COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report.

H. D. KAUTZ, M.D., *Secretary.*

This report, prepared by the Subcommittee on Breast and Genital Cancer, is the result of a 12-year collaborative undertaking to study the effect of androgen and estrogen therapy in the treatment of disseminated mammary cancer. As one of the earliest projects of this type, it has served to blaze a trail for a number of studies which have followed. It will undoubtedly serve as a base line for comparative evaluation of studies which are under way in the field of cancer. A great deal could be said about the devotion of the two men who originally headed the project and who have since died, namely, Drs. Ira T. Nathanson and Earl T. Engle. The enthusiasm and effort of the collaborators and the members of the subcommittee speak well for the participants. Credit should be given to those firms in the pharmaceutical industry which cooperated and so generously provided the products used by the investigators. The present members of the Subcommittee on Breast and Genital Cancer, headed by Dr. Ian Macdonald, are to be congratulated on their integrity and resolution in assuming the responsibility for the follow-up and reanalysis and in discharging their duties to the medical profession by assembling and interpreting the data from which this report is derived. Copies of the data and statistics used in preparing this report ("Accumulated Statistology") are available on request from the Secretary, Committee on Research.

NORMAN DE NOSAQUO, M.D.,
Secretary,
Committee on Research.

ANDROGENS AND ESTROGENS IN THE TREATMENT OF DISSEMINATED MAMMARY CARCINOMA

RETROSPECTIVE STUDY OF NINE HUNDRED FORTY-FOUR PATIENTS

In the fall of 1947, the Therapeutic Trials Committee (later designated the Committee on Research) of the American Medical Association undertook the sponsorship of a co-operative investigation of the effects of steroid hormones in the treatment of advanced or disseminated carcinoma of the breast. This investigation was co-ordinated by a Subcommittee on Steroids in Cancer including Drs. Ira T. Nathanson (deceased), Frank E. Adair, Willard M. Allen, and Earl T. Engle (deceased). In 1956, the subcommittee was reconstituted and redesignated the Subcommittee on Breast and Genital Cancer. Members of the Subcommittee on Breast and Genital Cancer of the Committee on Research are Drs. Ian Macdonald (Chairman), Los Angeles; Alfred Gellhorn, New York; B. J. Kennedy, Minneapolis; and Samuel G. Taylor, III, Chicago. With the support of the Committee on Research, and especially of its chairman, Dr. Stuart Mudd, the subcommittee has brought to completion the study which started a decade ago. The material consists of pooled data contributed by the following 60 collaborating investigators, without whose original and continued co-operation this report would not have been possible: Drs. Paul D. Abramson, Frank E. Adair, T. J. Anglem, Lionel S. Auster, H. C. Ballon, R. W. Begg, Frederick Hardy Bowen, A. J. S. Bryant, William Y. Burton, Franz Buschke, L. R. Chauncey, R. L. Clark, William A. Cooper, A. R. Curreri, Charles Eckert, Lucille Ellison, George C. Escher, Louis A. Eshman, Barry Friedman, L. H. Garland, Leonard B. Goldman, L. W. Gorham, Robert C. Grauer, Robert B. Greenblatt, Charles B. Hanna, Margaret Hardie, Joseph A. Hepp, Roy Hertz, Robert Huseby, B. J. Kennedy, Morton Kligerman, Edwin A. Lawrence (deceased), George Q. Lee, Henry Lemon, Edward F. Lewison, Champ Lyons, Ian Macdonald, S. S. Marchbanks, E. Perry McCullagh, Barton McSwain, John M. Modlin, Paul J. Murison, Ira T. Nathanson, H. E. Nieburgs, Kenneth B. Olson, Robert J. Parsons, Karl E. Paschkis, R. W. Postlethwait, Rieva Rosh, W. C. Sealy, Reginald A. Shipley, Joseph Silverstein, Arthur G. Siwinski, James A. Stapleton, Augustus Street, Samuel G. Taylor, III, G. M. Tice, Keene M. Wallace, Grant E. Ward, and Benjamin

B. Wells. The consultants in radiology included Drs. L. H. Garland and Leo G. Rigler. The consultants in pathology were Drs. Lauren V. Ackerman, Fred Stewart, and Arthur Purdy Stout. Dr. Stanley C. Harris served as consultant in biometrics.

At intervals, usually every two years, a conference of the collaborating investigators was held at the headquarters of the A. M. A. in Chicago. At the 1956 conference, the subcommittee determined the necessity of a complete reanalysis and recoding of the information which had been contributed concerning 1,983 patients. The successful completion of this laborious project was facilitated by Dr. Alex Sahagian-Edwards, College of Physicians and Surgeons, Columbia University and Francis Delafield Hospital, New York City, who served as Research Associate to the subcommittee for a 15-month period, 1956 to 1958.

Objectives of Study

The original objectives of this investigation, as established by the parent subcommittee, were outlined at the First Conference on Steroid Hormones and Mammary Cancer in Chicago, April 4-7, 1949.[1] It soon became apparent in a study of this magnitude that certain objectives could not be achieved practically or accurately. Specifically, some of the objectives were to establish which morphologic types of breast cancer were affected by androgen and estrogen therapy, the dosage necessary to achieve favorable effects, the duration of palliation, and the criteria by which improvement could be judged. Arrangements were made with the Armed Forces Institute of Pathology for a central registry, through which surgical and autopsy specimens could be reviewed by a group of consultants. Histological changes in responsive cases were comparable to the effects of irradiation, in both epithelial and stromal elements. No histological criteria for recognition of responsive tumors were apparent, nor did these studies provide any explanation of the mechanism of hormonal action.[2] Serial roentgenograms submitted to the consultants in radiology were impossible to evaluate, due to variations in techniques. Effort directed toward the elucidation of hormonal action was considered impractical in a group study. Such areas as the metabolic aspects of hormonal therapy, cytochemical effects, and the morphologic and functional changes induced in various tissues were not investigated.

TABLE 1.—*Cases Submitted for Analysis*

Cases complying with criteria for inclusion in study:		
Androgen-treated	580	
Estrogen-treated	364	
Total accepted for study		944
Cases not complying with criteria for inclusion in study:		
Not mammary cancer	19	
Male breast cancer	2	
Information lacking	372	
Not disseminated disease	309	
Radiation-treated	105	
Castrations	60	
Combined treatment	25	
Not sex steroids	22	
Ancillary treatments	14	
Inadequate dosage	101	
Miscellaneous	1	
Total rejected from study		1,039
Total submitted for analysis		1,983

It was the current subcommittee's opinion that the data available were sufficient to allow the following analyses: (1) determination of the objective responses of the neoplasm to estrogenic and androgenic hormones when administered to women with disseminated mammary carcinoma, (2) comparison of the effectiveness of androgens and estrogens, (3) clarification of the criteria for selection of patients and indications for hormonal treatment by estrogens and androgens, and (4) elaboration of certain aspects of the natural history of the disease.

Methods and Materials

Reports of 1,983 patients with mammary carcinoma treated by steroidal hormones were submitted to the subcommittee by the 60 investigators. This report is concerned with 944 cases (table 1) which fulfilled the following criteria. 1. The diagnosis of mammary carcinoma was established histologically in every patient. 2. Unequivocal evidence of distant dissemination of the disease was present, which was unsuitable for radiotherapy or surgical palliation. Specifically, it was required that spread beyond the regional (axillary) nodes be demonstrable in multiple foci, or be of such extent in dominant areas that irradiation was impractical, or both. Each patient represented genuine, distant dissemination so advanced as to require a systemic approach in treatment. 3. The patient must not have been irradiated or castrated within the six-month period immediately preceding hormone therapy. This did not exclude patients with multiple lesions who received x-ray therapy to a single symptomatic area, unless such irradiation resulted in any possibility of ovarian exposure, e. g., treatment to lumbar spine and pelvis. 4. No more than one hormone was administered during a single period of observation. 5. The hormone was administered for at least one month. 6. The patient received hormones designated by the subcommittee, with dosages in reasonable accordance with established protocols. 7. A completed initial case report was submitted and was followed by progress reports at suitable intervals.

The material consisted of an initial case report of the patient, with historical data concerning (1) diagnosis and treatment of the primary disease, (2) menstrual history, (3) past illnesses and operations, (4) treatment of metastases prior to admission to this study, (5) description of size and location of lesions as indicated on appropriate diagrams, and

(6) specification of compound and dosage schedule to be employed. The progress reports provided the following information: (1) total dose of hormone, (2) duration of therapy, (3) reason for interruption or discontinuance of therapy, (4) general condition of patient, (5) objective changes observed in each

TABLE 2.—*Androgen Series**

Patients, No.	Substance	Schedule of Dosage	Amount, Mg.	Frequency	Route of Administration
415	Testosterone propionate	A	25	3 times weekly	Intramuscular
		B	50	3 times weekly	Intramuscular
		C	100	3 times weekly	Intramuscular
		D	200	3 times weekly	Intramuscular
12	Testosterone cyclopentylpropionate		200	3 times weekly	Intramuscular
45	Stanolone		100	3 times weekly	Intramuscular
20	Methandriol		100	3 times weekly	Intramuscular
88	Methyltestosterone	A	100	Daily	Oral
		B	200	Daily	Oral
580					

* Standard of reference was testosterone propionate, 100 mg., 3 times weekly. Recommended dose of other agents in terms of estimated androgenic equivalents, as determined by an advisory panel.

lesion, (6) side-effects and other observations relevant to hormone therapy, and (7) date of death.

Despite the attempt to centralize pathological and roentgenographic interpretations, it was impractical to interpret these data. Therefore, the interpretation of the investigator and his own radiologist or pathologist was accepted as evidence for or against tumor regression.

In the evaluation of effectiveness of hormone treatment, only evidence of objective improvement was accepted as constituting reasonably satisfactory proof of a tumor-suppressive action. The definition of objective regression, which was rigidly adhered to in the following analysis, was stated as follows: a distinct, measurable decrease in one or more dominant metastatic areas by clinical or radiographic examination, without progression of any other metastatic lesions and with no new foci of disease having appeared. Indications of subjective improvement were ignored in this study of objective data; gain in weight, relief of pain, increase in feeling of well-being, improved blood chemistries, and improvement of hematopoiesis were not regarded as objective criteria. Patients classified as exhibiting "progression" included not only those with evidence of an increased extent in any lesion or lesions while under treatment but also those in whom the disease apparently remained stationary under therapy. The static cases numbered only 29.

The primary data concerning response and survival are based on the initial treatment of 944 patients. Calculations on survival were limited to patients treated by a single sex hormone, excluding those patients who subsequently received other steroid substances or who were subjected to endocrine ablative procedures. Two hundred eight patients subsequently received one or more courses of the same or another hormone. The response to these treatments is considered separately.

Androgen Series.—A total of 580 patients received androgen therapy as outlined in table 2. Although the majority of patients were treated in accordance with the dosage schedules outlined in this table, necessary variations in the individual management of patients not infrequently required changes from one schedule to another or, less often, some departure from the recommended protocol. For this reason, the criterion of adequate dosage is based in terms of total dosage. All patients in this group were treated for a minimum period of one month, according to one of the dosage schedules shown in table 2.

Estrogen Series.—A total of 364 patients were treated with estrogenic steroids as shown in table 3, for a minimum period of one month.

Follow-up: The clinical course of 844 patients (89.4%) was followed from the beginning of steroid treatment until time of death or the time of analysis. Of the 580 androgen-treated patients, 516 (89.0%) were followed to time of death or were still alive at the time of analysis; of the 364 estrogen-treated patients, 328 (90.1%) were followed to time of death or were still alive at the time of analysis.

Results

Androgen Series.—The frequency of tumor regression among the 580 androgen-treated patients was 21.4%. The distribution of these patients by age at the time of starting hormone therapy is shown in figure 1. Due to the recommendation of the subcommittee that estrogens be avoided in the treatment of premenopausal women, the prevalence of younger women among those receiving androgen treatment is conspicuous. There were 160 premenopausal patients in this group, of whom 32 (20.0%) manifested objective regression. Objective regression was recorded for 92 (21.9%) of the 420 postmenopausal, androgen-treated patients. Within

TABLE 3.—*Estrogen Series**

Patients, No.	Substance	Schedule of Dosage	Amount, Mg.	Frequency	Route of Administration
155	Diethylstilbestrol		15	Daily	Oral
62	Ethinyl estradiol		3	Daily	Oral
57	Chlorotrianisene		24	Daily	Oral
29	Conjugated estrogenic substances		30	Daily	Oral
25	Dienestrol		15	Daily	Oral
21	Diethylstilbestrol dimethyl ether		30	Daily	Oral
15	Estradiol dipropionate		5	2 times weekly	Intramuscular
364					

* Standard of reference is diethylstilbestrol, 15 mg. daily. Recommended dose of other agents in terms of estimated estrogenic equivalents, as determined by an advisory panel.

the postclimacteric group, menopause occurred naturally in 277, was induced in 104, and was of undetermined nature in 39 patients. (All reference to patients being premenopausal or postmenopausal indicates their status at the start of hormonal therapy. The term "induced menopause" refers to patients who had oophorectomy or castration by irradiation prior to the beginning of hormone therapy, whether related or unrelated to treatment of the primary carcinoma.)

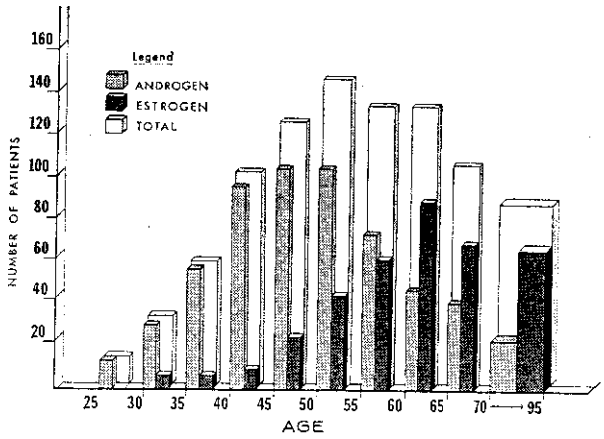

Fig. 1.—Distribution of patients by age at treatment of metastases.

The incidence of tumor regression was correlated with treatment beginning during successive 4-year intervals after the menopause through 16 years, and for those 17 or more years postmenopausal (table 4, fig. 2). The numerically largest group treated by androgens was in the immediate postmenopausal period of zero through four years. It is evident that nine or more years after the menopause there is an increased probability of obtaining an improvement with androgenic therapy ($\chi^2=6.65$, $p<0.01$).

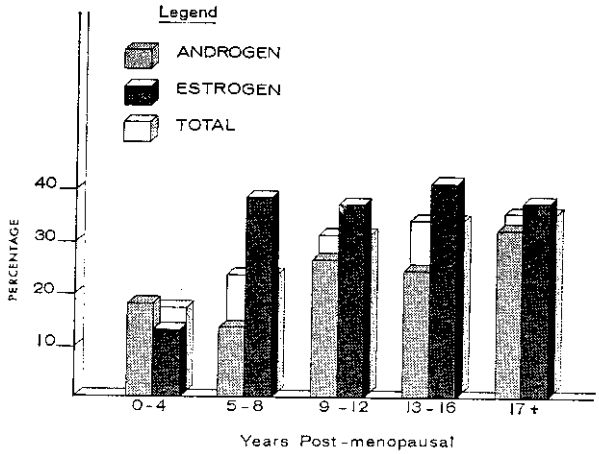

Fig. 2.—Frequency of regression by interval from menopause to treatment of metastases, shown as percentage within each 4-year group.

differences are due to chance. The smaller the "p" values, the less likely that observed differences may be attributed to coincidence. Thus, $p<0.05$ means that less than 5 times in 100 would a difference be attributed to chance; $p<0.01$ is less than 1 in 100. Conventionally, the rigid minimum requirement for significance is $p<0.01$, though a less critical but acceptable level of confidence is $p<0.05$. For those interested, statistical procedures [and their symbols] which have been applied to the data in this study are: "r," correlation of quantitative data; "r_pb" (point biserial), correlation of dichotomous values with quantitative values; "t" ratios, comparison of quantitative values; chi square, comparison of qualitative values. In every instance of chi square application, the correction for continuity has been included.)

An evaluation of frequency of regression according to anatomic sites was attempted. Comparison of the effectiveness of androgens on metastatic involvement in peripheral soft tissue, viscera, and bone for all cases showed no significant differences (table 5). An evaluation of effectiveness on involvement of multiple system (e. g., viscera and bone, soft tissue and bone) was not practicable.

TABLE 4.—*Incidence of Regressions Correlated with Interval Between Menopause and Beginning Hormone Therapy*

Interval Between Menopause and Hormone Therapy, Yr.	Patients, No.	Androgen			Estrogen			p^*	χ^2
		Patients Treated, No.	Regressions Patients, No.	Regressions %	Patients Treated, No.	Regressions Patients, No.	Regressions %		
0- 4†	186	154	27	17.5	32	4	12.5	>0.1	0.189
5- 8	103	61	8	13.1	42	16	38.0	<0.01	7.356
9-12	125	68	18	26.5	57	21	36.8	>0.1	1.112
13-16	92	38	9	23.7	54	22	40.7	>0.1	2.191
17+	185	60	19	31.7	125	46	36.8	>0.1	0.271
Premenopausal	167	160	32	20.0	7	...	...	...	...
Unknown	86	39	11	28.2	47	25	53.2	<0.05	4.489
Total	944	580	124	...	364	134	...	...	...

* As applied here, "p" means the probability that differences between percentage regression with androgens and estrogens are due to coincidence.
† Each time interval is inclusive, e. g., from 0 through the entire 4th year = 0-4 yr.

The average duration of life for all 427 patients receiving androgens as the only form of steroid therapy, and followed to time of death, was 11.4±9.9 months from institution of treatment. This period of average longevity was 19.1±12.2 months for those patients who demonstrated regressions and only 9.7±8.4 months in the nonresponsive patients (t=8.14, p<0.01). The average duration of survival of groups divided by menopausal status, primary treatment status, and responsiveness are presented in table 6. Longer survival associated with regressions is again demonstrated.

When the androgen-treated, naturally postmenopausal patients were grouped into responsive and nonresponsive groups, and the percentage of the sample still alive at selected intervals after beginning hormone therapy was graphed (fig. 3), a significantly greater (p<0.001) proportion of responders was found to be alive for periods up to 48 months.

TABLE 5.—*Correlation of Incidence of Regression and Location of Metastases*

		Androgen			Estrogen		
		Patients,	Regression		Patients,	Regression	
Menopause Status	Site*	No.	No.	%	No.	No.	%
All cases	Soft tissue	69	16	23.2	98	37	37.8
	Viscera	35	10	28.6	35	14	40.0
	Bone	162	39	24.1	38	9	27.3
Postmenopausal (natural)	Soft tissue	33	6	18.2	81	33	40.7
	Viscera	10	3	30.0	25	8	32.0
	Bone	80	25	31.3	23	7	30.4
Premenopausal	Soft tissue	21	4	19.0	...	...	...
	Viscera	17	5	29.4	...	...	...
	Bone	39	7	17.9	...	...	...

* Dissemination limited to these sites; cases with involvement of multiple systems excluded.

TABLE 6.—*Comparison of Average Duration of Survival of Responders and Nonresponders*

			Regression		Nonregression		
Treatment	Ovarian Status	Status of Primary Lesion	Patients, No.	Average Survival, Mo.*	Patients, No.	Average Survival, Mo.	p
Androgens	Premenopausal	Untreated	5	24	18	7	<0.001
		Treated	15	17	82	11	<0.07
		Av.	...	18	...	11	...
Androgens	Postmenopausal (natural)	Untreated	8	16	31	9	<0.05
		Treated	32	21	123	10	<0.001
		Av.	...	20	...	10	...
Estrogens	Postmenopausal (natural)	Untreated	26	20	40	8	<0.001
		Treated	45	31	87	12	<0.001
		Av.	...	27	...	11	...

* After start of hormone therapy.

Estrogen Series.—The frequency of regressions among 364 patients treated by various estrogens was 36.8%. This calculation included seven premenopausal patients, in all of whom progression of the neoplastic lesion was noted. Figure 1 demonstrates that the group treated with estrogens was comprised of chronologically older women (average age, 63 years) than the androgen-treated group (average age, 51 years).

Menopause occurred naturally in 294 cases, was induced in 16, and of undetermined type in 47. The menopause of 236 of 310 patients (table 7) occurred nine or more years before institution of estrogen therapy for metastatic disease. The regression rate of this group (37.7%) was not significantly higher than that of the group with recurrence at an earlier postmenopausal phase (27.0%). However, when the group was made more homogeneous by excluding patients whose primary lesions were untreated, or had occurred premenopausally, the r_{pb} is significant (p<0.05), indicating an increase in rate of regression as the time between institution of hormonal treatment and the menopause became longer.

The average duration of life for all 243 cases receiving estrogens as the initial and only form of steroid therapy was 16.5±16.1 months from institution of therapy (table 8). This period of average longevity was 27.3±18.2 months for those who manifested regressions and only 10.4±10.8 months for the unresponsive patients (t=9.08, p<0.001). Table 6 presents, for those women who had a natural menopause, the average months of survival after beginning hormone therapy, according to their response to treatment. Again it is obvious that patients in whom the disease regressed had a significantly longer period of survival than did those who failed to improve. In a survival curve (fig. 3), the proportion of patients alive in each period through 48 months after beginning hormone therapy was very significantly greater (p<0.001) for responders than for nonresponders.

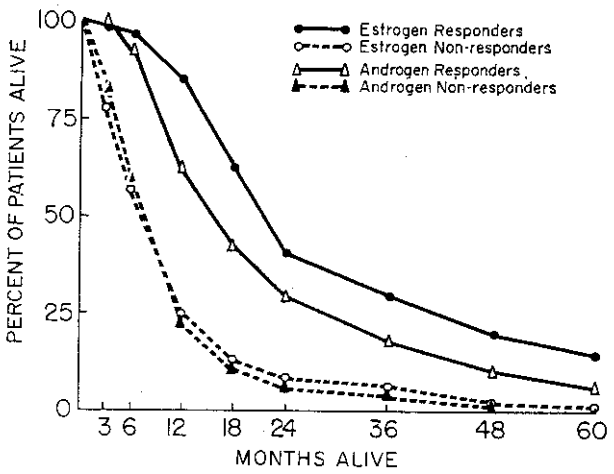

Fig. 3.—Comparative survival curves of natural postmenopausal patients from initial treatment of metastases.

Comparison of Androgen and Estrogen Series

The number of patients involved in this investigation would seem to provide an opportunity for comparing the efficacy of estrogenic and androgenic

hormones in groups homogeneous with respect to the incidence of regression, response of specific disease sites, physiological and chronological age, and duration of survival. However, such effort was unrewarding in many applications of this technique because samples became too small.

than nine years postmenopausal ($\chi^2=6.65$, $p<0.01$). The point biserial correlation of regression to postmenopausal interval was calculated within the more homogeneous population, achieved by using only patients whose menopause had occurred spontaneously and whose primary lesions had been treated

TABLE 7.—*Comparison of Incidence of Regression in Terms of Ovarian Status*

		Androgen			Estrogen				
			Regressions			Regressions			
Ovarian Status	Patients, No.	Patients Treated, No.	Patients, No.	%	Patients Treated, No.	Patients, No.	%	p	χ^2
Premenopausal	167	160	32	20.0	7	0	0	...	...
Postmenopausal									
0 through 8 yr.*	289	215	35	16.3	74	20	27.0	<0.06	3.46
9 or more yr.*	402	166	46	27.7	236	89	37.7	<0.05	3.93
Unknown interval	86	39	11	28.2	47	25	53.2	...	...

* Since last menses.

Because there is a significantly different distribution of ages in the androgen-treated and estrogen-treated groups (fig. 1), comparison of therapeutic effectiveness between the entire groups might be misleading. Nevertheless, when the frequency of regression after administration of androgen and after administration of estrogen was compared in groups of the same age (fig. 4), there was a higher frequency of response to estrogens in every decade. Statistically, the differences were significant only among patients who were over 70 years of age when hormone therapy was begun.

The older the patient was at the time steroid treatment was started the more likely was a regression to occur. In the androgen-treated cases, r_pb revealed a correlation with less than a 5% chance of being coincidental, whereas, within the estrogen-treated group, this correlation was much stronger, $p<0.0005$. Taken collectively, $p<0.005$ indicates that age of the patient at the beginning of treatment is an important factor in responsiveness.

As indicated in figure 2 and table 4, regressions occurred more often after estrogen therapy than after androgen therapy in groups which were comparably postmenopausal. When the postmenopausal interval was arbitrarily divided into less than nine

TABLE 8.—*Average Survival of Patients According to Treatment*

	Androgen		Estrogen			
Status of Patients	Patients, No.	Av., Mo.	Patients, No.	Av., Mo.	t	p
All patients	423	11.4	243	16.5	5.054	<0.001
No regression	345	9.7	156	10.4	0.784	...
Regression	78	19.1	87	27.3	3.345	<0.005

years and nine or more years, the advantage of estrogens over androgens was of modest statistical significance (table 7). Vertical comparisons in table 7 are not without some interest. However, the only such comparison which is statistically significant is in the androgen series among those patients less than nine years postmenopausal and those more postmenopausally. This correlation was statistically significant among the estrogen-treated ($p<0.05$), not significant among the androgen-treated, and significant when androgen-treated and estrogen-treated patients were pooled ($p<0.01$).

So few premenopausal patients (seven) were treated with estrogens that comparisons with androgens within this limitation were not feasible.

The incidence of regression by androgen and estrogen treatment and by site of metastases is compared in table 5. In comparing the largest, most homogeneous sample available (natural postmenopausal), it is apparent that there was no difference in the incidence of regressions in patients with visceral or osseous lesions. In patients with soft tissue lesions (lymph nodes, skin nodules, and breast), regressions occurred significantly ($p<0.05$) more often after estrogen treatment (40.7%) than after androgen therapy (18.2%).

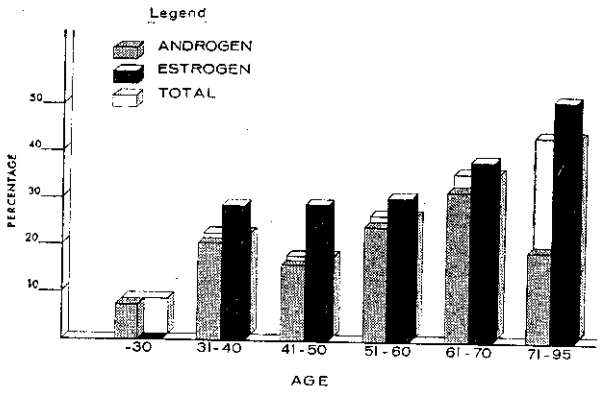

Fig. 4.—Frequency of regression by age of patient at treatment of metastases, shown as percentage within each 10-year interval.

The excellent follow-up to time of death of this large series provided an opportunity to compare the effect of androgen and estrogen therapy on duration of survival. The most physiologically homogeneous sample available for this purpose was

composed of those whose menopause had occurred spontaneously (table 6, fig. 3). Fortunately, the samples were almost equal in size, 194 having been treated by androgens and 198 by estrogens. Of the combined total of 392, 111 (28.2%) were responders, and 281 (71.8%) were unresponsive to hormonal treatment. Despite the type of hormone employed, longevity in the nonresponders was virtually identical, or an average of 10 and 11 months (after beginning hormonal therapy) for patients receiving androgens and estrogens respectively. Such uniformity in lethal end-point, unrelated to treatment, is evidence of a comparable tumor-host relationship at the beginning of treatment and a further indication of the homogeneity of the sample under analysis. In table 6 it may be seen further that, among patients enjoying regression, the estrogen-treated patients survived significantly longer, on the average, than did the androgen-treated patients, or 27 and 20 months respectively ($p<0.05$).

The advantage of estrogen treatment on survival may be seen also in figure 3. Statistically, more estrogen-treated patients are still alive 6 months ($\chi^2=7.49$, $p<0.01$) and 12 months ($\chi^2=4.40$, $p<0.05$) after beginning treatment.

Repeated Courses of Hormone Therapy

One or more courses of the same, or another, hormone were used for 208 patients not included in the calculations of survival just described. Evaluation became more difficult as multiple courses of treatment constituted added variables and made comparisons more complex; a much larger sample than was available would be required for comparisons of any significance. It was apparent that, after an initial regression and subsequent reactivation, a second interval of objective regression might be obtained with hormones of the same or the opposite type. In fact, repeated regressions were obtained in some patients. Also worthy of mention was the observation of renewed remission, in occasional patients, after withdrawal of the hormonal substance which had induced the initial period of regression. Such examples of a "therapeutic" effect by omission of therapy are unusual, and the duration of the favorable response ordinarily is brief.

Comment

Validity of Study.—Certain aspects of this retrospective, co-operative study and the methods used in analyzing the available data deserve some comment. It is unfortunate that over one-half of the case records submitted were unacceptable. Contributing factors included too many investigators submitting too few cases, inadequate resources for ideal liaison with contributors and for prompt correction of deficiencies and collection of follow-up information, and failure to achieve a more effective experimental design during the planning stage over 10 years ago. Of practical importance are those exclusions suspect of producing a selective effect or making the sample for analysis biased. The exclusion of 101 cases because of inadequate dosage is justified by three items of evidence: 1. The frequency with which androgens and estrogens were used in the rejected cases was about the same as in the accepted cases. 2. Previous reports of the subcommittee have provided evidence indicating that the potential effectiveness of the sex steroids on the neoplasm is related directly to their virilizing or feminizing titer, and that regression of disease does not occur to any significant degree until clinical evidence of the physiological effect of androgens or estrogens is apparent. The minimal requirements of dose and of duration of treatment for this study are both well below the levels required for virilizing or feminizing effects and must be regarded as almost equally inadequate in antitumoral effect. 3. Another objection might be that the rejection process resulted in the acceptance of cases treated by androgens and estrogens which are not as representative as an unselected group would be, resulting in a comparison of atypical groups. The present report demonstrates conclusively that the patients treated by androgens and estrogens were comparable groups; among those who were unresponsive to treatment, average survival time was virtually identical in each series (table 6, fig. 3).

TABLE 9.—*Regression Rates According to Total Dose*

Ovarian Status	Testosterone Propionate <3 Gm.	Testosterone Propionate >3 Gm.
Premenopausal, %	8.8	21.5
Postmenopausal (natural), %	12.5	30.1

The criterion of a minimum period of one month of treatment was exceedingly lenient. For androgens, one month of schedule C, testosterone propionate, most commonly used, produced a dose of 1.3 Gm.; schedule A, least often used, was at the rate of only 325 mg. per month. The relative inadequacy of these dosage levels was obvious when regression rates were calculated with reference to a total dose of known effectiveness, or 3.0 Gm. in two major groups (table 9). With estrogens, a total dose of 1.0 Gm. of diethylstilbestrol is an effective level, as the following rates of regression, in naturally postmenopausal patients, will demonstrate: <1.0 Gm., 26.3%; >1.0 Gm., 47.3%. The minimum criterion of one month of treatment, at the recommended rate of 15 mg. of the substance daily, amounts to less than 500 mg., but even this is frequently an overestimate because of the number of patients with an initial intolerance and the necessity of graduated dosage at the beginning of treatment.

The duration of treatment is as important as, or perhaps of greater significance than, the total dosage. The situation just indicated for the orally administered estrogens is pertinent; some of the

accepted cases were women who did not reach the minimum total dose until two or even three months had elapsed, because of difficulty in developing tolerance. A few never reached the recommended daily dose. Yet the length of treatment was an important consideration. If a total of 3 Gm. was ingested, a three-month period was required before full effectiveness of estrogens was approached, though not entirely realized for soft tissue metastasis, whereas skeletal deposits frequently required even longer intervals before objective changes of regression were demonstrable. With androgens, it seems probable that remissions were about twice as frequent in those treated for more than three months than in patients whose therapy was of briefer duration.

With such minimum criteria of dosage and duration of treatment established, it is obvious that the lenient requirements for admission to this study had a dual effect: (1) inclusion of patients in whom a favorable response may have been triggered by hormonal influences of minute dimensions, and (2) admission of potential responders in whom more prolonged treatment at recommended dosage would have achieved measurable palliation. As the latter group exceeded the former by a large margin, the process of selection was such as to diminish, rather than enhance, the true dimensions of the usefulness of hormonal therapy.

TABLE 10.—*Averages of Free Interval for Three Groups*

Patients, No.	Group	Mean, Mo.	Standard Deviation, Mo.
124	B1	31.36	33.77
48	B2	87.10	57.25
377	B3	39.19	36.60

Evidence of progressive disease before starting treatment was not required. This was compensated for by designating as nonresponders those 29 patients whose disease remained static during treatment and follow-up, thus lumping them with the failures in this evaluation of the effectiveness of hormonal therapy. To do otherwise would require a largely artificial grouping of patients with static or "arrested" disease, contributed to in some part by the phenomenon of spontaneous arrest. The experience of the subcommittee, which led to the most elementary classification of "responders" and "nonresponders" as employed here, by rigid criteria of objective improvement, also suggests that more divisive groupings with such terms as "arrested," "remission," and "equivocal" are of dubious value.

In the analysis of responsiveness of postmenopausal patients to treatment, the samples were limited, in most instances, to those women who had experienced a natural climacteric. The intent was to obtain groups as homogeneous as possible for such comparisons, and, in a significant number of those whose "menopause" had been induced, the cessation of the menses was attended by uncertainty of the artifactive process used. Most frequently a pelvic operative procedure followed by amenorrhea was not accurately recorded as including ovarian ablation. In other instances, pelvic irradiation apparently had resulted in amenorrhea, but, without details of tissue (midpelvic) dose, no impression of the physiological effectiveness of this measure was possible. Actually, when the induced-menopause group was combined with the natural postmenopausal patients, and the aforementioned calculations repeated, there was no significant variation between the total postmenopausal "population" and the more physiologically homogeneous fraction.

Indications of Variations in Natural History of Mammary Carcinoma

Several trends which emerged during this review are reflections of the variable natural history of mammary carcinoma, apart from their correlation with the results of hormonal treatment.

Free Interval.—A phenomenon of intriguing interest to any observer of the clinical course of cancer of the breast is the activation of metastatic disease after many years of good health following eradication of the primary growth in the breast. Late manifestations of metastasis are so common that the traditional yardstick of survival for five years is of little value; it is not uncommon for the initial evidence of distant spread to appear 15 to 20 years after definitive, primary treatment, and in one carefully studied and verified instance the first local (axillary) recurrence was noted after 37 postoperative years. The lapse of time between primary, definitive treatment (usually mastectomy) and, in this view, the initial use of hormonal therapy is an approximate index of the latent period of foci of metastasis and necessarily must be an expression of the biological balance between host and neoplasm. The time during which metastasis remains occult, or subclinical, is referred to hereafter as the free interval.

A number of analytical procedures have been applied to available free-interval data, one of which indicated a natural division of the sample at hand into three groups. In the first group, both primary treatment and metastatic growth occurred prior to the menopause (designated B1); the second group had mastectomy prior to the menopause and recurrence after a natural climacteric (B2); the third group was comprised of those in whom a natural menopause preceded both primary disease and appearance of metastasis (B3). The free-interval averages for these three groups are shown in table 10. Each of these average values is statistically different from each of the other two: $p<0.05$, comparing group B1 with group B3, and $p<0.001$ for the other two comparisons. (These statistical statements are made on data from which "untreated primaries" and "induced-menopause" groups were excluded. Cases treated with androgen or estrogen, responders or nonresponders were pooled.)

The identification of the B2 group, characterized by an inordinately long free interval averaging 87 months (7¼ years) and by the interposition of the menopause between primary treatment and metastatic activity, represents a unique and hitherto unrecognized, though minor, fraction of patients in whom the natural history is so disparate as to require its separation from the major groups of cases.

TABLE 11.—*Comparison of Relative Frequency of Regression by Free Intervals and Hormone Treatments*

		Free Interval, 0-36 Mo.			Free Interval, 37+Mo.				
		Patients,	Regressions		Patients,	Regressions			
Group*	Treatment	No.	No.	%	No.	No.	%	χ^2	p
A. All cases	Androgen	132	24	18.2	98	35	35.7	8.168	<0.005
	Estrogen	106	31	29.2	90	33	36.7	0.904	...
B. Only B2	Androgen	43	10	23.2	28	15	53.6	5.584	<0.025
	Estrogen	31	7	22.6	29	9	31.0	0.201	...
C. Without B2	Androgen	89	14	15.7	70	20	28.5	3.121	<0.075
	Estrogen	75	24	32.0	61	24	39.3	0.505	...

* Natural menopause cases only.

All prior studies with which the subcommittee is familiar have indicated comparably longer free intervals in patients who were older by either chronological or endocrinologic landmarks. This concept may be derived also from the study at hand, in which the average free interval of 124 premenopausal women was 31.4 months, whereas it was 44.6 months for 425 patients whose menopause had occurred spontaneously. Recalculation of free interval for the postmenopausal group after removing the influence of the B2 patients (i. e., all postmenopausal patients minus the B2 group, leaving residual B3 group), demonstrates a diminished free interval for these 377 women of 39.2 months, which is more comparable to the figure for premenopausal patients.

To explore the possibility that the effectiveness of hormone therapy might be related to duration of the free interval, it was tested for correlation, with two indexes of response. The correlation of the incidence of regression with increasing length of free interval was found to be significant ($r_pb=0.081$, $p<0.05$). Correlation of the length of free interval with duration of survival after beginning hormone therapy was also very significant ($r=0.138$, $p<0.01$) for the 518 cases with the necessary information. This correlation was significant, even when the test was applied separately to responders and nonresponders.

Because the free interval appeared to have some prognostic value, its association with the age of the patient at definitive treatment of the primary lesion was tested. Significant inverse correlations were found between these two values for 123 patients in whom primary treatment and metastasis preceded the menopause ($r=-0.248$, $p<0.01$), and for 375 patients whose primary and palliative therapy both followed a natural menopause ($r=-0.142$, $p<0.01$). This is to say that the younger the patient is at the time of recognition and treatment of her primary disease the longer the evidence of metastasis is likely to be postponed.

That the average free interval for the B1 group was 31.4 months and for the B3 group was 39.2 months does not contradict the surprising inverse relationship described. Although the average age and average free interval were both smaller in the B1 group, the statistical examinations produced significant inverse correlations, whether performed on data within each of the two groups or on the two groups pooled.

The unusually long free interval seen in the small B2 group suggests that in these patients there was some unusual biological or metabolic feature which favored a very long occult phase of metastatic disease. Nonetheless, the inverse correlation between primary age and free interval in this group was also significant ($r=-0.439$, $p<0.01$).

In analyzing the inverse relationship between the free interval and age, it became desirable to determine the influence of this interval on rates of regression in the B2 group, in view of postprimary free periods of such remarkable length, and to discover what differences might exist between the B2 cases and all other naturally postmenopausal women. Analyses of the entire series of naturally postmenopausal patients (at the time of beginning hormonal therapy), by division of androgen-treated and estrogen-treated groups into subgroups of free intervals through 36 months in duration and 37 or more months, appear in table 11. By this arbitrary subgrouping, the association of the longer free interval with a greater percentage of regressions was highly significant for those treated by androgens but was not statistically significant in those given estrogens.

The same analyses for the B2 group and for the remaining patients (131 and 295 cases respectively) of the naturally menopausal series are presented separately in B and C of table 11. Again, the longer free interval was unassociated with any significant increase in the occurrence of regression with treatment by estrogens. In both larger and smaller groups, the influence of the longer postprimary free interval was significant with androgenic therapy, although not as striking by statistical standards.

TABLE 12.—*Vertical Comparisons of Table 11*

	Free Interval,	Regressions			
Group	Mo.	Androgen, %	Estrogen, %	χ^2	p
A. All cases	0-36	18.2	29.2	3.451	<0.06
	37+	35.7	36.7	...	...
B. Only B2	0-36	23.2	22.6	...	...
	37+	53.6	31.0	2.129	<0.250
C. Without B2 ..	0-36	15.7	32.0	5.172	<0.025
	37+	28.5	39.3	1.250	...

It is revealing to examine the same data from another perspective, as shown in table 12. In the group from which the B2 cases were excluded, the

frequency of regressions was significantly greater (χ^2=5.172, $p<0.025$) among the estrogen-treated women than among the androgen-treated women whose free intervals were less than 37 months. If the values comparing androgen and estrogen effect are compared when the free interval exceeds 37 months, statistics indicate they are not different.

Within the B 2 group, androgen and estrogen were found to elicit equal frequencies of regression when the free interval was less than 37 months. After 37 months, a greater frequency of regression occurred after androgen treatment than after estrogen therapy (though it is statistically insignificant).

Comparing the frequency of regression under different treatments and by the arbitrary free-interval separation at 36 months, androgen was superior, though not statistically, to estrogen only when 53.6% is compared to 31.0%. Within the androgen-treated group the regression group is greater among the B2 group (53.6%) than in the B3 group (28.5%) when the free interval is more than 37 months (χ^2=4.41, $p<0.05$). Thus, it is possible to suggest that, in a B2 patient who had a free interval longer than 3 years, androgen is more likely to be of benefit than if she were not in the B2 group. These data do not show that androgen will be any more favorable to this B2 patient than will estrogen.

An even more valid endorsement of the prognostic value of the free interval was its significant correlation (r_pb=2.25, $p<0.025$) with the incidence of regression.

Survival.—The most significant and most consistent phenomenon in the behavior of the disease under hormonal treatment, both by androgen and estrogens, was the increased survival time of patients in whom objective regression of disease occurred (tables 6 and 8, fig. 3). It should be noted that the nonresponsive groups, whether premenopausal or postmenopausal, whether treated by androgens or estrogens, and whether postoperative or with primary neoplasm *in situ*, had average survival periods in a narrow range of 8 to 11 months after starting treatment. When the status of the primary site was disregarded, the over-all mean survival time for the premenopausal and androgen-treated or estrogen-treated postmenopausal groups was 11 months, 10 months, and 11 months respectively. These short, statistically equivalent periods of survival in nonresponders provided highly dependable base lines, consistent with the natural history of untreated disease in these groups (see below), against which the responders survived for average intervals of 18, 20, and 27 months respectively. Statistical significance of the disparity in survival of responders and nonresponders was at the critical level of $p<0.001$ in comparing four of the six subgroup pairs shown in table 6 and was within the area of confidence for data of this type in the other comparisons, considering the over-all trend.

The capacity for objective regression of neoplasm and the associated increase in survival which differentiated responders from nonresponders were important indications of fundamental biological differences between the two groups. The evidence of basic disparity was not so much in the presence or absence of tumor-suppressive effect as in the fact that regression was followed by a significant alteration in the course of the disease and in survival, whereas, without regression, the pattern of disease and survival remained unaltered. The significance of the data supporting this basic separation of patients provides both incentive and promise to efforts in research aimed at the elucidation of hostal or tumoral factors responsible for these reactions.

Results of Treatment

Distribution of Patients.—There were only 167 premenopausal women, compared to 777 postmenopausal patients, making up the total of 944 available for analysis. Of these, 580 were treated by androgens and 364 by estrogens, a resounding vote for androgenic substances, justification for which is lacking in the data presented herein. If a conclusion stated earlier had been followed in this series, namely, that estrogens are more effective than androgens after the fourth postmenopausal year, the ratio of their use would have been reversed, and 588 would have been treated with estrogens (table 4).

Although those treated by androgen were of an average age (51 years), 12 years less than the estrogen series (63 years), the difference was more chronologic than endocrinologic, and there was obviously a lesser disparity (6 years) in age by years in the only patients for whom such comparison was proper—those who were postmenopausal.

Of the 716 postmenopausal women for whom the elapsed years of diminished ovarian activity were recorded, there were 167 in whom the menopause had been induced prior to the activation of metastasis. Of these, 115 were treated by androgens and accounted for 21.3% of all patients so treated; 52 of the estrogen series, or 15.9%, were treated after an induced menopause. This distribution is reasonably analogous to the over-all androgen-estrogen ratio; e. g., 38.5% (364) of the total of 944 patients and 31.1% (52/167) of the induced menopausal group were treated by estrogens.

Chronological Age: As seen in figure 4, too few patients were treated with estrogens before age 40 to allow any comparison. It is no surprise that in women past 70 years of age estrogens were of significant superiority ($p<0.02$). In the decades from 40 to 50, 50 to 60, and 60 to 70, estrogenic therapy produced greater percentage rates of regression; although these were not statistically valid, the approximate number of regressions per 100 patients, estrogens over androgens, was 29 and 16, 30 and 24, and 37 and 31 respectively. This consistent superiority of estrogen through all ages past 40 gives no

indication that the performance of androgenic therapy was at a disadvantage due to factor of age.

Endocrinologic Age: In table 4 a review of percentage rates of regression, noted in successive periods beyond the menopause, shows that the estrogens reach a plateau of performance after the fourth postmenopausal year, with about 38 of every 100 patients obtaining regression. The androgen series records a similar plateau, but at a later phase, or after the eighth postclimacteric year, and at a less effective level than with estrogens, with regression occurring at a rate of nearly 27 of each 100 patients. On cross comparisons of differences within each of the two treatment series, significant values were found only between the intervals zero through four years and five through eight years among the estrogens ($\chi^2=4.804$). The possibility that the androgens are at a disadvantage due to their use in women who are younger than those in the estrogen series becomes less credible when the effectiveness of androgens at the two extremes of age is examined. In premenopausal patients in the decade from 31 to 40 years, androgens induced regression in 21.4% of 84 patients. In a group of patients aged 71 to 95 years, 21 were subjected to androgenic therapy and only 4, or 19.0%, experienced any regression. The corresponding regression rates for estrogens were 28.6% for those aged 31 to 40 years (postmenopausal women) and 51.5% for the oldest grouping.

Although the differences in these rates of regression are of statistical significance only in the postmenopausal interval of five through eight years (table 4), the consistent disparity is not without practical clinical overtones, which are amplified to a degree of real significance by considering larger samples, as in table 7. Here it is shown that, in the period ending with the eighth postmenopausal year, estrogens produced a 27.0% regression rate to 16.3% for androgens ($p<0.06$); during the years thereafter, the comparative rates were 37.7% and 27.7%, a significant difference of $p<0.05$. Inasmuch as an equally significant difference was demonstrated in the smaller samples (table 4) for the fifth through the eighth year after the menopause, it is reasonable to conclude that, in all women more than four years postmenopausal, the performance of estrogens is distinctly superior.

A recommendation that estrogens be used prior to five or more years after the menopause will seem hazardous to many clinicians, for some authors continue to sound warnings against their use for a full decade beyond the climacteric. The persistent apprehension which attends the therapeutic use of estrogens is accounted for by a number of factors: the emphasis on androgens only in the early years of treatment by hormones (1940-1945), uncertain knowledge of the role of endogenous estrogens in the genesis of breast carcinoma in human and animal varieties, and the popularization of the concept of "estrogen-dependency" in recent years. This is, however, an appropriate reminder of an obligation to emphasize again that "therapeutic" amounts of any estrogenic substance in the menstruating woman may be followed by augmentation of breast carcinoma. Several of the investigators associated with this study in its early years had the misfortune of observing acceleration of the growth and spread of the neoplasm concurrently with estrogenic therapy. Of the seven premenopausal patients of this series given estrogen, all exhibited progression, but this is not to say that all, or even any of them, were in a true phase of augmentation as distinct from the behavior of the disease in an unfavorable, rapid pattern of growth of natural origin.

Sites.—In the consideration of effectiveness by location of metastasis in patients with dominant involvement in single systems, there were no statistical differences of really critical degree in either the androgen or the estrogen series (table 5). In terms of practical probability, androgens were of lesser efficacy before a natural menopause than afterwards in metastasis to bone. For all cases, there was a striking similarity in the androgen-associated regressions in the three systems.

For estrogens, the greatest percentage of regression for the natural postmenopausal women occurred in soft tissue deposits. Regression of 40.7% of soft tissue lesions in elderly women seems more notable than the 31% control of visceral and osseous spread.

When a comparison of androgens and estrogens was limited to their effectiveness in the homogeneous group of natural postmenopausal women, regression in practically identical proportions was noted for both visceral and skeletal locations with the use of each type of hormone, or in 31 of each 100 patients. The greater control of metastasis in soft tissue by estrogens is again apparent, or in 41 of each 100 patients, compared to 18 of each 100 with use of androgens ($\chi^2=4.347$, $p<0.05$). The observation of greatest practical importance is an equally effective control of skeletal metastasis by androgens and estrogens. The notion that the andogens are of greater value at all ages for bony involvement is still widely entertained. For postmenopausal patients, many clinicians cling to a routine of using estrogens for soft tissue and visceral spread and androgens when skeletal involvement is demonstrable; the fallacy of this approach is indicated in the inconsequential difference of 0.9%.

Survival.—In responsive patients, average survival time of the estrogen-treated (table 8) is significantly longer than that of the androgen-treated. This demonstrates a more effective antitumoral function for estrogens in their contribution to greater longevity, of very significant degree in estrogen responders ($p<0.005$). Although the disease be-

comes less lethal with increasing time beyond the menopause, the criterion of the free interval is less favorable than in premenopausal women, as outlined earlier. The older woman therefore realizes longer survival than the younger, on the average, but she also tolerates the presence of clinically detectable cancer for a greater fraction of that increased life span. This is a denial of the usual concept that both types of hormones became more effective by reason of a predominant trend of aging women to develop neoplasms of a less aggressive pattern generally. Such a concept is now inadequate, to the extent of our recognition of earlier

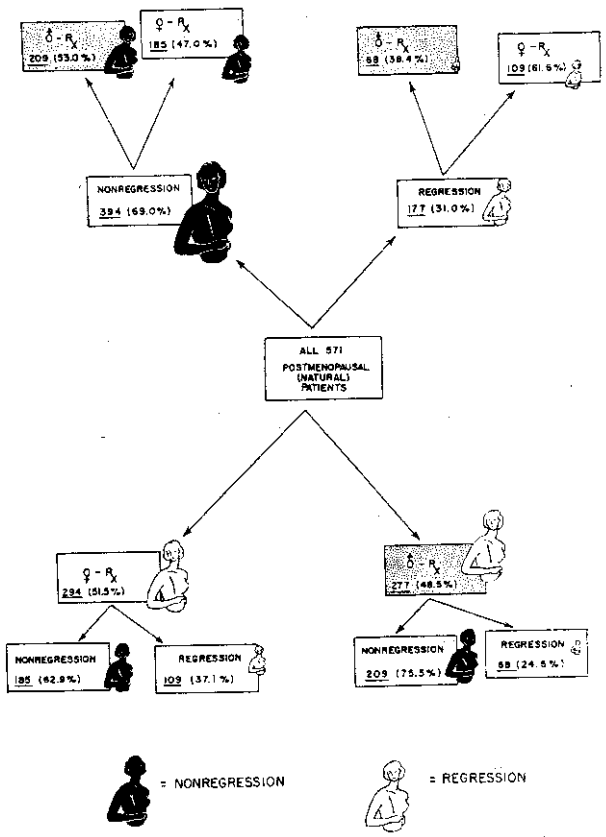

Fig. 5.—Incidence of response to treatment of natural postmenopausal patients.

metastatic activity and a longer time of active growth (shorter free interval) than in the younger woman, and to a similar extent that estrogens and androgens must both be credited with a greater degree of carcinostatic potency. Further, the estrogens now must be recognized as inherently superior to androgens in a qualitative fashion and by a significant degree.

Summary of Comparative Effect—Androgens and Estrogens.—There can be no reasonable doubt concerning the advantage of estrogens in the initiation of regression in postmenopausal women. For a final look at comparative performance, there are striking features in the data in table 6 and figure 5. Of the 571 natural postmenopausal women there are less than 5 chances in 1,000 that estrogen superiority in either grouping is coincidental.

In brief, at all ages past 30 (if the patients were postmenopausal, either induced or natural), at all phases of postmenopausal life, in each anatomic spread to single systems, and by average duration of life in responsive women, estrogens were equal to androgens, and more often of some advantage, in the frequency with which their use was associated with objective regression. The instances in which calculations indicated roughly equal rates of regression for both groups of hormone-treated patients were as follows: during the period of zero through four years after the menopause, in most of skeletal spread, and in visceral foci in (natural) postmenopausal women. At all other chronological and endocrinologic intervals (except, of course, the premenopausal) and in other situations of unisystemic metastases, the results were at least presumptive of a greater effectiveness for estrogens. Although the differences were of statistical significance less often than of an apparent, percentile order, there were instances in which consolidation to produce a larger sample or a more homogeneous group provided statistical validation at critical levels.

Side-effects.—A final consideration of considerable importance to the physician in his selection of hormonal agents, and of still greater moment to the woman with disseminated carcinoma of the breast, is a comparison of the extreme physiological effects on various target tissues, or side-effects, of the two groups of substances. In the physiologist's orientation, the tumor-suppressive action is the "side-effect," but the most favorable endocrinologic milieu for maximum rates of regression requires doses of a magnitude commonly producing the clinician's "side-effects." In clinical thinking this term does not include such favorable phenomena as the anabolic or hematopoietic effects but indicates rather the distressing manifestations, which, in general, are due to either virilization or feminization, the anorexia, nausea, and vomiting much more common with estrogens, the hazard of hypercalcemia, which is likely to be more frequent with androgens, and many others.

Although a review of side-effects has not been a part of the current study, progress reports of the subcommittee, based largely on the same series of patients reported here, have detailed their incidence and significance.[2] A comprehensive review of the subject was published in 1953 by Kennedy and Nathanson,[3] as an informative document ancillary to the published data from this subcommittee.

With this evidence of prior interest in the problems of side-effects and the study and publication of data pertaining to the series reported here, it is the consensus of the subcommittee that the distressing physical, psychic, and emotional side-effects of the androgens were of greater magnitude than were

those of the estrogenic substances, in the doses required for the therapy of cancer. The dilemma may be epitomized by stating that a biological system conditioned for a dominant response to feminization will tolerate more kindly the insults of its untimely resurgence than it will the physiological travesty of a reversal in sexual polarity.

If this philosophy born of clinical experience is valid, a preference for estrogenic therapy is obvious whenever the probability of regression is equal, or superior, to that which may be secured by the use of androgens. Specifically, the results of this study indicate that all patients beyond the fourth postmenopausal year (or, perhaps, even earlier after the climacteric) should have initial hormone treatment by estrogens.

Summary

Reports on a series of 944 women with disseminated mammary carcinoma treated by androgenic hormones (580 women) and estrogenic hormones (364 women), from 1947 through 1956, by 60 participating investigators, have been subjected to reanalysis and an evaluation of the results. The follow-up, until time of death or the date of the analysis, was successful in 89.4% (844 women). Androgens produced objective regression in 20% of premenopausal patients and in 21% of postmenopausal women. Estrogens, limited properly to postmenopausal patients, induced regression in 36% of patients. Both types of hormones were more effective after the eighth postmenopausal year, at which time both reached a plateau of performance, but with the estrogens inducing a higher relative frequency of regressions (38%) than did the androgens (27%).

In cases with unisystemic dissemination, estrogens produced a greater degree of control in soft tissues at all postmenopausal ages and were equal, or superior, to androgens for skeletal and visceral metastasis.

Responsive patients had significantly longer survival rates with androgenic or estrogenic therapy, whereas the unresponsive women with either mode of therapy had almost identical average periods of survival comparable to untreated patients. Steroid sex hormones are sufficiently effective in naturally postmenopausal women to deserve a primary trial in the treatment of disseminated mammary carcinoma. After the fourth postmenopausal year, estrogenic substances are the agents of choice.

The hormonal substances used in this study were supplied by Abbott Laboratories, North Chicago, Ill.; Ayerst Laboratories, Inc., Division of American Home Products Corporation, New York; Ciba Pharmaceutical Products Inc., Summit, N. J.; Charles E. Frosst & Co., Montreal; Lakeside Laboratories, Inc., Milwaukee; The Wm. S. Merrell Company, Cincinnati; Organon, Inc., Orange, N. J.; Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.; Rare Chemicals, Inc., Harrison, N. J.; Schering Corporation, Bloomfield, N. J.; E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, New York; The Upjohn Company, Kalamazoo, Mich.; Maltbie Laboratories Division, Wallace & Tiernan Inc., Belleville, N. J.; White Laboratories, Inc., Kenilworth, N. J.; Winthrop Laboratories, New York.

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HOW THE KIDNEYS GOVERN THE DISTRIBUTION OF WATER.—In the intact animal with metabolism proceeding steadily, extracellular osmolarity controls the water balance of the cells. Hence thirst and water diuresis, which rather precisely guard against excessive or deficient levels of extracellular osmolarity, may be regarded as mechanisms controlling the volume of intracellular fluid. Since they do this by stabilizing an extracellular osmolarity which is mostly due to sodium salts, they also set the stage for the regulation of extracellular fluid volume by adjustments of the renal excretion of sodium. For so long as its osmolarity is held constant, the volume of extracellular fluid must be proportional to the amount of sodium which it contains, and this depends upon how much of the daily intake the kidneys retain. Hence the kidneys, directed in ways which largely remain to be elucidated . . . are able to regulate the volume of water inside the cells by controlling the excretion of water, and the volume outside the cells by controlling the excretion of sodium. . . . Thus the organization of intracellular as well as of extracellular fluids, together with the exchanges both between compartments within the body and between the body and the external environment, may be described to a remarkable extent, in Gamble's . . . happy phrase, as a "Companionship of water and electrolytes."—J. R. Robinson, Metabolism of Intracellular Water, *Physiological Reviews*, January, 1960.