Press, 1975.
- Ganzina, F. High-dose medroxyprogesterone acetate (MPA) treatment in advanced breast cancer. A review. *Tumori*, **65**: 563-585, 1979.
- Harris, A. L., Dowsett, M., Smith, I. E., and Jeffcoate, S. L. Endocrine effects of low dose aminoglutethimide alone in advanced postmenopausal breast cancer. *Br. J. Cancer*, **47**: 621-627, 1983.
- Marsh, D. A., Romanoff, L. P., Williams, K. I. H., Brodie, H. J., and Brodie, A. M. H. Synthesis of deuterium and tritium labelled 4-hydroxyandrostene-3,17-dione, an aromatase inhibitor, and its metabolism *in vitro* and *in vivo* in the rat. *Biochem. Pharmacol.*, **31**: 701-705, 1981.
- Ball, P., Knuppen, R., Haupt, M., and Breuer, H. Interactions between estrogens and catecholamines and other catechols by the catechol-O-methyltransferase of human liver. *J. Clin. Endocrinol. Metab.*, **34**: 736-746, 1972.
- Brodie, A. M. H., Marsh, D. A., and Brodie, H. J. Aromatase inhibitors. IV—Regression of hormone dependent mammary tumors in the rat with 4-acetoxy-androstene-3,17-dione. *J. Steroid. Biochem.*, **10**: 423-429, 1979.
- Brodie, A. M. H., Romanoff, L. P., and Williams, K. I. H. Metabolism of the aromatase inhibitor 4-hydroxyandrostenedione by male rhesus monkeys. *J. Steroid. Biochem.*, **14**: 693-696, 1982.
- Brodie, A. M. H., Brodie, H. J., Romanoff, L., Williams, J. G., Williams, K. I. H., and Wu, J. T. Inhibition of estrogen biosynthesis and regression of mammary tumors by aromatase inhibitors. *Hormones Cancer. Adv. Exp. Med. Biol.*, **138**: 179-190, 1982.
- Brodie, A. M. H., Garrett, W. M., Hendrikson, J. R., Marcotte, P. A., and Robinson, C. H. Inactivation of aromatase *in vitro* by 4-hydroxyandrostenedione and 4-acetoxyandrostenedione and sustained effect *in vivo*. *Steroids*, **38**: 693-702, 1981.

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