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University of Minnesota Hospitals
and
Minnesota Medical Foundation

Hormonal Therapy Of Breast Cancer

Volume XX | Friday, January 21, 1949 | Number 13

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
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INDEX

*William A. O'Brien Professor of Cancer Research

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I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

January 24 - 29, 1949

No. 232

Monday, January 24

8:00 -	Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.
9:00 - 9:50	Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.
9:00 - 10:50	Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.
10:00 - 12:00	Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.
11:00 - 11:50	Roentgenology-Medicine Conference; Staff; Veterans Hospital.
11:00 - 11:50	Physical Medicine Seminar; E-101, U. H.
11:00 - 12:00	Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.
12:00 - 1:00	Physiology Seminar; Hyperventilation Paradox; Mr. E. B. Brown; 214 M. H.
12:15 - 1:20	Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.
12:30 - 1:20	Pathology Seminar; Mycosis Fungoides; Stanley Huss; 104 I. A.
12:30 - 1:30	Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Class Room, Minneapolis General Hospital.
1:30 - 2:30	Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.
1:30 - 2:30	Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.
4:00 -	Pediatric Seminar; Progress in Current Investigations in Anemia and Intestinal Insufficiency; Chas. May; 6th Floor, Child Psychiatry, U. H.
5:00 - 5:50	Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.
5:00 - 6:00	Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.

Tuesday, January 25

8:00 - 9:00 Fracture Conference; Auditorium, Ancker Hospital.

8:30 - 10:20 Surgery Seminar; Lyle Hay; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

1:00 - 2:30 X-ray-Surgery Conference; Auditorium, Ancker Hospital.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:00 - 5:30 Surgery-Physiology Conference; Parasitic Carcinogens; R. A. Huseby and C. R. Hitchcock; Eustis Amphitheater, U. H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Drs. Fink, O'Loughlin and Staff; Veterans Adm. Hospital.

Wednesday, January 26

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 9:30 Clinico-Pathological Conference; Auditorium, Ancker Hospital.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans Hospital.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:00 - 12:50 Radio Isotope Seminar; Demonstration of Instruments for Monitoring and for Personal Protection; James Marvin; Rm. 216, Hospital Court, Temporary Bldg.

3:30 - 4:30 Journal Club; Surgery Office, Ancker Hospital.

4:00 - 5:00 Infectious Disease Rounds; Main Lecture Room; Minneapolis General Hospital.

4:00 - 6:00 Public Health Seminar; 113 MeS.

Thursday, January 27

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Craig Freeman and H. M. Stauffer; M-109, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, Minneapolis General Hospital.

12:00 - 1:00 Physiological Chemistry Seminar; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Class Room, Minneapolis General Hospital.

4:00 - 5:00 Bacteriology and Immunology Seminar; Genetic Studies of a Bacterial Virus; Mrs. M. Sussman; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Report of Gastric Cancer Conference; Leo G. Rigler; Todd Amphitheater.

8:00 p.m. J. B. Johnston Lecture in Neurology; The Cerebral Control of Muscular Activity; Paul C. Bucy, Ill. Neuropsychiatric Institute; Natural History Museum Auditorium.

Friday, January 28

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Roentgen Aspects of the Inferior Vena Cava; B. J. O'Loughlin; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 3:00 Pathology-Surgery Conference; Auditorium, Ancker Hospital.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, January 29

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:30 - 9:30 Surgery Conference; Auditorium, Ancker Hospital.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, H. M. Stauffer, and Staff; Todd Amphitheater, U. H.

9:00 - 12:00 Neurology Conference; Powell Hall Amphitheater.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 11:50 Urology Seminar; Surgery in Metastatic Hypernephroma; Arnold Kremen; E-101, U. H.

11:00 - 12:00 Anatomy Seminar; Vital Staining of Blood Vessels, W. L. Williams; Effect of Sex Hormones on Reproductive Tract and Dimorphic Glands of the Female Mouse, Marthella Frantz; 226 I. A.

II. ESTROGEN THERAPY OF ADVANCED CANCER OF THE FEMALE BREAST

Robert A. Huseby
Stuart W. Arhelger

Assisted by grants from the Minnesota Division of the American Cancer Society and the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

Introduction

That human breast cancer can be favorably influenced by altering the hormonal status of the patient, a thesis proposed many years ago[4,20] and later widely debated, has been, in recent years, firmly established by means of the administration of the sex hormones to persons with advanced, inoperable disease. To date the bulk of the pertinent literature has considered the effects of the administration of testosterone (for salient articles see 1,2,5,7,8,10,11,12, 13,17,19,21,22) with only a few papers dealing with the beneficial effects of the estrogenic hormones (6,9,14,15,16, 17,18). These latter reports have concerned themselves almost solely with the establishment of the phenomenon of breast cancer regression following the administration of estrogenically active compounds. The purpose of this presentation is not only to re-emphasize the occurrence of this phenomenon but in addition to present, rather completely, data concerning the subsequent course of the disease in patients so treated in an effort to establish the usefulness of this type of palliative therapy in the management of advanced breast cancer.

The early reports of the British workers[6,9] stressed the transient nature of the favorable responses noted and the relationship of the age of the patient to the response obtained with the treatment resulting, not infrequently, in an acceleration of the disease in younger women. Following these suggestions and those of Nathanson[15,16,17], which are in accord with the more recent suggestions of the Subcommittee on Steroids and Cancer of the Therapeutic Trials Committee of the A.M.A.[3], only patients with advanced, inoperable breast cancer who were five or more years postmenopausal were considered for treatment. The observations of others have also indicated that metastatic disease involving the bony skeleton seldom responds favorably to this type of therapy. The cases reported here represent all the patients fulfilling the first two requirements who presented multiple lesions involving the soft tissues of the body, seen in the Tumor Clinic of the University of Minnesota Hospitals from March 1946 through June 1948. In addition three patients were treated during this period whose only demonstrable lesions involved the bony skeleton, and one patient who, because of the hopelessness of her situation, was treated although she was less than five years postmenopausal.

Orally administered diethylstilbestrol* was the estrogenic compound employed in all cases, the dose routinely prescribed being 15 mg. per day. The majority of the patients tolerated this dosage well, but in seven cases the amount of drug was decreased, at least during a portion of the therapy, to 5 to 10 mg. per day because of the appearance of distressing side effects. The nature of these reactions will be discussed later.

In all but two** of the 22 cases with superficial soft tissue lesions, biopsy of at least one of the lesions followed

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* Since early 1948, Abbott Laboratories has supplied the diethylstilbestrol used in this study.

**Case No. 20 - a rapidly progressing "inflammatory" carcinoma involving much of the anterior chest wall.

Case No. 12 - a slowly growing, large ulcerating recurrent lesion at the site of a previous mastectomy (histological diagnosis of cancer at the time of operation).

was obtained establishing the diagnosis of carcinoma. Metastatic disease involving the lungs and bony skeleton was diagnosed from roentgenographic evidence: all films were interpreted in the Department of Radiology of this hospital.* All cases included exhibited either visually or roentgenographically observable lesions, and in no instance was subjective improvement of the patient a sufficient criterion in itself to judge a response as being favorable. In only one case (No. 10) was x-ray therapy, or any other specific treatment, carried out during the initial phase of estrogen therapy, i.e., before the effect of the drug could be evaluated. In several cases x-ray therapy had been given to some portion of the body within six months prior to the institution of hormone therapy. In all these cases at least two months was allowed to elapse before the estrogen was administered, and in all, with two possible exceptions (Nos. 3 and 24), the lesions considered in this study were observed to have progressed during the period just prior to the beginning of therapy.

During the time interval included in this study, stilbestrol was prescribed for 36 patients fulfilling the above outlined requirements. Five did not return to the Clinic for follow-up examinations, and attempts to obtain information concerning these has been, in general, unsuccessful. Information was obtained in two instances, however; one refused to continue therapy because of initial nausea (total dose 30 mg.), the other continued therapy under the supervision of another physician who reports complete regression of multiple lung lesions as evidenced by follow-up roentgen examination. It seems justified, therefore, to include in this report only the 31 cases followed in our Clinic.

Results

In considering the response of the patient to estrogen therapy only objective improvement will be considered. In general two types of favorable responses occurred: a definitely measurable diminution in the size of the lesions which then remained stationary for an appreciable period of time or a clinically complete disappearance of the lesions. It must be stressed that by "complete regression" we are referring to the complete disappearance of lesions macroscopically, for in at least one case microscopic examination of biopsy material removed after such a regression revealed recognizable tumor cells. Lesions that remained stationary in size without an initial period of regression or lesions that decreased in size for only two to four weeks after which time they again grew progressively were considered, for the purpose of this report, as not having shown a favorable response.

The lesions were considered to have reactivated when definite enlargement of partially regressed lesions or the reappearance of completely regressed ones first became evident. In addition, the time of reactivation in one case (No. 17) was dated at the reappearance of respiratory distress even though x-ray evidence of progression of the lung pathology was not demonstrable. It should be pointed out, in this connection, that in the several cases in which reactivation has occurred one to four months elapsed following the appearance of the first definite signs of this process before the lesions in question or the recurring symptomatology regained their pre-treatment proportions.

A brief resume' of all the cases is presented in Table I, and in Table II, the response of the various lesions has been tabulated according to their location. Of the 31 patients, seven had demonstrable lesions in tissues included under two of the headings in Table II, while one case presented lesions in three, In 17 of the patients definite or complete regression of lesions was observed; as a matter of convenience, these have been listed in the first portion of Table I without regard to the chronological order in which therapy was instituted.

*The authors particularly wish to thank Dr. Leo Rigler who personally reviewed many of the x-ray films.

TABLE I - RESUMÉ OF 31 CASES TREATED WITH DIETHYLSTILBESTROL

No.	Age	Post-meno. (yrs.)	Status at onset of Estrogen Therapy (b.t. = beginning of treatment)	Duration of Therapy	Followed since b.t.	Course
1	66	17	Rad. mast. (lt.) 27 m. before b.t. Supraclav. metas. 6 m. before b.t. treated with x-ray therapy. Lung metas. with progressive pleural effusion.	9 m.	13 m.	Lung metas. dec. rapidly in size. Absent by x-ray 6 m. after b.t. Pleural effusion almost completely resorbed. No reactivation after 13 m.
2	61	9	Rad. mast. (lt.) 27 m. before b.t. then p.o. x-ray therapy. Lt. supraclav. metas. 12 m. before b.t. Treated with x-ray therapy. Multiple skin recurrences on chest wall.	11 m.	14 m.	Complete clinical regression 3 m. after b.t. Medication disc. 7 m. after b.t. Reactivation of skin nodules after 2.5 m. Therapy resumed with regression complete in 3m. No reactivation on continued treatment.
3	69	17	Rad. mast. (rt.) 17 m. before b.t. then p.o. x-ray therapy. Metas. to cerv. vert. 5, 6 and 7, 2 m. before b.t. with x-ray treatment, followed by progression of lesions and symptoms (relieved only by morphine).	12 m.	19.5m. (exp.)	Dramatic pain relief within 1 m. X-rays showed improvement for 6 m. Reactivation (x-ray evidence 11 m., symptomatic 12 m.) after b.t. with deterioration.
4	50	7 (X-ray cast.)	Rad. mast. (lt.) 7 yrs. before b.t. then p.o. x-ray therapy and x-ray castration. Metas. to skin of chest; rt. femur, pelvis, lumbar vert., 6 m. before b.t., given x-ray therapy. Multiple new recurrences in skin of chest and scalp. Metas. to lung with pleural effusion 2 m. b.t.	1. 11 m.	11 m. (exp.)	Complete regression of skin lesions on chest. Dec. in size of scalp lesions. Marked relief of resp. symptoms. X-ray improvement of lung lesions. Therapy changed to Estinyl* 3mg. daily 7.5 m. after b.t. Reactivation of lung and scalp in 1 m. Stilbestrol restarted, deterioration continued.
5	60	9	Rad. mast. (lt.) with p.o. x-ray therapy 8 yrs. before b.t. Local recurrence treated by excision and x-ray therapy 6 yrs. before, another by excision 6 m. before b.t. New nodule on chest wall, nodular pleural metas. with effusion.	19 m.	19 m.	Dec. in pleural effusion. Pleural nodules disappeared. Local recurrence unchanged for 10 m. of therapy, then excised. No reactivation of pulmonary lesions.

1. Dose = Stilb. 15 mg 1.5 m.; 10 mgm. 5 m.; Estinyl 2 mgm daily for 2 m.; then stilb. 10 mgm for 3.5 m.

* Supplied by Schering Corp.

No.	Age	Post-meno. (yrs.)	Status at onset of Estrogen Therapy (b.t. = beginning of treatment)	Duration of Therapy	Followed since b.t.	Course
6	54	13	Rad. mast. (lt.) 2 yrs. before. Skin recurrences with lt. axillary nodes treated by x-ray with response 11 m. before b.t. Rt. axillary and supraclav. node metas. treated by x-ray with partial response 7 m. before b.t. New subcut. recurrences, entire upper one half of trunk, metas. to ribs and lumbar vert. Progression of lt. axillary nodes.	5 m.	6 m. (exp.)	Complete clinical regression of all subcutaneous nodules after 5 m. One axillary node remained. Bone metas. not improved. Then x-ray therapy given to bone metas. without improvement.
7	63	15	Massive primary carc. rt. breast (15 x 8.5 cm.) fixed to chest wall. Ulc. rt. axillary nodes. Metas. to thoraco-lumb. spine and sacrum.	22 m.	22 m.	Gradual regression of all soft tissue lesions to $\frac{1}{2}$ original size for 11 m. Axillary ulc. healed. X-ray evidence of marked progressive bone regeneration in spine and sacrum f r 6 m. Complete relief of symptoms. No reactivation of primary or metas. lesions at 22 m.
8	57	8	Rad. mast. (rt.) with p.o. x-ray therapy 9 yrs. before. Axillary recurrence treated by x-ray 4 m. before b.t. Multiple bilateral metastases to lungs.	11 m.	12 m.	Slow regression of lung metas. complete by 7 m. Reactivation of lesions by 11 m.
9	73	?	Inop. carc. lt. breast treated with x-ray and radon 10 m. before. Rt. axillary and supraclav. nodes Diffuse induration lt. breast with skin metas.	2. 9 m. (Irreg.)	11 m.	Complete regression supraclav. and axillary nodes in 3 m. Induration of breast softened. No change in skin nodules. 6 wks. after disc. stilb. all lesions reactivated and new nodules occurred. Given 5 mg. daily for 2 ms. with no change. Then progression of all lesions despite inc. to 15 mg. daily.

2. Dose = 15 mg daily for 3 m.; 5 mg. daily for 3.5 m. and 15 mg. for 2.5 m.

No.	Age	Post-meno. (yrs.)	Status at onset of Estrogen Therapy (b.t. = beginning of treatment)	Duration of Therapy	Followed since b.t.	Course
10	61	8	Huge untreated primary carc. lt. breast, multiple skin lesions, large axillary and supraclav.nodes. Metas. to lumbo-sac. spine, pelvis and femurs.	8 m.	11 m.	Entire primary area softened. Axillary and supraclav. nodes dec. to $\frac{1}{2}$ size. Bone metas. treated with x-ray. Reactivation of nodes 6 ms. after b.t.
11	60	12	Untreated primary carc. of entire lt. breast with many satellite skin nodules.	9 m.	9 m.	Dramatic regression of primary lesion within 4 m. of treatment. A few small skin nodules remain. No reactivation after 9 m. of treatment.
12	55	8 (Surgical)	Rad. mast. (lt.) with p.o. x-ray therapy 8.5 yrs. before. Large 10 x 7 cm. ulc. local recurrence 14 m. before b.t., progressive.	3. 19 m.	32 m.	Gradual regression, complete after 18 m. of treatment. No reactivation 32m. after b.t.
13	77	30-35 (Surgical)	Rad. mast. (rt.) with p.o. x-ray therapy 5 yrs. before. Small chest wall recurrence excised 2 m. before b.t. Exploratory laparotomy revealed extensive metas. to omentum, mesentery and mesocolon 2 m. before b.t.	6 m.	6 m.	Gradual regression of abdominal mass. Re-exploration 5 m. after b.t. revealed no gross intra-abdominal metas. Four biopsies from previous sites of metas. negative for cancer.
14	62	14	Inoperable carc. (rt.) breast treated by x-ray 10 m. before. Reactivation of primary lesion, satellite nodule and several axillary nodes.	9 m.	15 m.	Complete clinical regression of all lesions for 5 m. Reactivation at 6 m. with gradual progression. New metas. to bone since reactivation.
15	55	9	Rad. mast. (rt.) 3.5 years before. Local recurrences 2 yrs. before b.t. treated by excision and x-ray. Multiple fresh nodules of chest wall with diffuse induration. Axillary metas.	13 m.	13 m.	Complete clinical regression of skin lesions within 1 m. Partial regression of acillary nodes. Reactivation 11 m. after b.t. Slow progression.

3. Stilb. dose = 15 mgm. daily for 2.3 m., 10 mgm. daily for 16.5 m. followed by Estinyl 3 mgm. daily.

No.	Age	Post-meno. (yrs.)	Status at onset of Estrogen Therapy (b.t. = beginning of treatment)	Duration of Therapy	Followed since b.t.	Course
16	61	13 (surgical)	Local excision (rt.) with p.o. x-ray therapy 13 yrs. before. Supraclav. and axillary metas. treated with radon 5, 3, and 1 yrs. before b.t. Many new subcu. metas. upper trunk. Metas. to lung, pleura and retina.	9 m.	9 m.	Complete clinical regression of subcut. lesions within 4 m. Marked improvement of resp. symptoms, retinal, and pulmonary lesions. Reactivation of some skin nodules 6 m. after b.t. Pulmonary metas. static.
17	60	?	Rad. mast. (lt.) 6 m. before. Lung metas. with dyspnea and cough.	11 m.	11 m.	Marked relief of resp. symptoms. Partial regression of lung metas. Reappearance of symptoms 10 m. after b.t.
18	61	11	Rad. mast. (lt.) 23 m. before. Local recurrence, metas. to spine and sacrum treated by x-ray 5 m. before. Lesions progressive.	2 m.	4 m. (exp.)	Progression of lesions.
19	59	12	Rad. mast. (rt.) with p.o. x-ray therapy 6 m. before. Lung metas.	9 m.	12 m. (exp.)	Progression of lesions.
20	78	28	Inflammatory carc. rt. breast axillary metas. X-ray therapy 3 m. before b.t. without response.	5 m. (irreg.)	7 m.	Primary became brownish purple and softened for 3 wks. while spread to opposite breast occurred. Then progression of all lesions.
21	59	5	Rad. mast. (lt.) with p.o. x-ray therapy 1 yr. before b.t. Then metas. to lungs.	4. 9 m.	15 m.	Gradual progression of lung metas. Supraclav. metas. during therapy.
22	63	8	Large ulc. primary carc. lt. breast. (Entire ant. lt. chest wall) Lung metas., pleural effusion.	1.5 m.	2.5 m. (exp.)	Softening and slight healing of ulc. margins for 3 wks. Then progression. Lung metas. unchanged. Severe nausea 4 wks. after b.t.
23	83	27	Rad. mast. (rt.) 27 m. before b.t. Two subcu. nodules on chest.	1.5 m.	6 m.	Initial change in color of lesions to reddish purple. Then inc. in size and a new nodule occurred. Given x-ray therapy 6 wks. after b.t.
24	65	?	Bilat. rad. mast. with p.o. x-ray therapy 5 yrs. before. Recurrence to sternum treated by x-ray 19 m. before b.t. Partial regression.	5. 5 m.	8 m. (exp.)	No change for 5 m. Surgical excision including sternum 8 m. after b.t.

4. Dose = 15 mgm. daily for 4 m. Disc. 2.5 m. Then 15 mgm. daily for 5 m.
5. Dose = 15 mgm. daily for 1 m. Disc. 1 m. Then 15 mgm. 4 m.

No.	Age	Post-meno. (yrs.)	Status at onset of Estrogen Therapy (b.t. = beginning of treatment)	Duration of Therapy	Followed since b.t.	Course
25	74	?	Large ulc. primary carc. of rt. breast with satellite skin metas.	2.3 m.	3.5 m. (exp. p.o.)	Decrease in size of primary for 2 wks. Satellite skin lesions completely regressed. Reactivation of primary treated by simple mast. (palliative).
26	55	7	Large ulc. primary carc. lt. breast, satellite skin nodules, bilat. axillary nodes, lt. supraclav. node.	2.3 m.	4 m.	Dec. in size of primary for 2 wks., then progression of all lesions and new skin lesions appeared.
27	58	7 (surgical)	Simple mast. (lt.) with p.o. x-ray therapy 2 yrs. before b.t. Numerous recurrent skin nodules (1-3 cm.dia.) 3 m. before b.t.	1.5 m.	3 m. (exp.)	Color of lesions changed to reddish purple and some softening occurred. Progression of size and new lesions appeared.
28	53	2-3	Rad. mast. (lt.) 29 m. before b.t. Chest wall recurrence 6 m. before b.t. Lung and pleural metas. (Diabetic)	1.5 m.	1.5 m.	Rapid progression of all lesions and development of several new lesions. (Rapid course possibly due to estrogens.
29	61	15	Rad. mast. (rt.) (pre-op. x-ray therapy) 1.5 m. before b.t. Multiple lung metas. rapidly progressive.	3 wks.	3 wks. (exp.)	Continued rapid inc. in size of lung metas.
30	61	6	Rad. mast. (lt.) and p.o. x-ray therapy 6 yrs. before. Now metas. to skull, cervical spine. Seventh nerve paralysis (peripheral)	2.3 m.	5 m. (exp.)	No improvement. Metas. to pelvis and femurs during treatment.
31	60	16	Excision of large primary carc. of rt. breast and chest wall 4 m. before b.t. Excision of lt. axillary metas. 1 m. before b.t. Metas. to rt. humerus.	6. 15 m.	32 m.	Progression of lesions for 5 m. X-ray therapy to humerus without response for 6 m. Stilb. restarted and 2nd course of x-ray given. Then good bone regeneration in humerus.

6. 2 courses of therapy - 5 m. and 10 m. each.

Table II.

A TABULATION OF THE RESPONSE OF LESIONS ACCORDING TO THEIR LOCATION.
(Regression of lesions occurred in 17 of the 31 patients treated)

Location of Lesions	Instances of Definite Regression	Instances of no Appreciable Regression	Total Number
Skin, subcutaneous tissue and superficial lymph nodes	11	10	21
Lung and Pleura	6	5	11
Bone	2	4	6
Mesentery	1	0	1
Retina	1	0	1

It seems noteworthy in view of the original British reports and the general experience with testosterone therapy that in none of our cases did any of the lesions involving soft tissues regress while other soft tissue lesions progressed. In two cases, however, lesions involving the pleura (No. 5) and lymph nodes (No. 9) regressed either completely or nearly so while relatively small skin nodules remained stationary in size. In several cases complete regression of some of the lesions involving soft tissues was accompanied by only partial regression of others. The most notable example of this latter phenomenon occurred in case No. 4 where a large number of subcutaneous lesions on the upper trunk disappeared completely while the many nodules in the scalp decreased considerably in size and then remained static. Where bony and soft tissue lesions occur in the same individual, the situation is, in all probability, considerably different. In two such cases presented here, as well as in two others more recently placed on estrogenic therapy, the soft tissue lesions have regressed while those involving bony structures have progressed.

The initial response of lesions closely adherent to the skin most frequently are seen to follow a definite pattern, as described in the British reports[6,9]. Usually within two to three weeks after the initiation of treatment a definite color change, from a reddish to a purplish hue, is noted, often accompanied by a softening and flattening of the lesion. This response occurs in lesions that do not eventually regress as well as in those that do, suggesting that some alteration of the tumor occurs in a considerably higher per cent of cases than evidence actual tumor regression. Following this initial response, which may be accompanied by a measurable decrease in the size of the mass, the lesions in some patients again begin their progressive growth while in others regression proceeds, at times accompanied by a further darkening of the color of the lesion until it has a brown appearance.

The rate at which the tumor masses decrease in size varies greatly from patient to patient. In one case (no. 12) gradual diminution in size of a large lesion finally resulted in complete regression after approximately a year, while in other instances lesions several centimeters in diameter have become clinically undetectable within a few weeks.

Again, somewhat in variance with previous reports, in this group of cases, metastatic breast cancer in the superficial lymph nodes seemed to respond well to therapy. Eight of our patients had large, clinically involved nodes in one or both axillae and/or in the supraclavicular areas, and in six of these the nodes decreased measurably in size or became no longer palpable. Because of the difficulty in distinguishing in all cases, whether a metastatic nodule in the anterior axillary fold or low in the axilla is actually in a lymph node or is in the subcutaneous connective tissue, all lesions involving the superficial tissues of the body have been grouped together. Included in this group are six instances of primary lesions which had received no previous therapy: two of these showed remarkable regression, one definite but much less spectacular improvement while three showed only very short-lived or no demonstrable improvement.

Of some special interest are the two cases in which osteoclastic bone metastases apparently regressed with the filling in of the bony defects in response to estrogen therapy since such responses have rarely been encountered by others. In Case No. 7 the patient presented herself at the Clinic with a large untreated primary lesion involving the right breast, chest wall and axilla, and complained of persistent and increasing low back pain with radiation of the pain into her lower extremities. Roentgen examination revealed marked destruction in the lower lumbar vertebrae and sacrum and several areas of destruction in thoracic vertebrae. Within one month after the beginning of therapy the pain improved and x-ray examination revealed

evidence of considerable bone repair during the first six months of therapy after which time the situation has remained static. The patient has now received 22 months of continuous therapy with no return of symptoms or signs of reactivation of her partially regressed primary lesion.

The second case (No. 3) is less clear-cut, being complicated by deep roentgen therapy two months prior to the institution of hormone therapy. She received some temporary pain relief from the irradiation, but at the time hormone therapy was begun, her pain had returned to pre x-ray therapy proportions (she required morphine analgesia) and roentgen examination revealed minimal evidence of bone regeneration in some areas with other areas suggesting progression of the destructive process. In less than one month after beginning stilbestrol treatment, the pain was greatly improved and the patient no longer required opiates. Two and a half months later the pain had almost completely disappeared and considerable bony repair was evident on x-ray examination. This objective improvement continued for six months, at which time x-ray films showed extensive bone repair and calcification in the soft tissues about one vertebral body. Eleven months after the institution of hormone therapy, roentgenograms showed considerable decalcification of the vertebrae as well as of the soft tissue area previously calcified, and a month later the patient's symptoms returned. Although there are several aspects of this patient's response during the time she was taking stilbestrol which make it unlikely that the previous x-ray therapy could have been the sole agent responsible for the improvement noted, it is certain that no categorical statements can be made as to the role each type of treatment played.

It would appear from these two cases, as well as observed transitory increases in the serum alkaline phosphatase levels during the administration of stilbestrol in one of the other "non-responsive" patients with bony lesions, that occasionally metastatic lesions in the bony skeleton may be affected by estrogenic hormones. The experience of others[3] would seem to indicate, however, that such responses occur very infrequently.

Since the age of the patient is such an important factor in determining her response to this type of hormonal therapy and the British workers used 60 years of age as the dividing line for the presentation of their cases, it seems of considerable importance to analyze the cases in this series which were younger. Ten persons between the ages of 50 and 59 years were treated, nine of whom were five or more years past their menopause. In none of the latter group was there a suggestive increase in the rate of growth of the lesions following the administration of stilbestrol. On the other hand, five exhibited favorable responses, a response in one case (No. 12) that has been maintained for 32 months. In one person who was less than three years postmenopausal, the disease progressed at a very rapid rate following the administration of the drug and it seems very probable that the "therapy" resulted in an increase in the growth rate of the cancer in this patient. It may be of some interest also that in three of the cases menopause had been artificially induced, either by x-ray or surgery, and two of these patients showed favorable responses. From these relatively few cases it would appear, then, that the menstrual status of the patient may be a more important consideration than her chronological age, and that, as previously recommended[3] this type of therapy may be considered applicable to patients who are five or more years past the menopause.

Although the earlier reports might lead one to conclude that the duration of the favorable response to estrogen therapy is very short-lived, the shortest favorable response in this series was five months. In nine of the patients exhibiting a regression of lesions, reactivation first became evident, either objectively or subjectively, between five and eleven months after beginning therapy. One patient died of pyelo-

nephritis six months after beginning hormone therapy, at which time her soft tissue lesions remained completely regressed although lesions of the lumbar spine and ribs had progressed during the period of therapy. In five of the cases followed for more than one year, reactivation of the lesions has not occurred as yet, as is also the case for two patients now in their fifth and ninth months of therapy. In four of the five instances in which the satisfactory response has been of twelve months' duration or longer, the regression of the lesions has been macroscopically complete while in the other case the regression of the primary tumor has been only partial, with a period of approximately a year and a half during which the lesion has remained stationary in size. It is of further interest that in all the cases in which reactivation of the disease has occurred, such reactivation was noted first at the site of pre-existing lesions and most frequently a number of such areas reactivated at approximately the same time. In none of our cases, as far as we can determine, have new soft tissue lesions become manifest while the lesions that were present prior to the beginning of therapy remained in a regressed state. In none of the cases have the reactivated lesions progressed at a rate noticeably more rapid than that seen prior to the institution of therapy.

In general the side effects encountered in this group of patients have not been of great moment. During the first few days of therapy, nausea and general malaise of moderate severity were experienced by several individuals and minimal nausea during this period was common. However, in the great majority of instances, these symptoms disappeared within a week after beginning treatment. In three cases, however, sufficient nausea persisted to necessitate reducing the dose of stilbestrol to 5 or 10 mg. per day. Intermittent slight nausea has also been experienced by a few patients after having been on the drug for considerable periods of time. "Breakthrough" uterine bleeding has not been a problem of any magnitude. Several women noted occasional short episodes of slight "spotting," but in only one case has the bleeding been of sufficient magnitude to necessitate the discontinuation of the hormone for two week periods to allow withdrawal bleeding to occur.

The tendency of estrogenic hormones to cause the retention of fluid by the tissues is often manifested by weight gain and varying degrees of peripheral edema. This becomes of considerable practical importance in patients with impaired cardiac function in whom cardiac decompensation may be precipitated by the administration of large doses of estrogenic compounds. Two such cases were encountered in this series and in both instances the situation was rather adequately managed by the reduction of dietary N_aCl. The only other undesirable side effect of therapy noted has been the complaint of several patients of an increased inability to control urination. This has occurred most often in multiparous individuals who have manifested some degree of urinary urgency prior to estrogen therapy, but was encountered also in one nulliparous individual without prior symptoms of this nature. One wonders if the basis for this is not an alteration in the tone in the pelvic musculature.

Other side effects regularly noted are enlargement of the breasts and nipple accompanied by a progressive pigmentation of the areola. Patients generally mention a soreness of the breast and/or nipple during the first few weeks of treatment, but this discomfort subsides as therapy continues. As mentioned by Nathanson, pigmentation of the axillary skin is also frequently observed. In one of our cases a tendency for greying hair to return to its previous brown coloration also occurred. Particularly in patients who have shown favorable responses to therapy, a "rejuvenation" of the skin and subcutaneous tissues with an improvement in skin turgor may be very noticeable as is a subjective improvement of the patient's general physical status.

Discussion

Reviewing the cases treated to date in this Clinic one can hardly fail to be impressed with the protean nature of the responses to the administration of estrogen encountered from patient to patient and even within the same patient exhibiting lesions in different tissues. One could spend considerable time theorizing as to the mechanisms responsible for the various effects noted, the reasons for the peculiarities of response depending on the location of the lesions, etc. Since little or no laboratory data collected from patients receiving this type of treatment is available at present to substantiate or refute such speculations, it would seem best to postpone any discussion of this nature.

It would appear profitable, however, to attempt a very preliminary ascertainment of the place such treatment may have in the management of breast cancer. Our data emphasizes the fact that this type of therapy must be reserved for patients with inoperable primary or recurrent disease. It is, further, of great importance to consider the "menstrual age" of the patient. In previous reports 60 years of age has been used most frequently as the division point, at least in the presentation of cases, with a smaller percentage of favorable responses and almost all of the instances of growth acceleration occurring in patients below this age. It would appear, however, that younger women can be treated with relative safety and with a good percentage of favorable responses if they are five or more years beyond the menopause.

There would seem to be little doubt that some of the patients in this series received considerable palliation as a result of therapy. Most notable among these are the individuals who possessed metastatic lesions involving the lung parenchyma and/or nodular lesions of the pleura. Four of the six cases with these types of lesions that responded to treatment were experiencing moderate to severe respiratory symptoms prior to the institution of therapy. In three of these the symptoms cleared completely during the period of demonstrable response (one has not reactivated after 13 months) and the other showed considerable improvement in this respect. Since x-ray therapy of these lesions is most often not feasible, estrogen administration would seem to have a definite place in the palliative care of such patients.

Where the disease involves the soft tissues near the surface of the body, the use of the estrogenic hormones would appear to be a definite addition to our therapeutic armamentarium. Its most obvious use is in patients whose recurrences are located in areas previously treated with radiation in which skin atrophy precludes further roentgen therapy and in cases where the involvement is so widespread that the application of adequate doses of irradiation to all the areas of involvement is difficult. Patients falling in this latter group should, however, be followed very closely so that if the disease continues to progress in the face of hormonal treatment, radiation therapy can be instituted.

It is evident that there are many features of the mechanics of estrogenic therapy in advanced breast cancer that still remain to be worked out. There is as yet little or no data available as to the effects of different dosage levels upon the response obtained: 5 to 15 mg. per day has been used most frequently where diethylstilbestrol was the estrogenic compound employed. Another point concerning which there is no available information is the schedule of treatment, i.e., continuous versus interrupted therapy. In all of our cases except four, the hormone has been continued until it was fairly certainly established that the patient was not going to react favorably or until reactivation of the lesions occurred. In two of the cases in which therapy was discontinued, reactivation of the lesions followed in a relatively short time (in one of these re-administration of the drug resulted in a second regression of the lesions) while in the

other two no reactivation has become evident after four and eleven months.

Because of the necessarily restricted application of this type of therapy, the irregularity of response and the relatively short duration of many of the favorable responses, it is evident that at present the contribution of estrogen therapy to any overall improvement of the results of the treatment of breast cancer is indeed small. However, it would seem that in properly selected cases, estrogen therapy can be a useful addition to our armamentarium for the palliative treatment of advanced breast cancer. It is only to be hoped that future research in this field may lead to improvement in the results obtained as well as to a better understanding of the pathological physiology of this disease entity.

Summary

1. 31 cases of advanced carcinoma of the female breast treated with diethylstilbestrol since March 1946 have been reviewed.

2. In 17 patients definite regression of lesions was noted.

3. The influence of the "menstrual age" of the patient and the location of the lesions upon the frequency of occurrence of favorable responses was discussed.

4. The duration of favorable responses has varied from 5 to 32 months.

5. The data presented would seem to indicate that in selected cases estrogen therapy can be a useful addition in the palliative treatment of advanced breast cancer.

III. A NOTE CONCERNING THE SELECTION OF THERAPY FOR CASES OF ADVANCED BREAST CARCINOMA INVOLVING THE BONY SKELETON

Robert A. Huseby

Several of the salient articles dealing with the beneficial effects obtained from the administration of testosterone propionate in cases of advanced breast cancer are referred to in the preceding paper. These reports have concerned themselves mainly with the establishment of the fact that administration of this hormone is followed, at times, by a remarkable regression of the metastatic lesions. Since the hormone has been coming into more frequent general use of late it seems worthwhile to attempt a preliminary evaluation of the role that testosterone may best play in the overall treatment of advanced breast cancer. This is made difficult by the newness of the therapy and the lack of published data collected from a large series of cases followed for a considerable period of time. The ideas to be formulated here have evolved from conversations with several investigators who have had considerable experience with the use of this drug as well as from our own as yet rather limited experience.

As published reports would indicate, testosterone seems to be most effective in cases with bony metastases, less so in cases with involvement of the lung and pleura, and least effective against primary lesions or metastases to soft tissues. For this reason the main part of this note will deal with the attempt to formulate indications for its use where the bony parts are involved.

At present it is impossible to give a meaningful figure as to the per cent of cases that respond favorably to the drug since criteria for improvement are somewhat difficult to set up. A high percentage of patients will receive temporary (lasting from a few weeks to a few months) relief from bone pain, which in some cases may be of very significant proportions. This occurs not infrequently,

however, in patients in whom the lesions are seen roentgenologically either not to improve or to actually progress during the period of pain relief. The proportion of patients showing x-ray evidence of bone regeneration and filling in of the lesions appears to be not more than about 20 per cent. Furthermore, in a considerable number of these, some of the lesions will be seen to calcify while others show no such tendency. It should be stressed also that the time required for demonstrable calcium deposition varies considerably but generally ranges from one to three months.

Taking these points into consideration, it seems justifiable to suggest tentatively the following guides to the therapy of metastatic breast cancer involving bony parts. Since irradiation appears to give more uniformly good results where adequate treatment can be delivered to the involved areas, x-ray therapy would seem to be the treatment of choice wherever the demonstrable involvement is fairly well localized to a few treatable areas. It would seem best to reserve testosterone therapy for those cases in which the involvement is rather widespread or in which the lesions are radioresistant or in which no further irradiation to the area can be tolerated. Because bone repair during testosterone therapy may be slow in occurring and, indeed, does not occur in all areas of involvement in the majority of cases, it would seem best to treat involved bones that bear considerable weight (particularly the lower thoracic and lumbar spine, the acetabulae, and the heads of the femora) with irradiation. This seems all the more important since patients in whom no bony repair becomes demonstrable roentgenologically generally experience at least temporary relief of pain thus increasing the probability of vertebral collapse and pathological fracture as a result of increased physical activity on the part of the patient. This has been emphasized to us by one patient who, after three months of therapy and apparently without significant trauma to the spine experienced a collapse of a lumbar vertebra resulting in an almost complete paraplegia. During the course of treatment, she received good relief of pain and had completely calcified several involved areas in the skull without roentgenologically demonstrable improvement of any significance in the lumbar spine.

The question of a reasonable period of treatment which may be considered as an adequate therapeutic trial is also difficult to answer at present. This much can be said. The Subcommittee on Steroids and Cancer of the Therapeutic Trials Committee of the A.M.A. recommends a minimum of three months of therapy as a trial unless serious side reactions occur. Very few lesions that have not shown x-ray evidence of improvement after three months of treatment, will show such a response with continued therapy even though pain relief sometimes persists in such cases for longer periods. Since one side effect of therapy which occurs frequently and is at times most troublesome, namely an increase in feminine libido, appears to increase with increasing length of therapy, it seems unwise to continue treatment much beyond three to four months in patients that continue to show progression of the lesions except, perhaps, where remarkable symptomatic relief continues.

The only dangerous side effect that has been recorded in the literature is the infrequent occurrence of significant hypercalcemia manifested clinically by nausea, vomiting and varying degrees of prostration. The serum calcium level should, therefore, be checked before beginning therapy and again at intervals during the first month or so of treatment, particularly in those patients exhibiting an elevated pretherapy level. Other side effects, as signs of masculinization and an increase in libido, occur regularly and may become bothersome particularly in patients who are treated over long periods of time. In this connection it seems well to recall that in women who are still menstruating regularly the discontinuance of ovarian function, either by means of surgery or irradiation, will improve the bony metas-

tases of breast cancer in approximately as high a per cent of cases as does testosterone therapy. The side effects from this latter procedure would appear, also, to be generally less severe and somewhat more readily controlled.

Based on our present information the following outline for the choice of therapies in cases of advanced breast cancer involving the bony skeleton therefore, seems justified:

X-ray: a) cases in which the demonstrable involvement is localized to a few treatable areas.
b) lesions involving major weight bearing areas.

Testosterone:
a) cases in which the skeleton is widely involved.
b) cases in which the lesions have not responded satisfactorily to x-ray therapy.

Oophorectomy:
younger women who are menstruating regularly (as with testosterone, x-ray therapy should be given to major weight bearing bones if they are involved).

It is hoped that the above notes may be of assistance to those who have patients with advanced breast cancer in whom hormone therapy may afford significant palliation.

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IV. MEDICAL SCHOOL NEWS

Coming Events

Jan. 27 - J. B. Johnston Lecture in Neurology - Dr. Paul C. Bucy - Illinois Neuropsychiatric Institute - "The Cerebral Control of Muscular Activity" - 8:00 p.m. - Museum of Natural History Auditorium.

Jan. 31 - Minnesota Mental Hygiene Society - Dr. Benjamin Spock, Mayo Foundation - "A Pediatrician Looks at Mental Health" - 8:00 p.m. - Museum of Natural History Auditorium.

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Medical School Grading System Study

Alumni and other friends of the Medical School will be interested to learn that the system of grading now in use at the Medical School was under scrutiny by the Curriculum Revision Committee which turned in its report in the spring of 1948. The committee recommended that final grades given at the end of the quarter be recorded simply as pass or fail. At present, such grades are expressed in the commonly used letters, "A" to "F".

The committee further recommended that class rank be established by the results of a separate "honors" examination given at the end of the sophomore year. Final class rank for the full four years of Medical School will be determined by a second "honors" examination given at the end of the senior year. Both of these examinations would be of comprehensive nature.

This matter may soon be taken before the University Senate to receive that body's opinion and recommendation. Dr. Richard L. Varco, chairman of the committee which will bring the matter before the Senate, is at present polling faculty opinion on this vital question. He would welcome comments of any interested alumni.

Ophthalmology Course

Physicians working in ophthalmology will come from all of the states in the midwest to attend a continuation course in Ophthalmology to be given at the Center for Continuation Study on January 24-28. The course is being given under the direction of Dr. Erling W. Hansen, Professor and Director of the Division of Ophthalmology at the University of Minnesota Medical School.

Distinguished visiting ophthalmologists who will participate in the course as faculty members include Dr. James H. Allen, University of Iowa; Dr. William L. Benedict, Mayo Foundation; Dr. William F. Hughes, University of Illinois; and Dr. A. B. Reese, Columbia University. J. C. Copeland, Director of the Scientific Instrument Department of Riggs Optical Company, Chicago, will also participate.

Clinical and full-time members of the Division of Ophthalmology and other departments of the University complete the faculty which will present the course.

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New Minnesota Medical Foundation Members

Dr. G. T. Nordin, 914 S. 8th St., Minneapolis
Dr. Alfred T. Kapsner, Princeton Clinic, Princeton
Dr. A. D. Mattson, St. James
Dr. Wm. H. Ylitalo, 2413 - 4th Ave. E., Hibbing
Drs. Lowe & Lowe, 158 N. Concord St., So. St. Paul
Dr. Ralph B. Kettlewell, Sauk Centre
Dr. Peter S. Rudie, 1010 Medical Arts Bldg., Duluth
Dr. B. A. Flesche, Lake City
Dr. Otto B. Fesenmaier, New Ulm
Dr. A. A. Meyer, Melrose
Dr. Xarl R. Butturff, 5605 Pleasant Ave. S., Minneapolis