content of 290 mg. per 100 cc. and a carbon dioxide combining power of 14 vol. %.

After we received this report, our impression was that we were dealing with some overwhelming infection and diabetic coma. In view of the report that the urine was normal prior to hospitalization, it was decided to withhold insulin therapy until further laboratory study. Intravenous administration of fluid in the form of 1/6 molar lactate and distilled water instead of glucose solution was begun. Antibiotic therapy was given, consisting of one million units of penicillin intramuscularly every three hours and 100 mg. of oxytetracycline (Terramycin) in 50 cc. of distilled water intravenously every four hours. Adrenal cortical extract was administered, with 10 cc. given initially and 5 cc. every four hours.

At 8:20 that evening the temperature rose to 106 F, and the child began to have tonic and clonic convulsions. Phenobarbital was given intramuscularly to control the seizures. At 9:20 p. m. the blood glucose level fell to 210 mg. per 100 cc., without insulin therapy; there was 3+ glucosuria, but the twitchings and seizures still persisted and the temperature remained high. A spinal tap done at this time revealed normal fluid content. After continuous antipyretic and hydrotherapy, the temperature fell to 103 F at midnight and the glucosuria was 2+. The convulsions were diminishing. At 6 a. m. the child called for its mother and began taking fluids by mouth. At 10 a. m. the temperature was 100.2 F, and the child sat up. The following day, 48 hours after admission the child was afebrile, and all the laboratory findings were within normal limits. The child was discharged on the fifth day of hospitalization.

One week after the child was discharged, we were notified by the mother that the child confessed to having eaten some berries picked off a bush in the park, just prior to the onset of the illness. A twig with some of the berries was submitted to the Brooklyn Botanical Garden for identification and was subsequently shown to be Rhodotytos of the rosacea family, a bush imported from Japan whose berries are called "jet beads."

These berries contain the glycoside amygdalin, which, when ingested, breaks down into hydrocyanic acid. Dr. John C. Krantz, professor of physiology of the University of Maryland Medical School, advanced a possible explanation of the clinical condition found in our case. He stated that "it was possible that this drug (hydrocyanic acid) has a centric action in the region of the hypothalamus and that as one has here a glycemic center as well as a heat center, each of these may have been effected by the drug, producing a hyperthermia and simultaneously contributing to the hyperglycemia."

COMMENT

It is difficult to estimate the actual number of accidental poisonings that occur in children, because as a rule only unusual or fatal cases are reported. Aikman [1] considers that the fatal cases alone amount to about 800 a year in the United States. Where the clinical picture is irregular and confusing and poisoning is suspected, the parents and other persons in close contact with the patient must be questioned closely. Although we did not elicit such a history, our clue that this might not be a true diabetic coma was suggested by the report of normal urine obtained several hours prior to admission. A public health question is also posed by this incident because of the evident availability to children of poisonous berries in city parks.

895 Eastern Parkway (Dr. Rascoff).

1. Aikman, J., in Brenneman's Practice in Pediatrics, McQuarrie, I., editor, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 1, chap. 17, p. 3.

COUNCIL ON PHARMACY AND CHEMISTRY

REPORT TO THE COUNCIL

The Council has authorized publication of the following report from its Committee on Research.

R. T. STORMONT, M.D., *Secretary.*

*The Committee on Research, through its Subcommittee on Steroids and Cancer, is sponsoring a collaborative study on steroids and mammary cancer. Reports summarizing this work have been published (Estrogens and Androgens in Mammary Cancer: A Progress Report, report of the Council on Pharmacy and Chemistry, J. A. M. A. **140**:1214 [Aug. 13] 1949. Proceedings of the First Conference on Steroid Hormones and Mammary Cancer, American Medical Association, Chicago, April 4-7, 1949. Current Status of Hormone Therapy of Advanced Mammary Cancer, report of the Council on Pharmacy and Chemistry, J. A. M. A. **146**:471 [June 2] 1951). In the following report, the conclusions expressed are those of the authors, and final conclusions of the Subcommittee must await evaluation of the studies now in progress.*

PAUL L. WERMER, M.D., *Secretary.*

EFFECTS OF INTENSIVE SEX STEROID HORMONE THERAPY IN ADVANCED BREAST CANCER

B. J. Kennedy, M.D.
and
Ira T. Nathanson, M.D., Boston

Intensive therapy with estrogens and androgens is employed in the palliative treatment of advanced cancer of the breast.[1] Since observations of the systemic effects and complications of this therapy may provide a clue to the mode of action of the sex steroids in breast cancer, they may be important. Many effects of sex hormone therapy have been recorded, but additional manifestations not commonly recognized have become prominent and more frequently noted at the higher dosages usually employed in breast cancer. The purpose of this report is to record these reactions and their relative frequency with intensive and prolonged hormone therapy.

The duration of treatment varied from a few days to several years. Deleterious reactions occurred early in some patients, necessitating discontinuance of therapy. Thus, effects that might have occurred at later intervals could not be recorded. Most of the patients, however, were treated for a minimum of one month, and a large majority received continuous therapy for considerably longer periods. The causes of the shorter periods of observations were as follows: (1) development of later re-

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Because of lack of space, the bibliographic references have been omitted from THE JOURNAL and will appear in the authors' reprints.

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From the Medical Laboratories of the Collis P. Huntington Memorial Hospital at the Massachusetts General Hospital; the Tumor Clinic of the Massachusetts General Hospital; and Pondville Hospital (Massachusetts Department of Public Health) Walpole, Mass. Dr. Kennedy was formerly Public Health Service Research Fellow of the National Cancer Institute and Clinical Research Fellow of Harvard University at the Massachusetts General Hospital; he is now Assistant Professor of Medicine, University of Minnesota School of Medicine.

The following pharmaceutical firms supplied the hormones used in this study: Ayerst, McKenna & Harrison Limited, conjugated estrogenic substances (Premarin); Ciba Pharmaceutical Products Incorporated, testosterone propionate (Perandren) and ethinyl estradiol (Eticylol); Schering Corporation, testosterone propionate (Oreton) and ethinyl estradiol (Estinyl); E. R. Squibb & Sons, diethylstilbestrol and dienestrol; Wallace & Tiernan Products, Inc., mestilbol (Monomestrol) and dimethyl ether of diethylstilbestrol; and White Laboratories, Inc., dienestrol.

actions necessitating cessation of therapy; (2) discontinuance of use of the hormone because of rapidly progressing disease; (3) systematic interruption, a procedure in the therapy program, whenever an excellent response was obtained;[1k] or (4) death of the patient.

It will be shown that the incidence and degree of effects continued to increase as therapy was prolonged. Since some of the effects were not recognized at the beginning of the study, the data presented represent the absolute minimum but reflect the potentialities of long-term therapy.

TABLE 1.—*Minimal Incidence of Side-Effects of Testosterone Propionate in Eighty-Two Patients with Advanced Breast Carcinoma*

Side-Effects	No. of Cases Analyzed *	No. Demonstrating Side-Effects	Incidence, %
Hoarseness	77	47	61
Hirsutism	75	40	52
Hair loss	55	12	22
Acne	71	21	30
Ruddy complexion	64	28	44
Drowsiness	70	7	10
Nausea	71	13	18
Vomiting	70	8	11
Feeling of well-being	76	58	76
Weight increase	76	54	71
Libido increase	59	22	37
Edema	67	11	16
Hypercalcemia	73	7	10
Uremia	72	3	4

* Figures in this column represent those patients in whom positive or negative observations were recorded.

SPECIFIC EFFECTS OF ANDROGENS

These data are based on an analysis of 82 consecutive female patients with advanced breast cancer who received 50 to 100 mg. of testosterone propionate in oil, intramuscularly, three times weekly (table 1).

Hoarseness.—Hoarseness, which was the commonest of the masculinizing phenomena resulting from androgen therapy, occurred in a minimum of 61% of the patients. The incidence increased with prolonged or more intensive therapy (fig. 1). The changes varied from slight huskiness to a coarse, deep, masculine voice. Some patients complained of a persistent cold, sore throat, or rasping voice; others experienced constriction of the larynx and easy fatigability (or "cracking") of the voice. Singers found they could utter only discordant sounds. Apparently, these laryngeal changes are similar to those that develop in boys at puberty. Androgenic hormones produce hypertrophy of the vocal cords and, if continued, may lead to enlargement of the larynx.[2] Laryngoscopic examination of women in whom these changes develop reveals a generalized, suffused swelling, with injected blood vessels running the length of the cord. A pale, off-white color is a consistent feature of the late changes.[3] Edema occurs first, but hypertrophy of the muscle of the cord may result later. In the majority of our patients, discontinuation of the male hormone was usually followed by a gradual return of an essentially normal voice. In others, the voice failed to return to pretreatment quality, which undoubtedly resulted from persistence of the hypertrophy of the vocal cords.

Hirsutism.—Hirsutism occurred in at least 52% of patients and was generally more noticeable in brunettes and in women with a tendency to hirsutism. The degree of hirsutism varied. With intensive and prolonged treatment, hirsutism usually increased and simulated a more typical masculine distribution (fig. 1). Extreme hypertrichosis, characteristic of masculinizing tumors, was also observed. Variants in the sites of hair distribution were commonly seen. This raises the question of the receptor capacities of the end-organ. The presence of increased hair, especially on the face, disturbed many women and prompted measures for its removal. This induced-hypertrichosis, as a rule, gradually disappeared after cessation of therapy.

Alopecia.—Partial loss of scalp hair, often associated with hypertrichosis elsewhere, was noted in 22% of the patients. The hair of the scalp became dry and coarse and fell out whenever it was combed. Recession at the temples was noted in some patients, and occasionally baldness of the vertex of the scalp resulted. When use of the hormone was stopped, hair reappeared in these areas. Although hair loss occurs in other debilitating diseases, these women generally felt well and maintained satisfactory nutritional states. Occasionally, the hair of patients who received large doses of androgens turned gray. It has been postulated that androgens produce alopecia primarily in persons who have a hereditary susceptibility to baldness. This was strikingly demonstrated in eunuchoids who received androgen therapy.[4] Queries of women in whom such changes developed revealed that their male predecessors had had a high incidence of spontaneous alopecia.

Dermatological Changes.—Aesthetically distressing was the appearance of acne. The lesions resembled those seen in puberal children and varied from small milia and scattered papules to extensive furuncles and papules over the face, back, and chest. Increased oiliness and thickening of the skin also were noted. Known effects of androgens have been suggested to explain the acne: an increase in sebaceous secretion and hyperplasia of the epithelial cells at the mouth of the hair follicle.[5] With superimposed infection, papules and pustule formation may follow. The customary measures for skin hygiene were of benefit in the treatment of the acne, although cessation of therapy was usually followed by remission of this complication. In addition, women with brittle nails noted softening, increased flexibility, and a decrease in chipping. These effects were previously unobserved after prolonged androgen therapy but were confirmed on examination.

Ruddy Complexion.—The complexion of patients treated over long periods frequently became ruddy and flushed, sometimes resembling the faces of patients with Cushing's disease. The face, anterior neck, chest, and occasionally the extremities became erythematous and blanched when pressed. The skin was usually warmer than normal, and patients complained of constant hot flushing unlike that of the menopause. Women who ordinarily had cold hands and feet were often relieved of this condition.

In a substantial number of patients with ruddiness of complexion, hemoglobin values rose from subnormal or normal levels to those as high as 19 gm. per 100 cc. An elevation of the red blood cell count to 6 million cells and an increase in the hematocrit values accompanied the rise in hemoglobin. The mechanism of this hemopoietic stimulation by androgens is unexplained, but bone marrow studies of 12 patients revealed hyperplasia of the erythroid elements. The apparent increase in red blood cell volume or a vasomotor response may account for the flushing. Both ruddiness and flushing disappeared rapidly after omission of testosterone, but the hemoglobin level remained elevated for weeks.

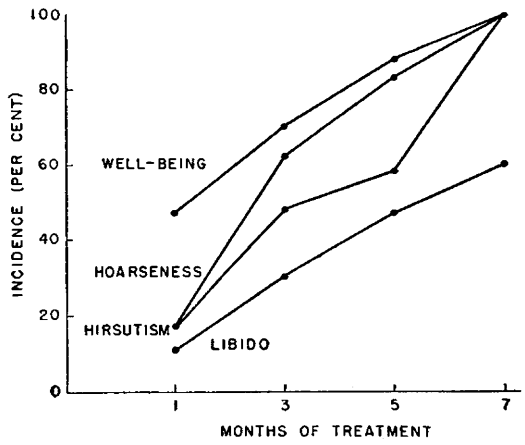

Fig. 1.—Incidence of side-effects of androgenic hormones with prolonged, continuous therapy.

Increased Weight and Well-Being.—One of the most consistent effects observed was a feeling of well-being, which was recorded in 76% of the cases. Patients depressed and debilitated by the disease often became euphoric. Well-being appeared to be an effect of the androgen itself, irrespective of the course of the disease. This symptomatic response was very noticeable in some patients, despite progress of the cancer. Patients frequently bedridden by pain and debility, particularly from osseous lesions, became rehabilitated. X-ray examination of these patients sometimes revealed actual progression of osteolytic lesions. This discrepancy between the subjective and objective responses, which occurred to a lesser degree in a fairly large percentage of patients, emphasizes the difficulties encountered in evaluating the response of the tumor when based on symptomatology alone.[6] Occasionally relief of pain as a result of testosterone therapy was more satisfactory than that obtained from morphine, which suggested an analgesic action.[7]

TABLE 2.—*Incidence of Side-Effects of Estrogens Observed in 235 Patients with Advanced Mammary Carcinoma*

Side-Effects	No. of Cases Analyzed *	No. Demonstrating Side-Effects	Incidence, %
Anorexia	228	129	57
Nausea	230	133	58
Vomiting	223	72	32
Abdominal distress	209	12	6
Diarrhea	201	10	5
Dizziness	189	8	4
Headache	189	13	7
Drowsiness	189	16	8
Libido increase	141	3	2
Nipple pigmentation	188	150	80
Areolar pigmentation	185	143	77
Axillary pigmentation	114	46	40
Scar pigmentation	68	12	18
Skin rash	142	2	1
Itching	143	6	4
Breast engorgement	178	36	20
Breast tenderness	179	29	16
Vaginal bleeding	186	63	33
Withdrawal bleeding	121	51	42
Amenorrhea	8	7	88
Urinary urgency and incontinence	149	41	28
Edema	193	65	34
Congestive failure	191	17	9
Congestive failure (deaths)	191	5	3
Hypercalcemia	...	2	..

* Figures in this column represent those patients in whom positive or negative observations were recorded.

Some patients gained so much weight that they became obese, dyspneic, and generally uncomfortable. At times, it was necessary to give these women a reducing diet during active androgen therapy. These effects can be partially explained by the anabolic capacities of the androgens, which may produce nitrogen retention and promote protein synthesis, with a resultant gain in body weight and increase in muscle tone. Fluid retention in some patients, which may be an accompaniment of androgen therapy without evidence of [redacted] can account for small weight gains as explained later.

Increased Libido.—After some months of androgen therapy, 37% of the patients noted an increase in libido; the incidence increased with prolonged therapy (fig. 1). This may not represent the true incidence, since some patients were reluctant to discuss it even during direct questioning. The sensation was expressed as a heavy feeling in the pelvis, an increase in the frequency of the sexual act, or a loss of previous frigidity. The degree of accentuation of these sexual impulses varied. Married women were emotionally less disturbed than widows or spinsters. Some found the change so unpleasant that use of the hormone was discontinued. A relatively prompt disappearance of the symptoms usually followed within a short time. This is in accord with previous studies, indicating that androgens cause an increased susceptibility to psychosexual stimulation, enlargement of the clitoris, increased sensitivity of the external genitalia, and a greater intensity of sexual gratification.[8] The clitoris of each patient was not examined systematically, but cursory observations revealed definite enlargement in a number of patients during androgen therapy. An incidence of 28% was reported.[9] The increased feeling of well-being and improvement of the breast cancer might possibly have contributed to this libido-inciting effect.

Drowsiness, Nausea, and Vomiting.—A few patients noted headaches, drowsiness, nausea, and vomiting of brief duration at the beginning of androgen therapy, apparently unassociated with hypercalcemia. Serum calcium determinations were normal. These effects seemed to be produced by other reactions of the hormone, although the presence of incipient or transient hypercalcemia must be considered when they occur. In no patient were these symptoms severe enough to necessitate discontinuance of therapy.

SPECIFIC EFFECTS OF ESTROGENS

Data were available for analysis of the effects of estrogens in 235 cases (table 2). Diethylstilbestrol was used as the reference standard in 178 patients. The usual dosage was 15 mg. per day orally, but variations from 5 to 400 mg. daily were used. Equivalent dosages of other natural and synthetic estrogenic hormones were employed. All but 20 patients included in the analysis received continuous treatment for at least one month and several for more than one year. The remaining patients discontinued the medication early because of severe anorexia, nausea, and vomiting.

Gastrointestinal Symptoms.—Anorexia, nausea, and vomiting, the commonest gastrointestinal symptoms, were fleeting at the start of therapy but persisted in some patients. Of 235 patients, 58% had variable degrees of nausea, and vomiting occurred in 32%. With careful attention to the management of these symptoms and adjustment of dosage, the patient usually became tolerant to more intensive and prolonged therapy. If the patient became severely nauseated by the initial dosage, the daily dose of the hormone was decreased or administered only at bedtime. Gradually the dose was increased as tolerated, until the desired dosage could be administered. Occasionally, despite all efforts, patients were unable to accept the standard dose of the initial estrogen but could tolerate smaller amounts or another estrogenic preparation. This latter phenomenon needs clarification. A small percentage of patients were unable to tolerate estrogenic hormones of any kind at any dosage. The incidence and degree of gastrointestinal symptoms decreased with advancing years (fig. 2). The usual measures to combat nausea and vomiting have seldom been of value in the management of patients treated with estrogen. Patients who tolerated an initial course of estrogens sometimes experienced nausea and vomiting during interrupted courses of the hormone or, occasionally, later during continu-

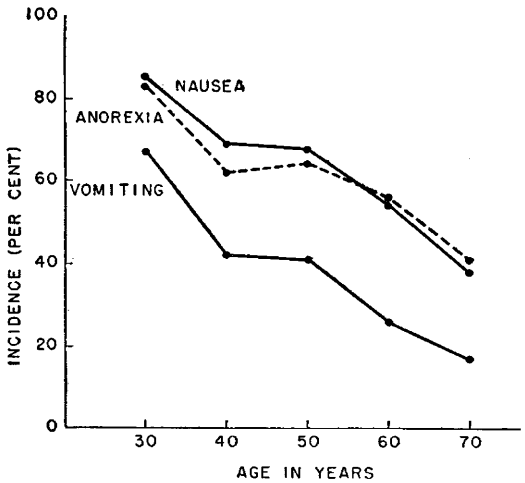

Fig. 2.—Incidence of gastrointestinal symptoms caused by estrogens, with respect to increasing age.

ous treatment. In a few patients, epigastric pains of short duration were noted. In others, soft or increased frequency of bowel movements or diarrhea occurred, but rarely were these symptoms severe enough to warrant treatment or discontinuance of the hormone.

Dermatological Changes.—In elderly women with dry, coarse, atrophic skin, occasionally increased tissue turgor and softening of the skin developed after prolonged estrogen

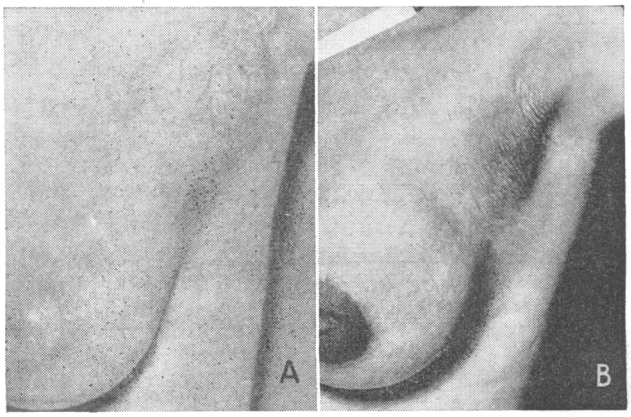

Fig. 3.—Appearance of areola, nipple, and axilla: *A*, prior to estrogen therapy, and *B*, after four months of estrogen therapy. Note the stippled appearance of the pigmentation in linear folds of the axilla.

therapy. A few patients noted flushing of the face, which was seen frequently after administration of testosterone. Itching occurred in a few persons. Rarely, skin lesions consisting of diffuse areas of small papules or erythema were noted.

Pigmentation.—Pigmentation of the nipples was present in about 80% of the women treated with estrogenic hormones. The earliest and sometimes the only change was a redness of the nipple and areola, particularly in patients who did not have previous pigmentation (fig. 3). True pigmentation varied from a faint to a deep brown, frequently covered by a thick, dark, waxy coating. Removal of this waxy substance revealed definite pigmentation beneath it. The pigmentation, sometimes limited to the nipple, usually involved the areola

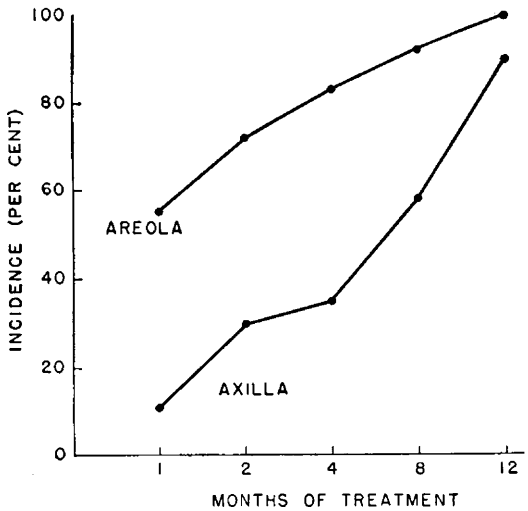

Fig. 4.—Incidence of pigmentation with prolonged estrogen therapy.

and was sharply demarcated at the border. As a rule, the pigment persisted as long as the hormone was administered, although occasionally the color became less intense. After cessation of therapy the pigmentation persisted in some patients for many months. X-ray treatment to the areolar areas usually prevented the formation of pigmentation or destroyed that already present.

During the study, some patients complained that the axillas could not be cleansed. The pigmentation was stippled and was diffuse or confined about the hair follicles in the linear folds (fig. 3). Approximately two-fifths of the patients in this series had axillary pigmentation. The incidence was probably larger, since this aspect was not specifically observed early in the studies. Prolonged estrogen therapy is usually associated with an increased incidence of pigmentation (fig. 4). Pigmentation also occurred in scars as well as in those areas usually affected during pregnancy. Pigmentation was noted in the labia, around or in the umbilicus, and in the linea alba. More recently, pigmentation of the linear lines of the anterior cervical region has been noted. Pigmentation of the buccal mucosa or palms was not seen.

Breast Alterations.—The clinically detectable response of the uninvolved breast tissue to estrogens varied, but it appeared to be governed, to some extent, by the age and menstrual status of the patient. Such signs as tingling or tenderness of the nipples, engorgement, or venous dilatation appeared. Although the group of patients was heterogeneous, about 20% of the entire group exhibited these signs. The changes were confined mostly to premenopausal and menopausal women. Clinical alterations in elderly women, except for pigmentary changes, were considerably less detectable (fig. 5). This implies that the atrophic breast tissue of the postmenopausal and aged woman is not capable of response to the stimuli provided in the prime of menstrual life.

Histological changes may occur without clinical signs, but ordinarily they accompany the overt manifestations.[10] It is quite possible that the status of the breast tissue at the be-

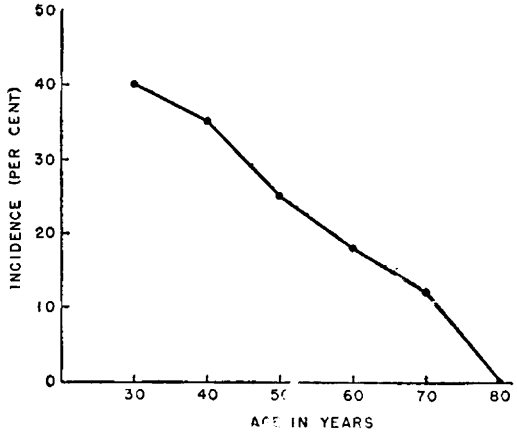

Fig. 5.—Incidence of breast engorgement from estrogen therapy in women with metastatic carcinoma of the breast.

ginning of estrogen therapy may be a determining factor in the responsiveness of the tumor.

Uterine Bleeding.—In contrast to the breast, the postmenopausal endometrium seems to be more sensitive to the action of estrogens regardless of the age of the patient. The latter, however, appears to be a factor in the responsiveness. Large dosages of estrogens produce amenorrhea in premenopausal women with breast cancer, which agrees with observations made in the treatment of patients with other abnormalities.[9a] This is thought to be partially accomplished by inhibition of pituitary gonadotropins, but estrogens may also act directly on the endometrium. These and other studies reveal that intensive estrogen therapy may exhaust the endometrium's capacity to respond. Continuous and intensive estrogen [illegible] in postmenopausal patients with breast cancer resulted in uterine bleeding in about one-third of the patients during therapy. The signs consisted of spotting or staining for brief intervals or a flow simulating a normal menstrual period. Generally, no measures were required for control of the bleeding except cessation of the hormone. In some cases, uterine bleeding could also be controlled by sharply increasing the dose of the estrogen. Occasionally, bleeding was sufficiently severe and prolonged to require curettage; the endometriums of the patients subjected to this procedure usually revealed hyperplastic changes. (Prolonged bleeding should lead to the suspicion of stimulated fibroids or cancer of the endometrium.) In younger postmenopausal patients, the bleeding occurred frequently during therapy and almost invariably happened

after treatment was withdrawn. Contrariwise, in elderly women with presumably atrophic endometriums, bleeding was encountered less often during therapy and after withdrawal of therapy. In this latter group, resumption of estrogen therapy resulted in the pattern commonly seen in younger women, for bleeding occurred during the therapy as well as after cessation of the hormone. The incidence of uterine bleeding increased with prolongation of therapy (fig. 6).

These observations prompt the following suggestions: 1. The endometrium, even though apparently atrophic, is sensitive to estrogens many years after the menopause. 2. Once an atrophic endometrium is primed, it responds differently, behaving like that of women in the immediate postmenopausal phase. Generally, however, the incidence of uterine bleeding decreases in successive years after the menopause, both during therapy or after withdrawal (fig. 7). This raises the question of receptivity of the endometrium, which involves blood supply and cellular responsiveness.

Urinary Urgency and Incontinence.—Another effect of large doses of estrogens is frequency and urgency of urination. The urgency of urination is frequently associated with urinary incontinence, usually of the stress type. This was not recognized early in the study because of reluctance of the patients to discuss it. So distressing was the urgency and incontinence that many patients wished to discontinue the medication. Omission of the estrogen was followed by prompt disappear-

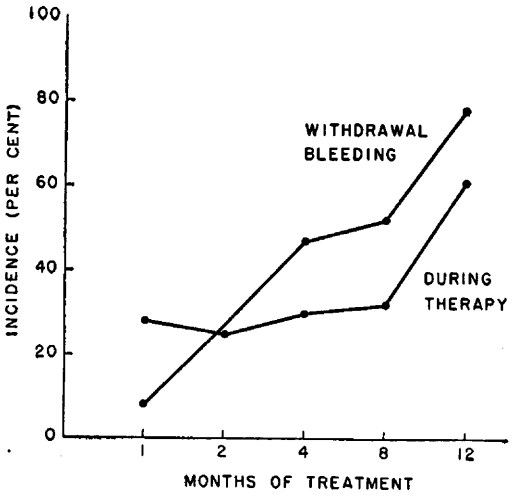

Fig. 6.—Incidence of uterine bleeding after prolonged estrogen therapy.

ance of these symptoms. These urinary symptoms occurred primarily in older women who had borne children. Although the mechanism is not understood, estrogens may affect the sphincter and bladder musculature.

Miscellaneous Effects.—Early in the course of therapy, a few of the patients experienced headaches and dizziness. These symptoms were present in patients receiving larger dosages of estrogens than those usually employed in this program. Cerebral edema might possibly account for these effects. Among other symptoms were drowsiness, "jumpiness," apprehension, lack of "pep," depression, and weakness; these disappeared after treatment was omitted. Increase of libido was reported in a very small percentage of patients.

Occasionally, glossitis, consisting of a bright red, smooth tongue resembling that caused by vitamin B deficiency, developed in patients receiving estrogens. These patients were on a diet apparently adequate in vitamin B complex, but it is possible that the estrogens increase the demand for or suppress the utilization of vitamin B.[11] Improvement followed supplementary vitamin therapy.

Four patients who received estrogens for more than one year had polydypsia and polyuria. Two of these who drank large quantities of fluid a day demonstrated positive tests for diabetes insipidus. Although this disease may possibly be caused by metastases, there was no evidence of this in two patients at autopsy. It can be postulated that the prolonged administration of estrogen may alter the secretion of the posterior pituitary gland.

EFFECTS COMMON TO BOTH ANDROGENS AND ESTROGENS

Extracellular Fluid Retention.—It has been demonstrated that androgens and estrogens produce a decreased excretion and an increased retention of sodium, with a corresponding increase in extracellular fluids.[12] Short-term pilot studies with radioactive sodium in a number of patients revealed an increase in sodium space.

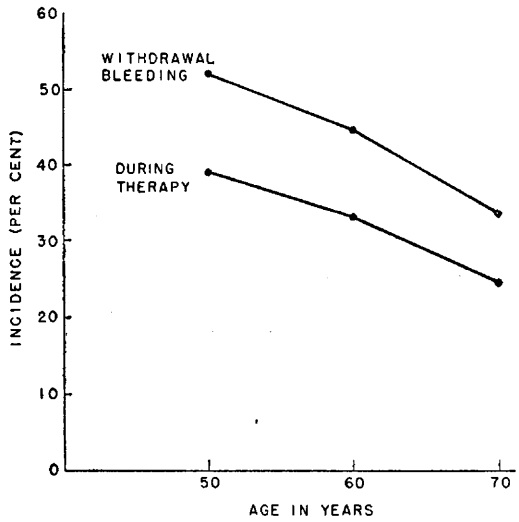

Fig. 7.—Incidence of uterine bleeding, with respect to age, during intensive estrogen therapy and after withdrawal of the hormone.

Early in the course of estrogen or androgen therapy, mild edema, which subsided spontaneously, developed in many patients. Prolonged hormone therapy produced no increase in the incidence of edema; however, a greater incidence of edema was noted in older women, possibly because the cardiovascular system of such patients is less able to cope with the burden of excessive retention of fluid (fig. 8). In the patients treated with massive doses of testosterone, edema of the legs was noted in about one-sixth of the cases. Prolonged estrogen therapy produced peripheral edema in one-third of the patients.

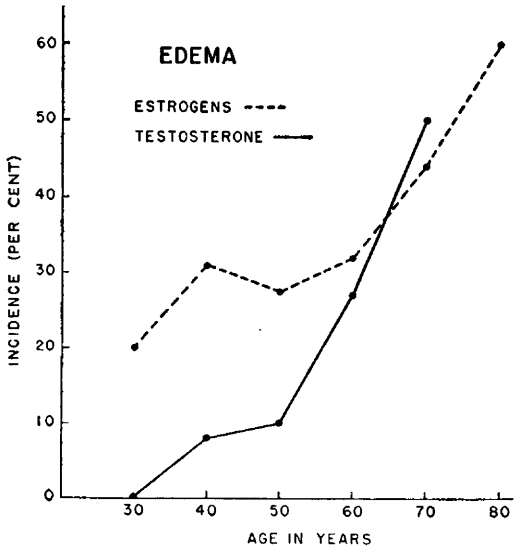

Fig. 8.—Incidence of edema during intensive hormone therapy in women with advanced carcinoma of the breast.

The degree varied from minimal late afternoon swelling to constant edema of the entire legs. Many patients undoubtedly had retention of fluid that could not be detected on clinical examination, because weight gains of 5 to 10 lb. (2.3 to 4.5 kg.) were recorded without gross evidence of edema. Discontinuance of the hormone in a number of patients of this group was usually followed by an obvious diuresis and rapid decrease in weight. These patients did not manifest any renal disease before therapy, as judged by routine urinalyses

or serum nonprotein nitrogen determinations. Existing lymphedema of the arm on the affected side was frequently exaggerated during steroid therapy.

In 17 patients (9%) of those receiving estrogen therapy, fluid retention led to congestive cardiac failure or exaggerated an existing mild decompensation. Five patients who had edema during estrogen therapy died of congestive heart failure at home, according to the family physicians; however, the investigators had not observed any evidence of this condition a short time previously. The breast disease did not appear sufficiently far advanced to cause death. Thus, the incidence of death apparently resulting from congestive failure was recorded as 2.6%. Four cases of acute congestive failure have been reported in men treated with diethylstilbestrol for advanced cancer of the prostate gland. Three of these patients had possible preexisting myocardial damage.[10] Testosterone led to congestive failure in only one member of the present series.

Thrombophlebitis of the lower extremities, which was often unilateral, was prone to occur in women in whom edema developed. It is our impression that this complication happened more frequently than could be expected by chance. Edema, superimposed on poor peripheral circulation, may be an important factor influencing the start of this complication.

TABLE 3.—*Comparative Study of the Incidence of Side-Effects of Synthetic Estrogens*

	Diethylstilbestrol	Conjugated Estrogenic Substance	Dimethyl Ether of Diethylstilbestrol	Ethinyl Estradiol	Dienestrol	Mestilbol
Dose, mg. per day	5 to 400	5 to 30	5 to 30	3 to 5	5 to 30	5 to 30
No. of persons treated	178	23	22	22	14	14
			Incidence of Side-Effects, %			
Anorexia	55.6	43	27	71	58	71
Nausea	56	43	31.8	71	57	71
Vomiting	34.9	23.8	13.6	25	28.5	35.7
Abdominal distress	5	5.6	5	5	14	0
Diarrhea	2.8	11	0	21	0	0
Dizziness	4.5	0	0	0	0	7.7
Headache	8.9	5.9	5.9	0	7.7	0
Drowsiness	7.6	5.9	0	16.7	8	7.7
Libido increase	1.9	0	7.7	0	0	0
Nipple pigmentation	84.7	35.7	78.9	86.7	63.6	83
Areolar pigmentation	78	23	88.9	87.5	70	91.6
Axillary pigmentation	38.6	0	54.5	46	33	50
Scar pigmentation	18.7	0	....	22	0	0
Skin rash	0.9	0	0	7	0	0
Itching	3.9	0	0	0	10	10
Breast engorgement	17	26.7	5.6	25	30	25
Breast tenderness	15	26.7	0	18.7	20	8
Uterine bleeding	34.8	37.5	15.8	6.7	18	35.7
Withdrawal bleeding	41.6	44	33	40	....	33
Urinary symptoms	29	7	7.7	40	42.8	11
Amenorrhea	87.5	....	....	....	....	....
Edema of legs	33	35	26	44	9	28.5
Congestive failure	10	5.9	5	0	0	7
Congestive failure (deaths)	....	5.9	....	....	....	7

Although fluid retention is a serious sequela of androgenic and estrogenic therapy, employment of specific measures will usually control or minimize this complication and in many instances enable continuance of hormone therapy. As a rule, the use of ammonium chloride and a low salt diet are sufficient. If these measures are inadequate, mercurial diuretics can usually correct the situation. Preexisting cardiac failure should be treated before the initiation of hormone therapy. In anticipation of possible fluid retention from steroids, it was our policy to include ammonium chloride and a low sodium intake as a part of the therapeutic regimen in elderly patients or those with known cardiac disease.

Hypercalcemia.—Hypercalcemia may occur with either androgens or estrogens during treatment of advanced breast cancer with osseous involvement.[13] On the basis of blood studies, it was determined that hypercalcemia occurs spontaneously in about 12% of breast cancer patients with osseous metastases.[13c] The number of cases induced by steroid hormones probably is less, but the syndrome is more serious and may be fatal. Spontaneous hypercalcemia may be corrected by steroids, so it does not contraindicate therapy, providing the patient is carefully observed; however, steroid hormones may also induce the syndrome in patients in whom there was no detectable evidence prior to the initiation of therapy. Hypercalcemia was observed in seven (9.6%) of the patients receiving androgenic hormones. Three of these died, apparently as a result of this complication. Hypercalcemia from estrogen therapy was rare in this series, occurring in only two of the total number of patients. Manifestations of hypercalcemia were anorexia, nausea, vomiting, apathy, weakness, drowsiness sometimes merging into disorientation, stupor, or coma, vascular collapse, and, in some instances, death. Although the initial symptoms may be subtle, the syndrome must be suspected in any patient who exhibits these mild symptoms. Serum calcium determinations should be performed at the beginning of and during therapy, especially if suggestive symptoms arise. In addition, the more rapid and simpler estimation of urinary calcium is often informative. Ideally, both assays are desirable. Clinical and laboratory evidence of uremia was present in four of the patients with hypercalcemia who were receiving testosterone. The hypercalciuria apparently produces damage of the renal tubules, with resultant renal insufficiency. Postmortem examination may reveal deposition of calcium in the tubules as well as in other tissues.[14]

The syndrome of hypercalcemia may be corrected, in many instances, by cessation of hormonal therapy, low calcium diet, and infusions of sodium chloride, glucose, and sodium citrate. A 25% solution of sodium citrate can be administered in an amount of 250 cc. intravenously every four hours until improvement occurs. Sodium citrate temporarily reduces the amount of ionized calcium in the blood caused by the formation of a soluble, nonionized calcium citrate complex.[15] However, we believe that correcting the abnormal electrolytic pattern in these patients is most important in treating this serious complication. When drug-induced hypercalcemia is corrected, further steroid therapy may be tried cautiously. The syndrome may recur, but some patients encountered no further difficulty and greatly benefited from the therapy.

Temporary hypercalcemia might have been present in patients noting drowsiness and nausea at the start of therapy, but it was undetected. The incidence of death resulting from hypercalcemia might possibly be reduced by more frequent serum calcium and nonprotein nitrogen determinations and close observation of the patient for early detection of this complication.

Amenorrhea.—Cessation of menstruation is common in women without cancer during treatment with high doses of androgens and estrogens.[5a] Such therapy may produce permanent amenorrhea in women passing through the menopause. Amenorrhea also occurs in menstruating women with disseminated breast cancer who are receiving androgens or estrogens. Of the premenopausal women receiving large doses of estrogenic hormones, 87.5% experienced amenorrhea during this therapy. The hormone-produced amenorrhea can be attributed to suppression of gonadotropic activity, especially since patients resume menstruation after cessation of therapy.[16]

COMPARISON OF NATURAL AND SYNTHETIC ESTROGENS

During the investigation of estrogen therapy in advanced breast carcinoma, both naturally derived and synthetic preparations were employed, in an attempt to evaluate the effectiveness of each. The commonly employed compounds, the average dosages, and the incidence of local and systemic reactions of cases in which synthetic estrogens were used are recorded in table 3. Since these data were compiled, the number of patients treated with compounds other than diethylstilbestrol has substantially increased; however, the relative incidence of reactions has not been altered significantly. At present, the data are insufficient to determine whether any single agent uniformly produces fewer reactions than any other. Further studies with various dosages are necessary to determine the relative incidence of side-effects at each level. No attempt has been made in this report to correlate the various compounds or the systemic reactions with the response of the tumors. The combined use of estrogens and androgens has been tried in a number of patients, but the data are too

few for critical evaluation, especially in respect to effects that are common to both groups of compounds. It appears, however, that more specific sex changes, usually attributed to typical estrogens and androgens, may be minimized with such a combination.

ESTROGENS IN MEN

Large doses of estrogenic hormones have been employed in the treatment of advanced breast cancer in men. Since the series is small, no statistical analysis was attempted. The reactions, which appear similar to those noted in the treatment of prostatic carcinoma, include anorexia, nausea, vomiting, nipple and areolar pigmentation, tenderness and hyperplasia of the uninvolved breast tissue, extracellular fluid retention, and loss of libido; hypercalcemia has not been observed.

SUMMARY AND CONCLUSIONS

Systemic and local reactions were studied in patients with breast cancer receiving intensive sex hormone therapy. A large variety of reactions occurred, which were not specifically related to the action of the hormone on the tumor but could be attributed to inherent qualities of the compounds. This was particularly true when larger dosages were used; they apparently caused a higher incidence of reactions than doses employed in other syndromes. Moreover, at these dose levels, reactions occurred that are not universally recognized.

Further study of the reactions discussed in this report may disclose additional information as to the physiological action of the sex hormones and an explanation of their mechanisms in the treatment of advanced breast carcinoma. Tabulation of the reactions may also contribute to an evaluation of sex steroid hormone therapy in general.

COMMITTEE ON COSMETICS

The following products have been accepted as conforming to the Rules of the Committee on Cosmetics. A copy of the rules on which the Committee bases its action will be sent on application. R. T. STORMONT, M.D., *Secretary.*

Athea Laboratories, Inc.

ATHEA HAND LOTION.—A white emulsion composed of lanolin, petrolatum, a vegetable oil, stearic acid, hexadecanol, magnesium stearate, propylene glycol, cetyl alcohol and perfume, intended to soften and protect the skin. (Bottle: 4 and 8 oz. and 1 gal.)

Cosmetic Laboratories, Inc.

BODY-LO.—A white emulsion composed of liquid petrolatum, polyol esters, a preservative, perfume, color and water, intended to soften and protect the skin. (Bottle: ¼, 3 and 8 fl. oz.)

HAND-LO.—A pink emulsion composed of triethanolamine, colloidal clay, fatty acids and esters, petrolatum, lanolin, alcohol, a preservative, perfume, color and water, intended to soften and protect the skin. (Bottle: ¼, ½, 1, 2, 3 and 8 fl. oz.)

HOMOGENIZED SKIN CLEANSER.—A pale yellow, heavy cream composed of lanolin, a polyol ester, petrolatum, a wax, magnesium sulfate, a preservative, perfume and water, intended to cleanse the skin. (Jar: 1⅞, 3¼, 8½ and 16 oz.)

PROTECTION (OILY, NORMAL AND DRY).—A white emulsion composed of vegetable gums, petrolatum, waxes, soap, borates, benzoic acid, propylene glycol and its stearate, a preservative, perfume, color and water. The ingredients are the same in each of the three forms. The ratio of the ingredients and the perfume content differs in each type. They are intended to keep the skin soft and smooth and to serve as a powder base. (Bottle: 2, 3 and 8 fl. oz.)

Luzier's, Inc.

LUZIER'S LIQUID MAKE-UP BASE.—A pigmented liquid containing glycerin, a fatty acid and its glyceryl and polyethylene glycol esters, an alcohol, a petrolatum, triethanolamine, a surface active agent, a preservative, water and colors, intended to serve as a make-up to provide color to the skin and a smooth appearance. (Bottle: 1 fl. oz.)

Pharma-Craft Corporation

FRESH CREAM DEODORANT.—A white cream composed of basic aluminum formate, aluminum chloride, urea, petrolatum, glycerin, a fatty acid and its glyceryl ester, a suspending agent, perfume and water, intended to temporarily retard the flow of perspiration. (Jar: 0.16, 0.42 0.75 and 1.20 oz.)

HEED DEODORANT SPRAY.—A clear, colorless solution composed of an aluminum chlorhydroxide complex, aluminum chloride, urea, perfume and water, intended to temporarily retard the flow of perspiration. (Plastic Bottle: 1.20 fl. oz.)

SPRITE SPRAY DEODORANT.—A clear, colorless solution composed of an aluminum chlorhydroxide complex, aluminum chloride, urea, alcohol, perfume and water, intended to temporarily retard the flow of perspiration. (Plastic Bottle: 1.5 fl. oz.)

Revlon Products Corporation

AQUAMARINE HAND CREAM.—An aquamarine-colored cream emulsion composed of lecithin, stearic acid, a glycol, glycol ethers and esters, inorganic alkali, a preservative, perfume, color and water, intended to soften and protect the skin. (Jar: 3½ oz. and 1 lb.)

AQUAMARINE LOTION DEODORANT.—An aquamarine cream emulsion composed of polyoxyethylene ethers and esters, cetyl alcohol, cholesterol absorption bases, fatty acid amide derivative, aluminum chlorhydrate, a buffer, a preservative, perfume, color and water, intended to temporarily retard the flow of perspiration. (Bottle: 2¾ fl. oz.)

AQUAMARINE MIST.—An amber-colored solution of essential oils, alcohol, color and water, intended to provide a pleasing scent. (Bottle: 3.12 and 7 fl. oz.)

CAKE ROUGE.—A pigmented cake powder composed of a mixture of talc, glycerin, tragacanth, covering agents, a preservative, perfume and colors, intended to enhance the color of the cheeks. (Cake: 7.8 gm.)

CHEEKSTICK.—A pigmented, waxy solid in stick form, composed of petrolatum, lanolin, a wax, a covering agent, a preservative, perfume and colors, intended to enhance the color of the cheeks. (Stick: 2.6 gm.)

CUTICLE OIL.—A rose-colored solution composed of petrolatum, color and perfume, intended to soften the cuticle. (Bottle: 1 and 4 fl. oz.)

CUTICLE REMOVER.—An off-white solution of a polyethoxy ether, a substituted ammonium hydroxide, propylene glycol, a preservative, a color and water, intended to soften the cuticle and permit its removal by gentle friction. (Bottle: 1, 4 and 16 fl. oz.)

DESTINA MAKE-UP REMOVER.—A clear green solution composed of a polyoxyethylene ester, alcohol, glycerin, perfume, colors and water, intended to facilitate the removal of make-up. (Bottle: 4 fl. oz. and qt.)

EYEBROW PENCIL.—A pigmented waxy solid composed of fatty acids, lanolin, waxes, a vegetable oil, glycerides, a resin and colors, intended to enhance the color of the eyebrows. (Pencil: 1⅜ in. by 0.115 to 0.120 in.)

HAND COLOGNE.—A clear pink solution composed of alcohol, polyethylene glycols, perfume, colors and water, intended to provide a pleasing scent. (Bottle: 4 and 16 oz.)

INDELIBLE CREAM LIPSTICK.—A waxy solid stick composed of waxes, glycol and a glycol ester, vegetable oils, a cholesterol absorption base, a covering agent, a preservative, perfume and colors, intended to enhance the color of the lips. (Tube: 4.5 gm.)

NAIL CREAM.—A pink cream composed of lanolin, petrolatum, a sorbitan ester, a wax, a covering agent, perfume, color and water, intended to soften the cuticle. (Jar: ½ and 2 oz.)

NIGHT HAND CREAM.—A thick pink cream composed of petrolatum, lanolin, a cholesterol absorption base, a preservative, perfume, colors and water, intended to soften and protect the skin. (Jar: 2¼ oz.)

PASTE POLISH.—A pink cream composed of a wax, a phthalate ester, lecithin, covering agents, perfume and color, intended to add gloss to the nails. (Jar: 0.95 oz.)

PINK LACTOL.—A thick pink cream lotion composed of a fatty acid and its ester, alcohols, triethanolamine, lanolin, preservatives, perfume, colors and water, intended to soften and protect the skin. (Bottle: 32 and 128 fl. oz.)

TOUCH AND GLOW.—A pigmented liquid composed of stearic acid, and its glycol ester, cholesterol bases, lecithin, covering and thickening agents, triethanolamine, a glycol, preservatives, perfume, colors and water, intended to serve as make-up to provide color to the skin and a smooth appearance. (Bottle: 1 and 2 fl. oz.)

Shepard Laboratories

SHEPARD'S CREAM LOTION.—A white emulsion composed of glycerin, a fatty acid and its glyceryl ester, triethanolamine, cetyl alcohol, preservatives, propylene glycol, carbitol, alcohol, sesame oil, perfume and water, intended to soften and protect the skin. (Bottle: 8 fl. oz.)

SHEPARD'S COLD CREAM.—A white heavy cream composed of waxes, petrolatum, a glyceryl ester, cetyl alcohol, a preservative, sodium borate, perfume and water, intended to cleanse the skin. (Jar: 3½ oz.)

SHEPARD'S DRY SKIN CREAM.—A yellow cream composed of a wax, lanolin, petrolatum, and perfume, intended to relieve skin dryness. (Jar: 1½ oz.)

Toni Company

TONI HOME PERMANENT (VERY GENTLE, REGULAR AND SUPER).—A creamy solution consisting of ammonium thioglycolate, free ammonia, ammonium salts, an emollient creaming agent, a surface active agent, perfume, color and water. This is provided in three strengths, very gentle, regular and super, intended for easy-to-wave, normal and hard-to-wave hair, respectively. This is a cold waving solution intended to be used with a chemical neutralizer. (Waving Lotion: 4 fl. oz.)

PROM HOME PERMANENT (VERY GENTLE, REGULAR AND SUPER).—A creamy solution consisting of ammonium thioglycolate, free ammonia, ammonium salts, an emollient creaming agent, a surface active agent, perfume, color and water. This is provided in three strengths, very gentle, regular and super intended for easy-to-wave, normal and hard-to-wave hair, respectively. This is a cold waving solution intended to be used without a chemical neutralizer. (Waving Lotion: 4 fl. oz.)