Medical Adrenalectomy with Aminoglutethimide:

Clinical Studies in Postmenopausal Patients with Metastatic Breast Carcinoma

SAMUEL A. WELLS, JR., M.D., RICHARD J. SANTEN, M.D., ALLAN LIPTON, M.D., DARROW E. HAAGENSEN, JR., M.D.
EDWARD J. RUBY, M.D., HAROLD HARVEY, M.D., WILLIAM G. DILLEY, PH.D.

The use of adrenalectomy and hypophysectomy in the management of postmenopausal patients with metastatic breast carcinoma is reserved for highly selected patients. As an alternate approach, a pharmacologic method of inhibiting adrenal cortical secretion was developed which consisted of the daily administration of 1000 mg of aminoglutethimide to block steroidogenesis and either dexamethasone (2.0–3.0 mg/day) or hydrocortisone (40–60 mg/day) as replacement glucocorticoid. This regimen markedly suppressed plasma levels of DHA-S, androstenedione, estrone, and estradiol, and urinary levels of aldosterone. Of 50 patients treated, 19 (38%) demonstrated either a complete (8/19) or a partial (11/19) objective disease remission which lasted for 18.05 ± 3.1 months (mean ± SEM). In 10 (20%) patients, there was stabilization of disease (7.8 ± 1.2 months), accompanied by symptomatic relief of bone pain in six (12%). There was disease progression in 20 (40%) patients. The acute side effects of aminoglutethimide therapy were significant and consisted of transient lethargy (41.5%) and a cutaneous rash (35.8%). Chronic toxicity was negligible. The medical adrenalectomy regimen of aminoglutethimide plus glucocorticoid offers a suitable alternative to surgical adrenalectomy or hypophysectomy in the management of postmenopausal patients with metastatic breast carcinoma.

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina and the Divisions of Endocrinology and Oncology, Department of Medicine and Specialized Cancer Research Center, The Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania

ADRENALECTOMY AND HYPOPHYSECTOMY are surgical procedures widely utilized in the management of postmenopausal women with metastatic breast carcinoma. The reported remission rate for each technique has been in the range of 25–50%.[5,8,9,14] There is an appreciable morbidity and a significant mortality[11,17] associated with these procedures which to some degree has limited their use to highly selected patients. Attempts to suppress ACTH and secondarily adrenal cortical secretion by the administration of high dose corticosteroid therapy have been undertaken; however, regression rates achieved have generally been lower and of shorter duration[6,10] than those resulting from surgical ablative methods. Furthermore, significant adverse side effects accompany the corticosteroid administration.

In 1960, the drug p-(α-amino-phenyl)-α-ethyl glutaramide (aminoglutethimide) was marketed in the United States as an anticonvulsant agent. It was soon apparent clinically, however, that significant side effects were associated with its administration. Approximately 50% of patients taking aminoglutethimide developed a transient morbilliform skin rash. Also some patients developed thyroidomegaly due to a "propylthiouracil-like" effect of the aminoglutethimide which blocked the organification of iodine.[18] The most serious side effect was the occurrence of a marked inhibition of adrenal cortical secretion.[3] Specifically, it was demonstrated that aminoglutethimide blocked the conversion of cholesterol to delta 5-pregnenolone[4] high in the biosynthetic pathway and thus the production of cortisol, androgens and aldosterone. In 1966, aminoglutethimide was recalled from commercial sale; however, it was immediately reinstated as an adrenal inhibitor with an Investigational New Drug status.

In 1969, Griffiths and Hall,[12] appreciating the adrenal cortical inhibiting properties of aminoglutethimide, reported the use of this agent (in doses of 1–2.5 grams/day) in the treatment of nine patients with metastatic

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

Supported in part by NIH Contract No. NCI-CB-53851-37, NCI, DHEW, Grant No. 1P30 CA 18450-01 and Grant RR-30 from the General Clinical Resources Center, Program of the Division of Research Resources, National Institutes of Health, Bethesda, Maryland 20014.

0003-4932-78-0500-0475-0105

carcinoma of the breast. Replacement glucocorticoid (dexamethasone; 0.75 mg/day) and mineralocorticoid (fludrocortisone acetate; 0.1 mg every other day) were also administered concomitantly. Although there was only transient suppression of urinary 17-hydroxycorticoids and 17-ketosteroids during aminoglutethimide therapy, three of their nine patients demonstrated objective tumor remissions persisting for two, seven and nine months. Tumor growth ceased for four and seven months in two other patients. Apparent permanent hypoadrenocorticism was induced in one patient receiving 2.5 g of aminoglutethimide daily, but bilateral adrenal metastases were not excluded.

In 1974, Santen and Lipton[22] further evaluated the aminoglutethimide-dexamethasone regimen and explained why complete adrenal blockade was not observed in previous studies. They demonstrated that aminoglutethimide enhanced the metabolic degradation rate of dexamethasone and thereby reduced its bioavailability. To achieve near-total blockade of adrenal cortical secretion, larger doses of dexamethasone (2–3 mg/day) were required. Unfortunately, the use of the aminoglutethimide-dexamethasone regimen clinically required careful metabolic evaluation of individual patients to determine the ideal dose of dexamethasone relative to aminoglutethimide. It was subsequently demonstrated[23] that hydrocortisone was a more suitable replacement glucocorticoid as its metabolic degradation was uninfluenced by aminoglutethimide.

The purpose of the current study is to report our experience with the aminoglutethimide-glucocorticoid "medical adrenalectomy" regimen in the management of 50 postmenopausal patients with metastatic carcinoma of the breast.

Materials and Methods

Patient Population

Fifty-five patients either from the surgical service at the Duke University Medical Center or from the Divisions of Endocrinology and Oncology at Hershey Medical Center were studied. All of these patients had previously undergone mastectomy for carcinoma of the breast and subsequently developed recurrent disease. Patients were excluded from the study if over 80-years-old, if malignancies of organ systems other than breast were present, or if metastatic breast carcinoma were evident in: more than one-third of the liver, the pulmonary lymphatics, or the central nervous system. Two of the 55 patients were lost to follow, and three were withdrawn from the study because of toxic reactions to the aminoglutethimide. Thus, 50 patients with metastatic breast carcinoma were included in the study, and all were evaluable except one. The relevant clinical data from these patients are presented in Table 1. Of the 50 patients, 35 (70%) had bone metastases, 29 (58%) had skin or soft tissue involvement, 22 (44%) had parenchymal lung involvement, 16 (32%) had liver involvement, and in two (4%) visceral metastases were noted.

Nineteen of the 50 patients when premenopausal had undergone surgical oophorectomy. In 14, the oophorectomy was therapeutic for documented metastatic disease, while in five, the oophorectomy had been "prophylactic."

Criteria of Clinical Response

Classification of a response as an objective complete remission indicated that during therapy all metastatic lesions disappeared for a period of at least three months. A partial regression was defined as a decrease of 50% or greater in the sum of the products of the two largest perpendicular diameters of all measurable lesions, and/or partial recalcification of osteolytic lesions for a period of three months. Regression of osteoblastic lesions or stability with regression of other lesions were also considered objective responses. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in metastatic lesions for at least three months. Progression required an increase of 25% or greater over original measurements.

Prior to therapy and at three monthly intervals thereafter, photographs of skin lesions, and radiographic studies including bone scans, metastatic bone surveys, and liver scans were obtained. Repeat physical examinations were performed on each patient at three monthly intervals, and all data were recorded on a standard patient evaluation flow sheet.

Treatment Protocol

Basal blood samples were collected daily at 8.00–9:00 a.m. for five days prior to the initiation of aminoglutethimide-glucocorticoid therapy. Also during this time, multiple 24 hour urines were collected, and aliquots stored frozen for subsequent hormonal determinations. Additional plasma and urine samples were then obtained at weekly intervals during the first 14 weeks and monthly thereafter until tumor progression was observed.

All patients received at least 250 mg of aminoglutethimide four times daily. In the earliest treated patients, 2 g a day of aminoglutethimide were given. The dexamethasone dosage ranged from 2–3 mg daily. In a selected group of 15 patients, systematic dose response studies were carried out. Dexamethasone was

TABLE 1. *Patients Treated with Aminoglutethimide*

Patient	Months Post-menop.	Dis. Free Interval (mos)	Age (yrs)	Pre-Treatment Involvement					Response	Duration of Response (mos)
				Sk	B	Lg	Lv	Vis		
1	120	24	67	+	–	–	–	–	CR	18
2	0*	9	42	+	–	–	–	–	PR	6
3	84	108	61	+	–	–	–	–	CR	44
4	72	43	59	+	–	–	–	–	CR	12
5	72	24	54	+	+	–	–	–	CR	12
6	60	36	55	+	–	–	–	–	PR	3
7	120	84	57	–	+	+	–	–	PR	9
8	240	78	71	–	+	+	+	–	CR	8
9	60	12	53	–	+	–	+	–	S	7
10	132	84	66	–	+	–	+	–	S	4
11	0	24	47	–	+	–	+	–	CR	40
12	0	3	56	–	+	–	+	–	P	—
13	0	24	44	+	–	+	+	–	P	—
14	120	0	62	+	+	–	–	–	P	—
15	0	24	42	–	–	+	–	–	P	—
16	0	12	49	+	+	+	–	–	S	5
17	96	0	59	+	–	+	+	–	P	—
18	156	20	56	+	+	+	+	–	P	—
19	0	60	51	–	+	–	–	–	P	—
20	460	48	80	+	+	+	+	–	P	—
21	60	108	53	+	–	+	+	–	P	—
22	168	—	67	–	+	–	–	–	Inadequate Follow-up	
23	0	30	49	+	+	–	–	–	P	—
24	0	156	46	–	+	+	+	+	P	—
25	120	72	63	–	–	+	–	–	P	—
26	0	108	43	–	+	–	–	–	CR	30
27	12	0	50	+	+	–	+	–	P	—
28	360	0	76	+	+	–	+	–	S	3
29	84	8	64	+	+	+	+	–	P	—
30	36	12	50	+	–	–	–	–	P	—
31	0	19	50	+	+	+	–	–	PR	18
32	72	36	60	–	+	+	+	–	S	5
33	360	36	74	–	+	–	–	–	S	7
34	0	13	38	+	+	+	–	–	PR	19
35	480	24	79	+	–	+	–	–	CR	21
36	24	0	51	+	+	+	–	–	P	—
37	0	24	45	–	+	–	–	+	PR	8
38	0	28	55	–	+	–	–	–	PR	20
39	0	24	61	+	–	–	–	–	PR	21
40	36	84	50	+	–	–	–	–	P	—
41	0	72	48	–	+	+	–	–	S	23
42	270	60	63	–	+	+	–	–	P	—
43	338	8	55	–	+	+	–	–	S	3
44	0	0	45	–	+	–	–	–	S	14
45	0	24	44	–	+	+	–	–	PR	7
46	168	12	60	+	–	+	–	–	P	—
47	180	36	63	+	+	–	–	–	S	7
48	0	26	49	+	+	–	–	–	PR	19
49	144	16	62	+	+	–	+	–	P	—
50	60	26	59	+	+	–	–	–	PR	11

mos = months, Sk = skin and soft tissue, B = bone, Lg = lung, Lv = liver, Vis = viscera.
* 0 = Therapeutic or prophylactic surgical oophorectomy in premenopausal period.
CR = complete remission, PR = partial remission, S = disease stabilization, P = progression.

given in an initial dose of 2.0 mg daily in four divided doses, and was increased to 2.5 mg daily after two weeks, and then to 3 mg daily after an additional two weeks. Patients were then given 20–30 mg of hydrocortisone daily rather than dexamethasone with dosage increments in a similar fashion at two weekly intervals to a maximum of 60 mg daily. Based upon these studies, the optimum regimen for blocking adrenal steroidogenesis was found to be 40 mg of hydrocortisone (20 mg at bedtime, 10 mg at 0800 hours and 10 mg at 1700 hours), and 250 mg of aminoglutethimide four times daily. The latter dose schedule was used exclusively in patients started on treatment after the dose response studies. Therapy was discontinued in all

TABLE 2. *Patient Response to Aminoglutethimide*

	N	Age (years)	Months Post Menopausal*	Disease Free Interval (mos)	Duration of Response (mos)
Complete Remission	8	60.1 ± 4.3	178.0 ± 66.0	54.1 ± 13.4	25.2 ± 6.3
Partial Remission	11	48.7 ± 2.6	80.0 ± 20.0	28.5 ± 6.0	12.8 ± 2.0†
Stable Disease	10	58.9 ± 3.4	214.6 ± 51.1	29.6 ± 9.3	7.8 ± 1.2†
Disease Progression	20	55.6 ± 2.0	127.6 ± 31.6	36.8 ± 9.4	—

* 19 patients deleted because of surgical oophorectomy performed in premenopausal period.
† $p < 0.02$ compared to Complete Remission.

patients when progression occurred, and chemotherapy or x-ray therapy initiated.

Hormone measurements. Urinary free cortisol was measured by a slightly modified competitive protein binding method of Murphy.[15] Dehydro-epiandrosterone-sulfate (DHA-S) was assayed in unextracted plasma with the radioimmunoassay method of Buster and Abraham.[2] Aldosterone and androstenedione were measured in urine and plasma respectively by radioimmunoassay after extraction and chromatography.[1,21]

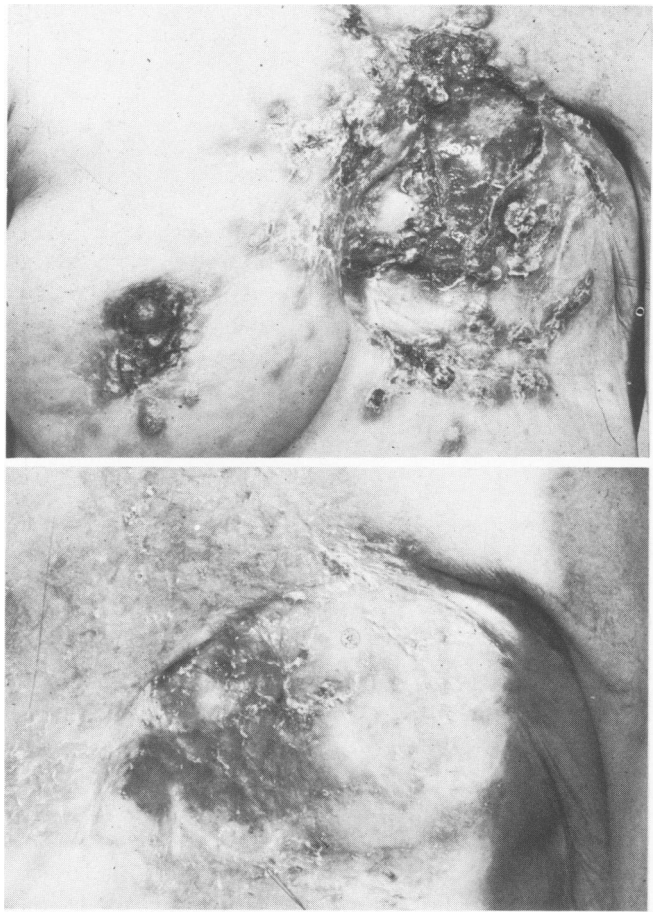

FIG. 1a and b. (a, top) Chest wall, soft tissue, and skin metastases in patient No. 4 prior to therapy. (b, bottom) Appearance of chest wall in the same patient after aminoglutethimide and dexamethasone therapy.

Thyroxine, TSH and prolactin levels in plasma were determined by double antibody radioimmunoassays using standard techniques.[7,16,25] Dr. John Kendall[19] of the University of Oregon measured ACTH levels in plasma with a previously published method of extraction and radioimmunoassay. Plasma estrone and estradiol were measured after extraction and celite chromatography according to the method of Abraham.[1]

Complete and detailed descriptions of the endocrine methodology and results have recently been published in detail,[20,23–25] consequently the following section describes a brief summary of these aspects.

Statistical Methods

For data evaluation and analysis, Student's t test and the Fisher exact probability test were used.

Results

Clinical Response

Of the 50 patients entered into the study, 8 (16%) underwent complete tumor regression, 11 (22%) demonstrated a partial disease remission, 10 (20%) had stabilization of disease, and 20 (40%) demonstrated disease progression. One patient remained on therapy for only two months, and was not evaluable. There appeared to be no statistically significant difference in patient response relative to age, disease-free interval (from mastectomy to tumor recurrence) or the number of months from menopause to tumor recurrence (Table 2); however, the sample groups were small. There was a statistically significant difference noted, however, between the length of complete (25.2 ± 6.3 months) compared to partial (12.8 ± 2.0 months, $p < .02$) remissions; and between the length of complete remissions compared to the length of disease stabilization (7.8 ± 1.2 months; $p < 0.02$). Of the ten patients who had stabilization of disease, there was marked symptomatic relief of bone pain in six (12%). Examples of the types of responses observed are exhibited in Figures 1–3.

Patient No. 4 (Table 1) primarily had skin and soft tissue metastases (Fig. 1a). After the initiation of aminoglutethimide and dexamethasone, she experi-

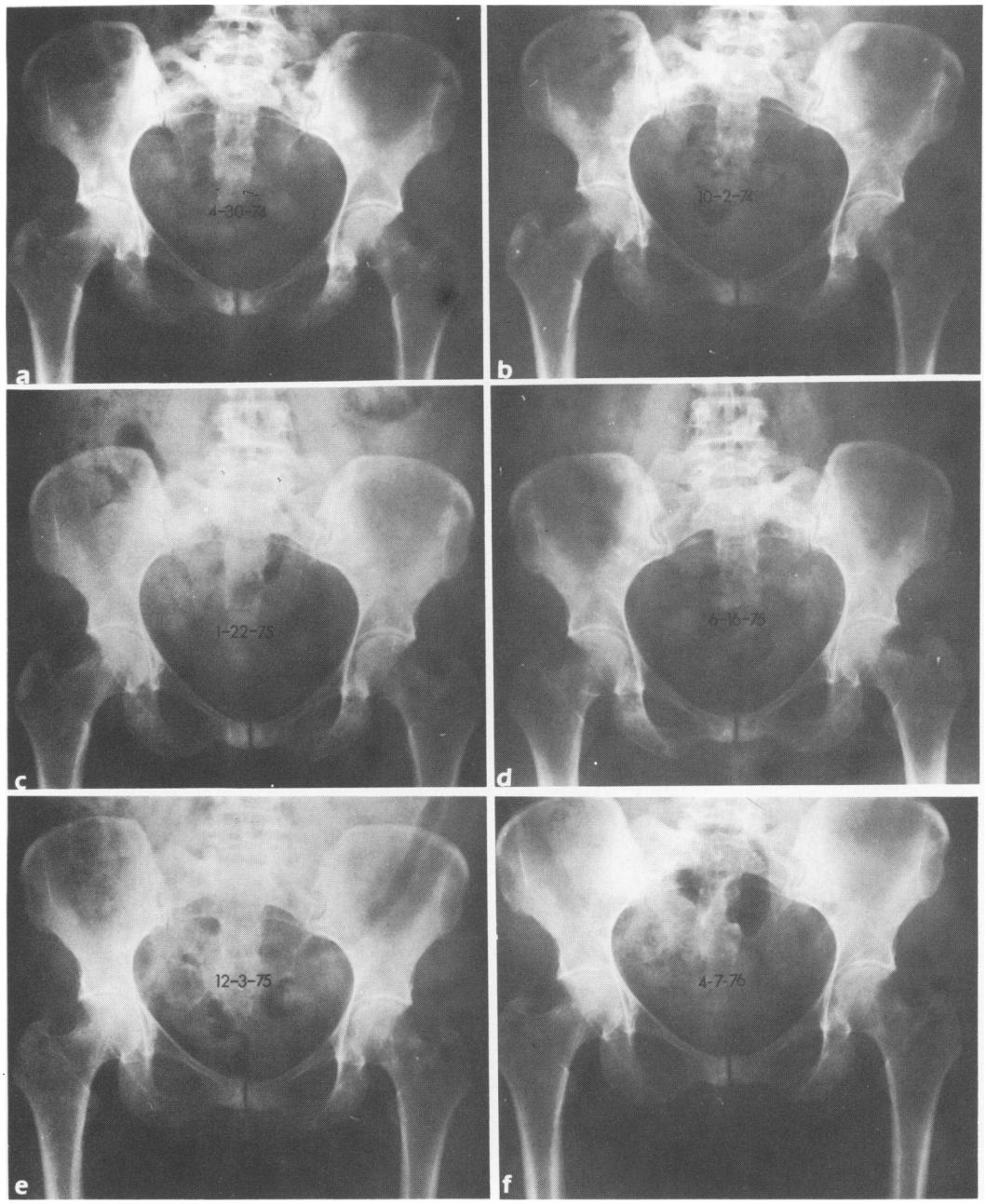

FIG. 2a–f. Pelvic radiographs of patient No. 11 prior to (a) and during (b–f), a prolonged course of aminoglutethimide and dexamethasone therapy.

enced a complete remission (Fig. 1b), which lasted for 12 months.

Patient No. 11 (Table 1) primarily had metastases to bone and liver. After beginning aminoglutethimide and dexamethasone, she underwent a complete remission which has lasted for 40 months. Progressive healing of lytic lesions in the pelvis of this patient is well demonstrated in Figures 2a–f.

Patient No. 35 (Table 1) had breast carcinoma metastatic to skin and lung. Following aminoglutethimide and dexamethasone therapy, she underwent a partial remission which lasted for 20 months. Evidence of this response is demonstrated in Figures 3a–d.

Response to Previous Endocrine Therapy

Thirty-four patients had received one or more forms of hormonal therapy prior to the initiation of the aminoglutethimide-glucocorticoid regimen, *i.e.* high dose corticosteroids (2 patients), oophorectomy (14 patients), hypophysectomy (2 patients), estrogens (17 patients), and/or androgens (23 patients). Of 19 patients who demonstrated a complete or partial remission to aminoglutethimide and glucocorticoid therapy, 12 (61%) had received prior endocrine therapy and a partial or complete remission had resulted in eight (75%). Conversely, of 20 patients who demonstrated

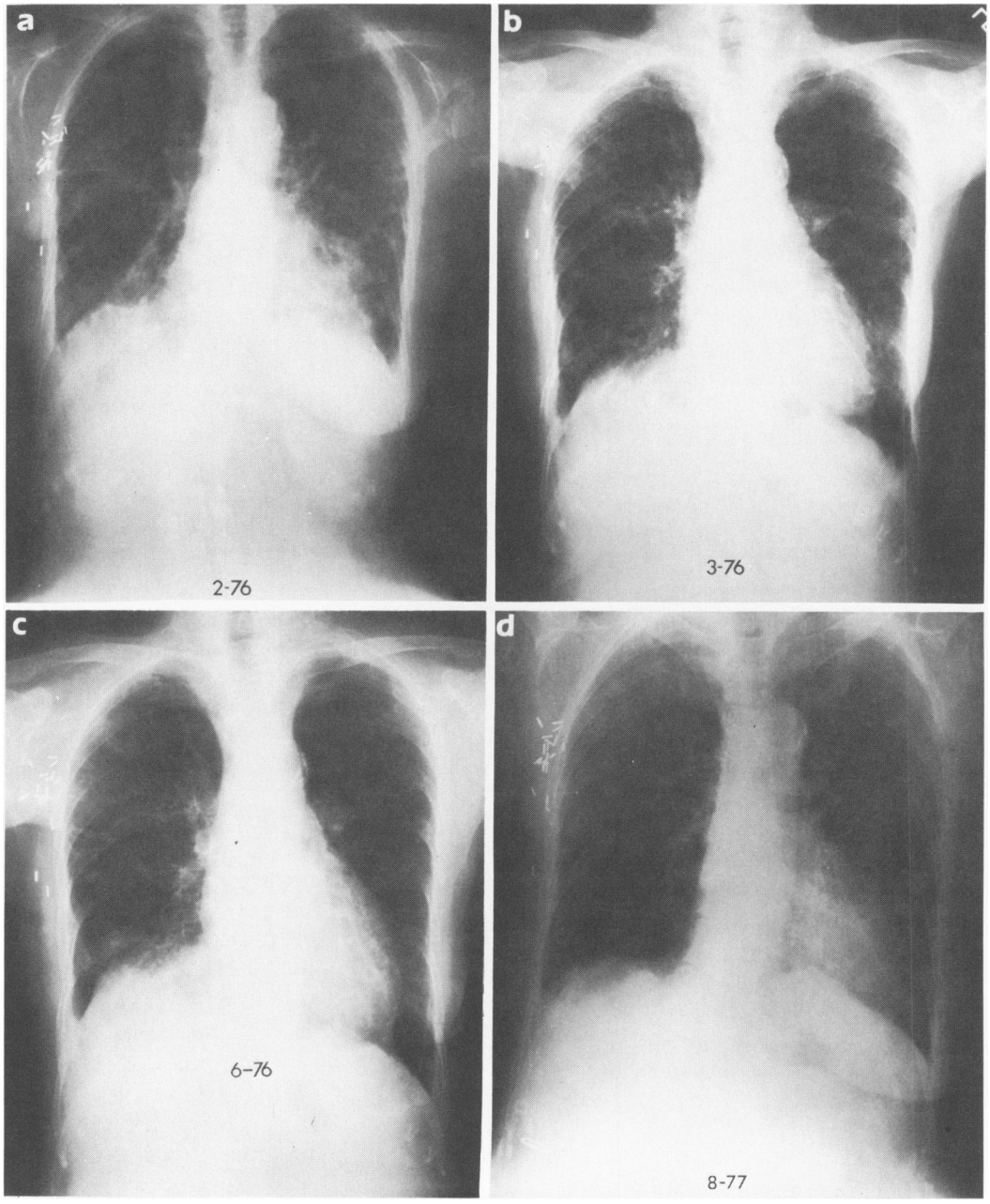

FIG. 3a–d. Chest roentgenographs of patient No. 35 prior to (a) and during (b–d) aminoglutethimide and dexamethasone therapy.

disease progression on aminoglutethimide and dexamethasone therapy, 15 (75%) had received prior endocrine therapy; however, a complete or partial remission had only occurred in three (20%). In our study patients, a previous favorable response to hormonal therapy seemed to predict a subsequent beneficial response to aminoglutethimide plus glucocorticoid ($p < 0.055$).

At the time that this study was begun, estrogen receptor (ER) status was not a criterion for stratification; however, this determination was made in metastatic tumors of six patients, five of which were ER positive. Three of the five patients responded to aminoglutethimide plus a glucocorticoid while the patient who was negative failed to respond.

Hormonal Studies

Evaluation of Plasma DHA-S Levels

Realizing that exogenous hydrocortisone is partially excreted in urine as free cortisol, it was necessary, before demonstrating the usefulness of hydrocortisone administration to develop an alternate method of monitoring adrenal function. The measurement of plasma DHA-S was validated by comparing urinary free corti-

sol and plasma DHA-S levels during dexamethasone and aminoglutethimide administration. The relative suppression of DHA-S and urinary free cortisol was remarkably similar,[24] and, therefore, it was considered valid to monitor adrenal function with DHA-S utilizing hydrocortisone as replacement glucocorticoid.

In 15 patients receiving aminoglutethimide and increasing doses of dexamethasone, the basal DHA-S levels (520 ± 90 ng/ml SEM) progressively fell to a nadir of 68 ± 21 ng/ml during 1000 mg of aminoglutethimide and 3 mg of dexamethasone daily ($p < 0.001$). During chronic therapy with 1000 mg of aminoglutethimide and 40 mg of hydrocortisone, DHA-S levels remained remarkably suppressed to 22.9 ± 5.0 ng/ml ($p < 0.001$). The mean degree of inhibition of DHA-S levels in patients was 93%. Furthermore, during the administration of aminoglutethimide and dexamethasone in eight patients, ACTH levels did not change significantly (64 ± 23 pg/ml) from basal values (81 ± 12 pg/ml). However, during the administration of aminoglutethimide and 40 mg of hydrocortisone, mean ACTH (36 ± 9 pg/ml) was lower than basal values, but remained within the normal range (20–150 pg/ml).

Estrone and Estradiol

In 13 patients receiving 1000 mg of aminoglutethimide and 2 mg of dexamethasone, basal plasma levels of estrone (43.7 ± 11.2 pg/ml) and estradiol (17.5 ± 4.1 pg/ml) fell quite rapidly to levels of 13.5 ± 1.6 pg/ml; $p < 0.02$, and 5.5 ± 1.0 pg/ml; $p < 0.01$ respectively. During prolonged suppression with aminoglutethimide and 40 mg of hydrocortisone, hormone values were further suppressed (estrone 9.3 ± 1.0 pg/ml; $p < 0.001$) and estradiol 5.0 ± 0.5 pg/ml; $p < 0.01$).

Androstenedione

Within two weeks after the initiation of 1000 mg of aminoglutethimide and 2 mg of dexamethasone daily, plasma androstenedione levels significantly increased from basal values of 570 ± 70 pg/ml to 950 ± 160 pg/ml ($p < 0.05$). With the administration of 3 mg of dexamethasone daily, androstenedione levels were suppressed to 340 ± 80 pg/ml ($p < 0.05$) and during chronic treatment with 40 mg of hydrocortisone and 1000 mg of aminoglutethimide daily, plasma androstenedione levels were 230 ± 50 pg/ml; $p < 0.001$.

TSH, Thyroxine and Prolactin

Of 29 patients evaluated during the first eight weeks of therapy, serum thyroxine levels fell by 18% from 8.03 ± 0.57 to 6.79 ± 0.44 ug/dl ($p < 0.01$). Accordingly, TSH levels increased to 178% of control values from 4.47 ± 0.41 uU/ml to 7.91 ± 1.00 ($p < 0.001$). With longer therapy (9–16 weeks) the mean TSH levels rose further to 10.8 ± 2.16 uU/ml. When patients were studied during chronic therapy for up to four years, thyroxine returned toward basal values and demonstration of a significant lowering over basal was no longer possible. The recovery in thyroxine synthesis appeared to result from increased stimulation by TSH which reached levels of 14.5 ± 3.7 uU/ml during chronic therapy. During this observation period, no patients developed clinical evidence of hypothyroidism or goiter.

Mean prolactin levels were in the normal range prior to initiation of therapy (21.5 ± 2.6 ng/ml), and no significant increase could be demonstrated during the 14 weeks when patients were receiving 1000 mg of aminoglutethimide and increasing doses of dexamethasone and hydrocortisone respectively.

Side Effects of Aminoglutethimide

The major side effects of aminoglutethimide therapy are a transient cutaneous rash and dose dependent CNS soporific effects. A morbilliform skin rash usually occurs within 10–14 days after initiation of aminoglutethimide therapy and is frequently associated with malaise and fever. With continuation of treatment, the cutaneous rash spontaneously disappears and patients on chronic therapy rarely have persistence of this complication after the first two to three weeks of therapy. The CNS effects are similar to those induced by the sleeping pill glutethimide (Doriden®) and include lethargy, ataxia, and dizziness. The CNS side effects are also transient, and almost always resolve after one to six weeks of therapy. Furthermore, they are dose related and are not common with the administration of 1000 mg of aminoglutethimide a day.

Of the 49 patients evaluable in our study, 22 (41.5%) experienced significant lethargy, 19 (35.8%) developed a transient cutaneous rash, 6 (11.3%) developed transient ataxia, and 5 (9.4%) complained of dizziness. Three patients (5.8%) noted nystagmus and hyponatremia was detected in two patients (3.8%). Two patients in our study developed an excoriative dermatitis and a third patient developed extreme lethargy early in the treatment course. These side effects resolved, however, following cessation of drug therapy. Compared to the acute effects (Table 3) of aminoglutethimide therapy, the chronic effects were almost nonexistent, there being no lethargy, skin rash, ataxia or nystagmus. Five patients complained of facial fullness, three of weight gain, and two patients experienced leg cramps.

TABLE 3. *Acute and Chronic Aminoglutethimide Toxicity*

	Lethargy	Skin Rash	Ataxia	Other
Acute	22/53 (41.5%)	19/53 (35.8%)	6/53 (11.3%)	5/53 (9.4%)*
Chronic	0/49	0/49	0/49	9/49 (18.5%)†

* Dizziness.
† Weight gain (5), facial fullness (3), leg cramps (2).

When evaluating the incidence of acute side effects of aminoglutethimide therapy, it was evident that patients who experienced either a partial or complete remission had a significantly higher incidence ($p < 0.01$) of a cutaneous rash (10/19; 54%) than did those patients who experienced tumor progression (5/20; 25%). Such an association, however, was not noted with either ataxia, dizziness, or lethargy.

No attempt was made to continue metabolic studies after the cessation of aminoglutethimide therapy in patients with progressive disease. However, no evidence of adrenal cortical insufficiency was noted in any patient. Adrenal tissue during treatment was available for histological examination in patient No. 8. She died acutely of a probable myocardial infarction during the eighth month of aminoglutethimide and dexamethasone therapy. At postmortem examination, her adrenal cortex appeared normal, both grossly and histologically (Fig. 4).

Discussion

Although surgical adrenalectomy and hypophysectomy have been effective in inducing disease remission in postmenopausal women with recurrent breast carcinoma, the associated morbidity accompanying these procedures is appreciable and there is a significant mortality. Furthermore, the nonsurgical methods of suppressing adrenal cortical secretion such as the administration of high dose corticosteroids have only limited effectiveness and carry an appreciable morbidity for the patient.

The described "medical adrenalectomy" regimen of 1000 mg of aminoglutethimide and 2–3 mg of dexamethasone, or preferably 40 mg of hydrocortisone, appears to have great utility in managing postmenopausal patients with metastatic breast carcinoma. It has been demonstrated by our studies that this drug combination markedly suppresses adrenal cortical secretion with significant reductions in the plasma levels of estrone, estradiol, DHA-S, aldosterone, and androstenedione. In our evaluation of 50 patients, 19 (38%) demonstrated a complete or partial objective remission during therapy. These results compare favorably with those obtained in other series[6,11] reporting the utility of surgical adrenalectomy in the treatment of patients with metastatic breast carcinoma.

There are several advantages to this proposed drug therapy which should be stressed. The combination of 1000 mg of aminoglutethimide and 40 mg of

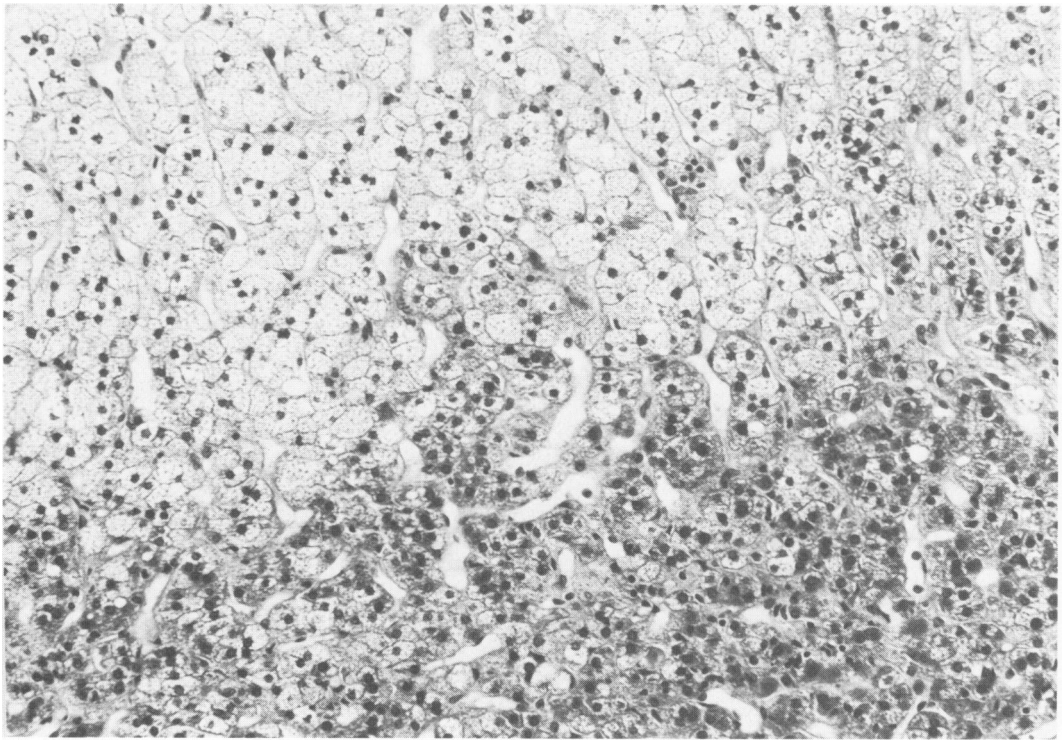

FIG. 4. Histologic section of the adrenal cortex in patient No. 8 who died suddenly of a probable myocardial infarction during aminoglutethimide and dexamethasone therapy. Hematoxylin and eosin ×100.

hydrocortisone administered orally is a simple regimen which can be used easily by primary care physicians. Since there is no drug interaction occurring between aminoglutethimide and hydrocortisone, one can reliably depend on these agents to induce adrenal cortical suppression. Whereas surgical adrenalectomy is an irreversible procedure requiring permanent mineralocorticoid and glucocorticoid replacement, such is not the case in patients treated with aminoglutethimide and hydrocortisone. The adrenal suppression in almost all cases is reversible and maintenance steroid therapy is not required after cessation of treatment. This is of a particular advantage if subsequent chemotherapy or radiation therapy are to be instituted since the addisonian state complicates the administration of these therapeutic modalities.

As demonstrated, there was an early increase in plasma androstenedione after the initiation of aminoglutethimide and dexamethasone. This was followed by a subsequent reduction in androstenedione levels with higher dosages of dexamethasone and even further suppression with the administration of hydrocortisone. The increase in androstenedione was temporally related to suppression of plasma estrone and estradiol levels. It has been demonstrated[13] that the main source of estrone and estradiol in postmenopausal women is the conversion of androstenedione into estrone in peripheral tissues by a process referred to as aromatization. It has also been shown that aminoglutethimide is a potent inhibitor of the aromatization of androstenedione to estrone[27] in placental microsome preparations. Our findings of an increase in androstenedione levels associated with a concomitant reduction of plasma estrone could be explained by an inhibiting effect of aminoglutethimide on peripheral aromatization. It is possible that the clearance of androstenedione is reduced or the metabolism of estrone increased to account for these findings; nonetheless, our data suggest that in many instances estrogen production is inhibited before total adrenal blockade is accomplished. This would be a potentially beneficial side effect of aminoglutethimide therapy in addition to its adrenocortical suppressive effects.

There was some concern that the goitrogenic effect of aminoglutethimide administration would cause an increase in plasma TSH levels and concomitantly elevated prolactin levels. Since it had been demonstrated by other investigators[27] that prolactin exerts a potential stimulatory effect on breast tumor growth, such an effect would be deleterious. As demonstrated by our findings, mean prolactin levels were not elevated in the subjects treated with aminoglutethimide and glucocorticoid replacement.

Significant side effects were demonstrated in a large percentage of patients during the first few weeks of treatment. Aminoglutethimide had to be withdrawn from three of the original 55 patients because of a severe drug rash in two and marked lethargy in one. A significant proportion of patients also experienced ataxia and nystagmus. Conversely, after the first two weeks of therapy and during the chronic administration of aminoglutethimide and hydrocortisone, there were minimal side effects. The drug rash spontaneously disappeared in the large majority (17/19) of patients with continuation of aminoglutethimide. A small number of patients on chronic therapy complained of weight gain and facial fullness. Approximately 20% of the patients in our group required mineralocorticoid replacement therapy primarily due to the marked suppression of plasma aldosterone levels.

With the recent availability of a technique for determining estrogen and progesterone receptors in the cytosol of breast carcinoma cells, it appears that an even greater selection factor can be exerted to determine which patients might be responsive to hormonal therapy. Our studies demonstrate that the "medical adrenalectomy" regimen of aminoglutethimide plus hydrocortisone provides remission rates similar to those obtained with surgical adrenalectomy. Currently, we are conducting a randomized trial of evaluating these two procedures in the management of postmenopausal patients with metastatic carcinoma of the breast.

References

1. Abraham, G. E. and Chakmakjian, Z. H.: Serum Steroid Levels During the Menstrual Cycle in a Bilateral Adrenalectomized Woman. J. Clin. Endocrinol. Metab., 37:581, 1973.
2. Buster, J. E. and Abraham, G. E.: Radioimmunoassay of Plasma Dehydroepiandrosterone Sulfate. Analyt. Letters, 5:543, 1972.
3. Camacho, A. M., Brough, A. J., Cash, R. and Wilroy, R. S.: Adrenal Toxicity Associated with the Administration of an Anticonvulsant Drug. J. Paediatr., 68:852, 1966.
4. Cash, R., Brough, A. J., Cohen, M. N. P. and Satoh, P. S.: Aminoglutethimide (Elipten—Ciba) As an Inhibitor of Adrenal Steroidogenesis: Mechanism of Action and Therapeutic Trial. J. Clin. Endocrinol. Metab., 27:1239, 1967.
5. Daicoff, G. R., Harmon, R. and Van Prohaska, J.: Effects of Adrenalectomy on Mammary Carcinoma. Arch. Surg., 85:800, 1962.
6. Dao, T. L. Y., Tan, E. and Brooks, V.: A Comparative Evaluation of Adrenalectomy and Cortisone in the Treatment of Advanced Mammary Carcinoma. Cancer, 14:1259, 1961.
7. Demers, L. M., Abt, W. J. and Krieg, A. F.: A New Combined Thyroid Hormone Index Based on Thyroxine, Triiodothyronine and Resin Uptake. Am. J. Clin. Pathol. 65:356, 1976.
8. Edelstyn, G., Gleadhill, C. and Lyons, A.: Total Hypophysectomy for Advanced Breast Cancer. Clin. Radiol., 19: 426, 1968.
9. Forrest, A. P. M.: Endocrine Treatment of Breast Cancer. Israel J. Med. Sci., 1:259, 1965.
10. Forrest, A. P. M., Benson, E. A., Ker, H., et al. Controlled Studies in Advanced Breast Cancer. *In* Forrest, A. P. M. and Kunkler, P. B. (eds.) Prognostic Factors in Breast Cancer, Edinburgh: Livingstone, 1968.

11. Fracchia, A. A., Randall, H. T. and Farrow, J. H.: The Results of Adrenalectomy in Advanced Breast Cancer in 500 Consecutive Patients. Surg. Gynecol. Obstet., 125: 747, 1867.
12. Griffiths, C. T., Hall, T. C., Saba, Z., et al.: Preliminary Trial of Aminogluethtimide in Breast Cancer. Cancer, 32:31, 1973.
13. Grodin, J. M., Siiteri, P. K. and MacDonald, P. C.: Source of Estrogen Production in Postmenopasual Women. J. Clin. Endocrinol. Metab., 36:207, 1973.
14. Hellstrom, J. and Franksson, C.: Adrenalectomy in Cancer of the Breast. *In* Currie, A. R. and Illingsworth, C. F. W. (eds.) Endocrine Aspects of Breast Cancer, p. 5, Edinburgh: Livingstone, 1958.
15. Murphy, B. P., Engleberg, W. and Pattee, C. J.: Simple Method for the Determination of Plasma Corticoids. J. Clin. Endocrinol. Metab., 23:293, 1963.
16. Odell, W. D., Wilbert, J. F. and Paul, W. E.: Radioimmunoassay of Thyrotopin in Human Serum. J. Clin. Endocrinol. Metab., 25:1179, 1965.
17. Pearson, O. H. and Ray, B. S.: Results of Hypophysectomy in the Treatment of Metastatic Mammary Carcinoma. Cancer, 12:85, 1959.
18. Rallison, M. L., Tyler, F. H. and Kumagi, L. F.: Goitrous Hypothyroidism Induced by an Anticonvulsant Drug. J. Paediatr., 65:1085, 1964.
19. Rees, L. H., Cook, D. M., Kendall, J. W., et al.: A Radioimmunoassay for Rat Plasma ACTH. Endocrinology, 89: 254, 1971.
20. Samojlik, E., Santen, R. J. and Wells, S. A.: Adrenal Suppression with Aminoglutethimide. II. Differential Effects of Aminoglutethimide on Plasma Androstenedione and Estrogen Levels. J. Clin. Endocrinol. Metab., 45:480, 1977.
21. Sampson, E. J., Derck, D. D. and Demers, L. N.: Comparison of Two Radioimmunoassay Kits for Aldosterone Determination. Clin. Biochem., 9:216, 1976.
22. Santen, R. J., Lipton, A. and Kendall, J.: Successful Medical Adrenalectomy with Aminoglutethimide: Role of Altered Drug Metabolism. JAMA, 230:1661, 1974.
23. 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, 1977.
24. Santen, R. J., Wells, S. A., Cohn, M., et al.: Compensatory Increase in TSH Secretion Without Effect on Prolactin Secretion in Patients Treated with Aminoglutethimide. J. Clin. Endocrinol. Metab., 45:739, 1977.
25. Santen, R. J., Samojlik, E., Lipton, A., et al.: Kinetic, Hormonal, and Clinical Studies with Aminoglutethimide in Breast Cancer. Cancer, 39:2948, 1977.
26. Smithline, F., Sherman, L. and Kolodny, H. D.: Prolactin and Breast Carcinoma. N. Engl. J. Med., 292:784, 1975.
27. Thompson, E. A., Jr. and Siiteri, P. K.: Utilization of Oxygen and Reduced Nicotinamide Adenine Dinucleotide Phosphate by Human Placental Microsomes During Aromatization of Androstenedione. J. Biol. Chem., 249:5364, 1974.

Discussion

Dr. J. Shelton Horsley, III (Richmond, Virginia): At the Medical College of Virginia, under the direction of Drs. Heber H. Newsome and Peter W. Brown, we have taken a little different approach.

(Slide) The objective of our study was to compare the response to medical adrenalectomy with subsequent surgical adrenalectomy.

(Slide) Twenty-two patients were treated by medical adrenalectomy, as Dr. Wells has outlined. Six patients who did not respond, subsequently had bilateral surgical adrenalectomy. None of these showed any response. The 16 patients who did respond to medical adrenalectomy over a period of three months all responded to surgical adrenalectomy.

We have had limited experience using this drug over a long period of time. If Dr. Wells' program continues to show these excellent results, surgical adrenalectomy for metastatic breast carcinoma may be a thing of the past.

At the present time, we are using it as a "predictor". We don't have any delusions that the 100% accuracy will continue, but it's very exciting that we seem to have a "predictor" that can give us much better results than any other criteria available.

I would like to ask Dr. Wells two questions. First, is there any correlation between response to medical adrenalectomy and the presence of estrogen receptors in the breast cancers of his patients? Secondly, after the patients have been on medical adrenalectomy, do they exhibit any change in tolerance to subsequent chemotherapy?

President Scott: Are there other discussants? (No one responded.) If not, I'd like to ask one question of Dr. Wells which is a little bit aside from the thrust of this particular paper, but that is: What about commenting, Dr. Wells, on the role of aminoglutethimide in Cushing's disease and in primary aldosteronism, if you would do so?

Would you close?

Dr. Samuel Alonzo Wells, Jr. (Durham, North Carolina): In regard to Dr. Horsley's question, we did not use estrogen receptor status to stratify patients preoperatively and this was primarily for two reasons. At the time that this study was initiated the clinical utility of estrogen receptor analysis was not clarified and, furthermore, this assay was not available commercially. Also, in patients with metastatic breast carcinoma it is often difficult to obtain adequate tissue at the time of disease recurrence.

Approximately 11 months ago we began a randomized study comparing the efficacy of surgical adrenalectomy to the aminoglutethimide glucocorticoid medical adrenalectomy regimen in postmenopausal patients with metastatic carcinoma of the breast. Every attempt is made to obtain metastatic breast tumor for estrogen receptor determination and all patients who are estrogen receptor negative are excluded from this study. I think that there is no question that the estrogen receptor protein determination is a pivotal test regarding the decision to use hormonal therapy or chemotherapy.

In regard to your second question, we did not notice that there was any effect of the aminoglutethimide glucocorticoid regimen on subsequent chemotherapy. Some of these patients, 34 to be precise, had some hormonal therapy prior to the time that they started on the aminoglutethimide glucocorticoid regimen. Those patients who had previously responded to a hormonal regimen had a greater incidence of complete or partial remission than did those patients who had not had a previous response to hormonal therapy.

Regarding Dr. Scott's question, I think that aminoglutethimide has some use in patients with certain forms of adrenocorticohyperplasia. It has certainly been used in selected patients with Cushing's syndrome, but probably has been most effective in subjects with aldosteronomas.

This drug has also been used to treat patients who have inappropriate ACTH secretion from various malignant tumors. Large doses of this drug have to be given to achieve adrenal blockade, but it has been effective in certain instances.

It certainly appears that aminoglutethimide has usefulness medically, and if the proper regimen is given, it is competitive with other hormonal ablative techniques in the management of patients with metastatic carcinoma of the breast.