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Metabolic Aspects Of Advanced Cancer

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INDEX

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I. METABOLIC ASPECTS OF ADVANCED CANCER*

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(From the Cancer Metabolic Research Laboratory, Department of Medicine, and the Tumor Clinic of the University Hospitals).

Important advances in the management of cancer have occurred in the fields of diagnosis, surgery, radiation, and chemotherapy. Despite the notable efforts in diagnosis, surgery, and radiation, a large group of patients exists in which these procedures have not proved adequate. Profound improvements noted in some cancers following alterations in the hormonal status or following the introduction of chemotherapeutic agents make it imperative that these be considered a further agent in the therapeutic armamentarium against specified advanced cancers.

The increasing number of patients with advanced cancer is a source of investigational material for those interested in the problem of tumor growth. One approach towards the investigation of this problem is the metabolic study. Such investigations are a means of studying the pattern of tumor growth as well as the response of the host to the presence of the tumor. Through metabolic studies new forms of therapy may be initiated and evaluated.

During the past year we have established a Metabolic Research Laboratory for the purpose of investigating patients with advanced cancer. Briefly, a metabolic investigation consists of rigid control of the hospitalized patient, the administration of a constant controlled diet, and the determination of chemical constituents of the blood, urine, and feces. The present presentation is a demonstration of alterations in the metabolic status of patients with advanced breast cancer during hormone administration or deprivation.

Though surgery and radiation remain the principal therapeutic methods for permanent control of breast cancer, hormone therapy can be employed as an effective therapeutic and palliative agent. Objective regressions of tumor masses have been repeatedly observed during administration or deprivation of hormones. These improvements consist in epithelization of ulcers and a decrease in size or disappearance of primary tumor masses, cutaneous nodules, involved lymph nodes, and pulmonary metastases. Osseous lesions are noted to calcify. At present, four methods of hormonal alteration are available: castration, androgenic hormones, estrogenic hormones, and bilateral adrenalectomy. The regression of advanced breast cancer following such hormonal therapy has been well established[1].

Interpretation of Results:

In order to provide for easy understanding of the charts to be presented, the method of charting metabolic balance data is described. The method utilized was that adopted by Bassett and employed by Albright and Reifenstein[2] (Figure 1). This method includes in the same chart the balance, the intake, and the urinary and fecal excretions. The scale for intake and balance in grams per 24 hours is given as the ordinate. The scale in time is given as the abscissa. The data are plotted in amounts per 24 hours although the measurements are made on pools of excreta covering the metabolic period. This period usually consists of 3 days, though single day determinations are also employed when fecal determinations are not performed. The horizontal line at 0 of the ordinate is the base line to which intake and balance refer. The intake is plotted as an area from the baseline toward the bottom of the diagram. The excretion is plotted as an hatched area from the bottom of the intake toward the top of the diagram. The urinary excretions are charted above the fecal excretions. If the total excretion reaches

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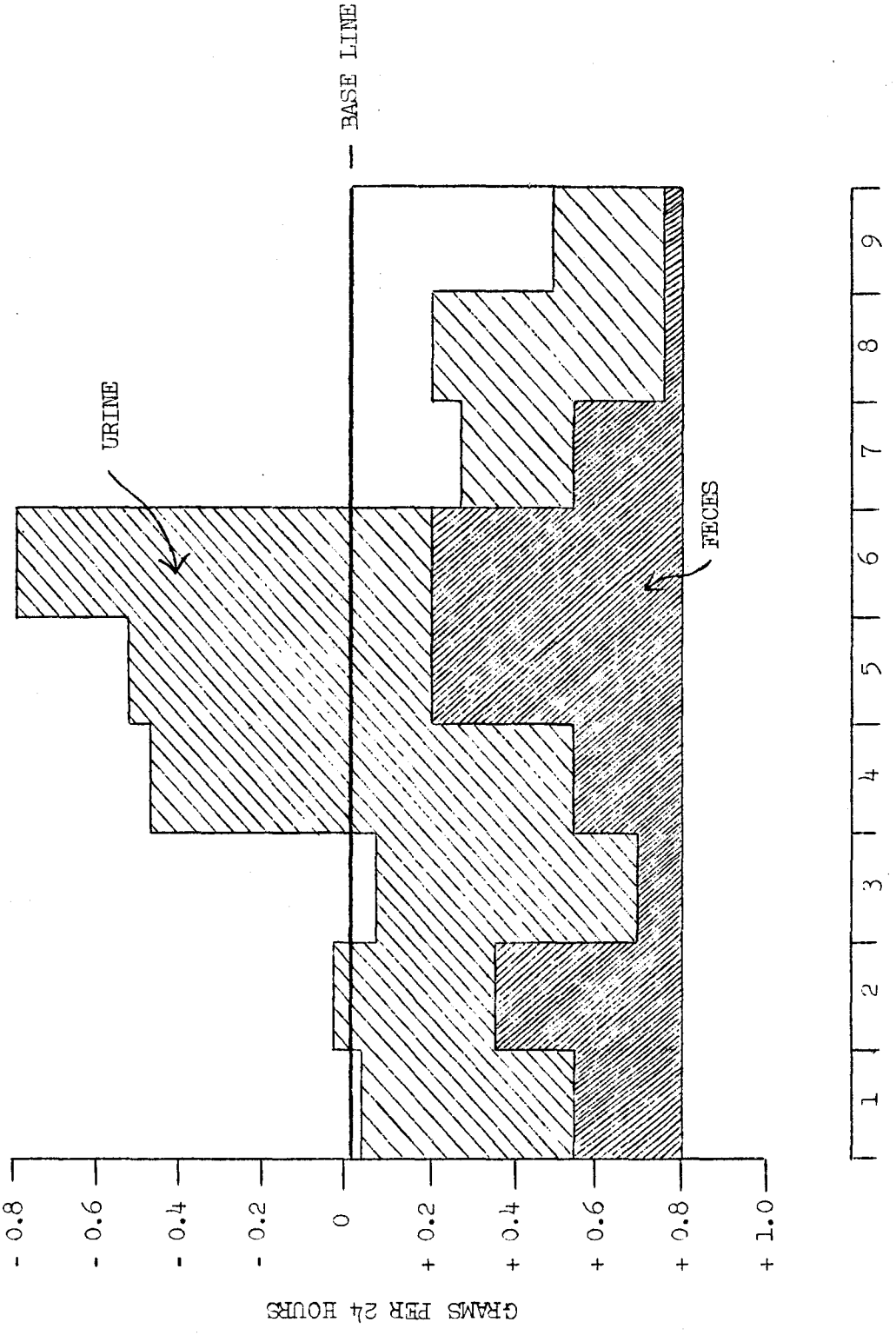
FIGURE 1


BASE LINE
URINE
FECES
- 0.8
- 0.6
- 0.4
- 0.2
0
+ 0.2
+ 0.4
+ 0.6
+ 0.8
+ 1.0
GRAMS PER 24 HOURS
1
2
3
4
5
6
7
8
9
THREE-DAY PERIODS

the base line, the balance is in equilibrium. If the total excretion exceeds the base line, a hatched area is left above the base line; this represents a negative balance. If the total excretion does not reach the base line, a white area is left between the excretion line and the base line; this represents a positive balance.

The advantage of this method of charting over the more conventional one where the intake and excretion are plotted from the same base line is that it allows one to focus on the most important feature of a balance study, namely the balance. Furthermore, if the intake is altered, which frequently occurs in patients with advanced cancer because of nausea, there is no resulting discontinuity in the balance.

Standardization and evaluation of variations of human disease have been achieved most successfully under the control conditions of a metabolic study. In disease involving the skeletal system studies of calcium, phosphorus, and nitrogen have been helpful in defining the nature of the disease process and in evaluating the effective therapy. Previous studies have demonstrated that immobilization of normal human subjects results in protein and mineral catabolism[3]. The negative mineral balance in osteoporosis has been investigated and the anabolic effects of androgen and estrogen demonstrated[4]. Therefore, it would be expected that similar studies of patients with skeletal metastases could also serve as a controlled experiment. This line of investigation has allowed us to evaluate the effect of palliative chemotherapeutic agents in the control of metastatic malignancies.

The mineral loss caused by osteolytic breast cancer metastases is characterized metabolically by high urinary excretion of calcium and phosphorus with negative mineral balances. The protein balance is not specific and even in advanced cases may be maintained in a state of nitrogen equilibrium. A similar mineral loss is seen in patients with osteolytic metastases secondary to other malignancies. Therefore, this metabolic process is not specific for breast carcinoma but is characteristic of skeletal destruction. The sequence of events in patients with excessive and prolonged mineral loss due to osteolytic metastases appears to be: excessive bone breakdown, mobilization of calcium and phosphorus, hypercalcuria and hyperphosphaturia, hypercalcemia, and eventually renal impairment[5]. These changes on a metabolic chart are demonstrated by a negative calcium balance and a negative phosphorus balance. Any method of therapy introduced which would divert this excessive loss or negative balance to that of the normal state is suggestive that this introduced agent is therapeutically effective. Such a metabolic study will gauge the effect of the therapeutic agent and study its modes of action.

The purpose of the present study is to demonstrate the effect of hormonal alteration on the metabolism of patients with osteolytic metastases secondary to breast carcinoma. If the therapeutic agent encourages the remineralization of osteolytic areas, the process would be evidenced by improvement in the mineral balances.

Metabolic Observations in Patients with Advanced Breast Cancer and Osteolytic Metastases

a. Calcium: The patient with advanced breast cancer and osteolytic metastases characteristically demonstrates an increased excretion of urinary calcium. In some patients, though not necessarily in all, an increase of fecal calcium is observed. These patients demonstrate a negative calcium balance. If the rate of bone destruction is sufficiently rapid, "spontaneous hypercalcemia" occurs. In many patients the serum calcium remains within normal limits, but may be increased if a high calcium diet is given. Persistence of an elevated serum calcium and hypercalcuria may result in deposition of calcium in renal tubules and an elevated blood urea nitrogen.

When improvement occurs following the introduction of therapy, a definite reduction in urinary and fecal calcium is

noted, negative calcium balance reverts to a positive one, and at a later date calcium equilibrium may be attained. In patients initially demonstrating "spontaneous hypercalcemia", the serum calcium reverts to a normal level[6].

b. Phosphorus: An elevation of urinary and fecal phosphorus manifests a negative phosphorus balance. The serum phosphorus is usually normal.

When improvement occurs as the result of hormonal therapy, the phosphorus balance reverts to a positive one; later attaining equilibrium. The serum phosphorus is observed to decrease to low values.

c. Nitrogen: Patients maintaining their weight will remain in nitrogen equilibrium. A negative nitrogen balance will be demonstrated only when weight loss occurs. Positive nitrogen balance is observed if an increase in weight occurs during improvement in the disease, or when anabolic agents are employed.

d. Serum alkaline phosphatase: The serum alkaline phosphatase is a measure of osteoblastic (reparative) activity of the bone. In patients with rapidly progressing tumors the serum alkaline phosphatase is normal. In slow growing metastases, the alkaline phosphatase may be elevated. This is interpreted as an attempted reparative process, and an area of sclerosis sometimes is demonstrated in X-rays.

During improvement of the disease osteoblastic activity increases, bone metastases calcify, and the serum alkaline phosphatase increases. A steadily increasing alkaline phosphatase signifies the presence of progressing liver metastases.

Effects of Therapy

1. Castration

Castration is beneficial primarily in premenopausal women in whom the metastatic breast cancer is beyond control by the usual methods. Profound regression of pulmonary, osseous, and cutaneous metastases may occur. These improvements are associated with relief from pain, weight gain, and rehabilitation.

A 25 year old woman with extensive osseous metastases from a breast cancer is presented. Initially, the patient demonstrated an increase in the urinary calcium with a marked negative calcium balance. Because of the rapid rate of bone destruction, spontaneous hypercalcemia and hypercalcuria were present. Associated with this was a negative phosphorus balance and an elevated serum phosphorus. Since the alkaline phosphatase was normal, it is presumed there was no increase in osteoblastic (reparative) activity. The overloading of calcium by addition of 6 glasses of milk a day accentuated the hypercalcemia during the fifth metabolic period. Patients with osteolytic metastases of breast cancer not demonstrating spontaneous hypercalcemia syndrome may do so when excessive amounts of calcium are administered. Following oophorectomy, improvement in the tumor was manifest by relief of pain and an increase in the density of osseous lesions on X-ray. An increase in the serum alkaline phosphatase activity was an indication of the attempt at osseous repair. Associated with the improvement and hence decreased rate of bone destruction was a decrease in serum calcium and phosphorus and decreased excretion of calcium and phosphorus. However, it appeared on X-ray examination that the rate of destruction exceeded that of repair since new lesions appeared while older lesions were undergoing repair. Furthermore, a positive balance for calcium and phosphorus was never attained. Six months after oophorectomy, the return to normal of the serum alkaline phosphatase was indicative of the decrease in osteoblastic activity. However, the presence of continued excessive bone destruction was indicated by the increase in serum phosphorus and greater phosphorus excretion.

Finally, 11 months after oophorectomy, it was obvious that the cancer was progressing at an uncontrolled rate. Hypercalcemia, hypercalcuria, hyperphos-

phatemia were present. Again, hypercalcemia was accentuated by increasing the intake of calcium. Administration of estrogenic hormone resulted in a decrease of serum calcium and phosphorus and urinary phosphorus. The progressive increase of serum alkaline phosphatase was due to liver metastases.

2. Estrogenic Hormones

Estrogenic hormones exert a favorable effect on almost all manifestations of advanced breast cancer in the post-menopausal woman. Healing of ulcerations and a decrease in size or disappearance of primary tumor masses, lymph nodes, cutaneous nodules, liver and pulmonary metastases have been observed. Calcification of osseous metastases during estrogenic therapy occurs in the same manner as with androgenic hormone therapy or castration. An example of a 63 year old woman with advanced breast cancer with osseous metastases is presented[6]. The only abnormal metabolic finding during the control period of study was a negative calcium balance. Immediately following the institution of estrogenic hormone therapy symptoms of hypercalcemia were noted. Such symptoms of hypercalcemia are chiefly nausea, anorexia, and drowsiness. There was an increase of urinary phosphorus and a decrease of serum phosphorus. Shortly thereafter a rapid and profound rise of serum and urinary calcium occurred. Continued nitrogen loss with a significant decrease in intake was accompanied by a decrease in weight. There was no evidence of renal insufficiency despite high excretion of calcium in the urine. The metabolic effects closely resemble those produced by the administration of parathyroid extract. This patient was of particular interest in that the hypercalcemia and strongly negative phosphorus and nitrogen balances apparently initiated by stilbesterol eventually were reversed with accompanying clinical improvement during continuation of the hormone. Regression of pulmonary and soft tissue metastases were noted and calcification of osseous lesions occurred. An increase in the serum alkaline phosphatase was associated with this ossification. The "induced hypercalcemic syndrome" is a frequent complication of androgenic hormone therapy and rarely does it occur during the administration of estrogenic hormones.

3. Androgenic Hormone Therapy

Androgenic hormones have been employed in women of all ages with advanced breast cancer. However, the improvement that occurs is dependent in part upon the site of the metastatic lesions. Subjective improvement consisting of pain relief, increase in appetite and weight and an increased feeling of well-being occurs in a high percentage of patients treated. Favorable objective improvement has occurred primarily in breast cancer with osseous metastases, though regression of lesions elsewhere has also occurred. The improvement in osseous metastases in the post-menopausal woman is similar to that occurring with estrogenic hormone therapy. The standard compound employed has been testosterone propionate. Recently, numerous synthetic androgenic compounds have been developed which produced similar results.

During the past year we have conducted clinical and metabolic investigations with the compound androstan-17 (B) - ol - 3 - one (also referred to as dihydrotestosterone, Stanolone, or Neodrol). Earlier this year Escher[7] presented a report indicating this compound was at least as effective as testosterone propionate in inhibiting the progression and causing regression of existing carcinomatous lesions of the breast. A lower incidence of the virilizing side effects was recorded and these were milder in degree than those induced by testosterone or its esters. From the report, this compound appeared to have a distinct therapeutic advantage over testosterone propionate in practical use because of its mild androgenicity.

Metabolic studies of patients receiving this compound at the University Hospitals were conducted to compare its effectiveness to testosterone propionate and to study its anabolic characteristics. During the past year this compound has been administered to 17 patients with ad-

vanced breast cancer and 1 patient with rheumatoid arthritis and psoriasis. These patients have been closely observed in the Tumor Clinic and observations of the side effects recorded. Of these patients, eight have been hospitalized for metabolic studies.

The following is a summary of our clinical and metabolic observations:

Sixteen patients with advanced breast cancer have been treated for periods of 1 to 7 months. The doses employed were 100 milligrams intramuscularly 3 times a week. Initially, however, several patients were given 400 milligrams a day for periods of no longer than 2 weeks during which time metabolic studies were conducted. The age group of the patients treated varied from 33 to 71 years, only 4 of these being over the age of 50. Thirteen of the patients had osseous lesions and 9 of the patients had soft tissue metastases (skin, nodes, lung, or liver). One additional patient was unable to tolerate the compound because of severe local reactions. Analysis of these 16 patients reveals that in 3 there is insufficient data to warrant recording at this time. One patient refused to return to the clinic after initial treatment was commenced and one patient had a brief metabolic study and no continuation of therapy; hence these are not included in the observations reported. In view of the small number, no attempt is being made to evaluate our results statistically. They are merely presented to demonstrate the types of regressions noted, the side effects recorded, and the metabolic observations.

Three of 6 patients with soft tissue metastases demonstrated an initial regression. In 2 of these, the metastases were cutaneous nodules and local recurrences, and the third had a decrease in the size of the liver and primary tumor mass. Of 10 patients with osseous metastases in whom X-rays have been taken as follow up procedures, 4 have shown a definite improvement in the osteolytic lesions in that more normal appearance of bone has appeared or increased calcification is present. In 1 patient, improvement occurred in some lesions but progression of other lesions has been noted. In 1 patient, there was definite acceleration of the disease process in that osseous metastases increased in size and severe pain was associated with the initiation of therapy.

The physiologic effects of the compound have been recorded (Figure 2). Three patients omitted therapy because of side effects.

FIGURE 2

Side Effect	Number of Patients Observed	Number of Patients Demonstrating Reactions
Hirsutism	9	8
Acne	9	6
Hoarseness	8	7
Libido increase	8	4
Fever	9	7
Anorexia	12	7
Edema	7	1
Weight gain	7	5
Local reaction	9	4
Flushing	8	5
Hair loss	6	3

Comment: During the Administration of androstanolone to patients with advanced breast cancer, regression of soft tissue metastases and osseous metastases have been noted similar to those observed during therapy with testosterone propionate. In contrast to the report of Escher, the physiologic effects which have occurred during the administration of androstanolone are similar to those noted when testosterone propionate was employed. The most striking observation not previously reported was the fever which occurred during the initial phases of therapy. Temperatures up to 101° F. were recorded and varied in duration from a few days to 2 weeks. Two different batches of androstanolone were employed and this fever was noted with both compounds.

Metabolic observations: Observations of calcium, phosphorus and nitrogen balance were conducted on 8 patients. Those patients demonstrating hypercalcuria and hypercalcemia had a decrease in urine calcium and serum calcium to more normal levels. Similar changes with phosphorus were noted in the urine. It would appear that this compound did produce an inhibition of tumor growth in that the rate of bone destruction was diminished.

Observations of the nitrogen balance were varied. In those patients with fever and anorexia, a negative nitrogen balance was demonstrated. However, following continued therapy or in patients not having fever and anorexia, a positive nitrogen balance could be demonstrated and the anabolic effect of this compound verified. Comparison of androstanolone with aqueous testosterone or testosterone propionate in the equivalent doses employed showed no appreciable difference in the anabolic potency of the compound.

4. Bilateral Adrenalectomy

More recently, bilateral adrenalectomy has been introduced for palliative control of advanced carcinoma of the prostate and breast. This procedure was employed on the assumption that in a previously castrated individual, the adrenal gland is an accesory source of androgenic hormones which might stimulate the growth of carcinoma of the prostate, or an accesory source of estrogenic hormones which might stimulate the growth of breast carcinoma. It is too early to evaluate the use of bilateral adrenalectomy in routine treatment of metastatic carcinoma of the prostate or breast, but it would appear that considerable subjective improvement may occur. Since cortisone produces an increased feeling of well-being in these patients, metabolic investigations offer an objective means of demonstrating improvement. The same patients also afford a further means for the investigation of steroid metabolism. Objective evidence of tumor inhibition has been demonstrated by other investigators[8] which are similar to those noted following oophorectomy or hormone administration.

The apparent subjective and objective improvement of patients following total bilateral adrenalectomy has indicated at least a temporary arrest of the progress of the cancer. The evidence seems to signify that this arrest is accomplished by means of altered metabolic processes persuant to changing of the hormonal environment of the neoplastic cell.

In one patient in this institution, a metabolic study has been conducted prior to and following bilateral adrenalectomy. This 43 year old woman had had a bilateral oophorectomy 1 year before total adrenalectomy. Bilateral adrenalectomy was performed in December 1952 and following this procedure the pulmonary metastases disappeared and osseous metastases were observed to calcify. This improvement persisted until July 1953 at which time back pain and increased calcium excretion in the urine were noted. It would appear that in this patient, by alteration of the hormonal environment of the neoplastic cells, a brief but objective improvement occurred in the disease process.

5. Metabolic Investigations of Patients with Cancer of the Breast Undergoing Radiation Therapy

The introduction to the radio-therapist of machines delivering more intensive doses of radiation to the body and the present atomic era have necessitated

investigation of the biochemical and physiologic effects of radiation in the human being. In reviewing the literature on the effects of radiation in man, one is impressed by the large amount of conflicting data and the wide variety of various chemical determinations of the blood and urine that have been carried out. Much of this conflict has been the result of a wide range of experimental conditions involving the types and dose of radiation, the amount of body exposed, the clinical status of the patient at the time of radiation, and the period of analysis following radiation. It appears necessary that further investigations of the effect of radiation on the normal human body are necessary, and in conjunction with such a study, the investigation of the effects of radiation on cancer tissue seemed pertinent. Metabolic balance studies as a means of investigation of this problem are being employed.

Age 38. During the sixth month of lactation this patient noticed a lump in her left breast. A mass occupied a large portion of the left breast. In the left lower quadrant there was puckering of the skin without edema. There was no fixation to the underlying muscles nor was there erythema present. A 0.5 centimeter node was palpable in the left axilla and multiple lymph nodes measuring up to 1 centimeter in diameter were present in the left supraclavicular area. The right breast and axilla were normal. X-ray examination revealed a metastatic lesion in the pelvis. Following a period of metabolic study, the patient received intensive radiation to the left breast and supraclavicular areas. This therapy was completed by radiation castration to the pelvis. The dose of X-ray therapy administered consisted of: 1500 r in air to each of 4 quadrants of the left breast, 1500 r in air to the posterior supraclavicular area, 1500 r in air to the anterior supraclavicular area, and 1500 r in air to the posterior axilla. This was administered over a period of 25 days. The depth dose of radiation was estimated to be approximately 5600 r to the tissue in the center of the breast. X-ray castration consisted of 800 r in air to the anterior port and 800 r in air to the posterior port administered over a 6 day period. The tissue dose to the ovaries was estimated to be 1000 r.

Throughout the period of study, there was a negative calcium balance; no alteration was noticed as a result of radiation therapy. The patient remained essentially in equilibrium with regard to nitrogen balance during the phases of radiation to the breast and regional areas. When radiation to the pelvis was commenced, a negative nitrogen balance occurred. An increase in phosphorus excretion was observed during the third metabolic period during which radiation to the breast was being administered. This increase in phosphorus excretion was largely in the feces. A negative phosphorus balance prevailed throughout the duration of the period of radiation to the breast. Complete regression of the tumor mass occurred concomitantly. Immediately on discontinuance of therapy, phosphorus equilibrium was attained.

Age 46. This woman had a large inoperable cancer of the left breast. There was retraction of the entire breast, and a large solid mass replaced the breast. There was dimpling and edema of the skin and extensive erythema. Large axillary nodes were palpable. X-rays demonstrated no osseous metastases. The lesion of the breast was regarded as inoperable clinically and the patient was admitted to the hospital for metabolic investigation and radiation therapy. The dose of radiation was the same as in the previous patient. Throughout the period of investigation a persistent negative calcium balance was observed, suggestive of osteolytic metastases. Nitrogen equilibrium was maintained. A negative phosphorus balance was maintained in the control period and during the period of radiation to the breast. Following discontinuance of radiation therapy there was an increase in phosphorus excretion and a more marked negative phosphorus balance persisted until termination of the study. In contrast to the previous radiated patient, there was no regression of the tumor mass in the left breast during the time X-ray therapy was directed to the tumor. A partial de-

crease in the size of the tumor, however, did occur during the period following completion of radiation. The tumor mass, however, has never completely disappeared.

In patients with lymphoma and leukemia, the excretion of phosphorus during the administration of ACTH or cortisone acetate is reported greater than the phosphorus excretion calculated from the actual nitrogen and calcium excretion. Chemical analysis of fat-free muscle and tumor tissue revealed 2.9 times as much phosphorus per unit of nitrogen in tumor tissue as in muscle[9].

In our two patients, the excessive loss of phosphorus appears to be related to tumor destruction. Tumor cell damage mobilizes the phosphorus, but there is no explanation as to the mechanism of the increased phosphorus in the feces. Such results demonstrate the necessity to conduct metabolic studies on radiated patients in an attempt to define the effects of radiation on tumor cells and the host.

Summary

Correlation of clinical and metabolic data of patients with metastatic malignancy leads to an understanding of the natural course and mechanisms of the disease process. A base line can be formed upon which therapeutic measures can be more accurately evaluated.

(I would like to extend my appreciation to the several departments that have cooperated in the conduction of metabolic investigations. I am indebted to Dr. K. W. Stenstrom and Dr. Don Mosser of the Department of Radiology; Dr. William Peyton and Dr. Lyle French, Department of Neurosurgery; Dr. William Caster, Department of Physiological Chemistry; Dr. Claude Hitchcock, Department of Surgery; and their respective staffs. Technical assistance by Mrs. Ethel Johnson and Miss Barbara Steele.)

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Cancer 2: 943-945 (Nov.) 1949.

II. MEDICAL SCHOOL NEWS

Coming Events

November 13	Special Lecture; "Fertilization of the Mammalian Ovum"; Dr. Richard J. Bladau, Professor of Anatomy, University of Washington School of Medicine; Owre Amphitheater; 4:00 p.m.
November 16	Medical School Faculty Dinner; "Medical Writing"; Dr. Morris Fishbein; Coffman Memorial Union Main Ballroom; 6:30 p.m.
November 16-18	Continuation Course in Fractures for General Physicians
November 19-21	Continuation Course in Dermatology for General Physicians
December 3-5	Continuation Course in Obstetrics for General Physicians

* * *

Alumni News

At last week's annual meeting of the Minnesota Medical Alumni Association, the following officers were elected for the coming year: President, Dr. Harold G. Benjamin; First Vice-President, Dr. William C. Bernstein; Second Vice-President, Dr. Byron B. Cochrane; Secretary, Dr. Sheldon M. Lagaard; and Treasurer, Dr. James C. Mankey.

* * *

Continuation Course

The University of Minnesota announces a contunuation course in Obstetrics for General Physicians which will be held in the Center for Continuation Study on December 3 and 4, 1953. On Saturday, December 5, sessions will be held at the Lowry Hotel, St. Paul, Minnesota. Emphasis will be placed on recent advances in the field which have practical clinical application and on problems which have come to light as a result of recent studies. Guest speaker will be Dr. LeRoy A. Calkins, Professor and Head, Department of Obstetrics and Gynecology, University of Kansas School of Medicine. The course will be presented under the direction of Dr. John L. McKelvey, Professor and Head, Department of Obstetrics and Gynecology, University of Minnesota. The remainder of the faculty will include members of the staff of the University of Minnesota Medical School.

* * *

Publications of the Medical School Faculty

Critchfield, L. R.: School Days Ahead: Health Checkup and Habit Training the Best Preparation. Everybody's Health, April, 1953.

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III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

November 16 - 21, 1953

Monday, November 16

Medical School and University Hospitals

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; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

11:30 - 12:30 Physical Medicine Seminar; The Effect of Posture on Low Back Pain; Frederic J. Kottke; Heart Hospital Auditorium.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:30 Physiology Seminar 201; The Interaction of Purified Enolase and DL-2-Phospo-Glyceric Acid with Metal Ions Activating Enolase; Bo G. Malmstrom; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

1:30 - 3:30 Dermatology Hospital Rounds; H. E. Michelson and Staff; Dermatology Histopathology Room, M-434, U. H.

4:00 - 5:00 Residents Conference; Presentation of Cases from Veterans Hospital; Heart Hospital Theater.

4:30 - ECG Reading Conference; Staff Room, Heart Hospital.

4:30 - Infectious Disease Rounds; Sta. 43, U. H.

4:30 - Public Health Seminar; A.P.H.A. Round-Up; 15 Owre Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

* 6:30 p.m. Medical School Faculty Dinner; Speaker: Dr. Morris Fishbein - "Medical Writing"; Coffman Memorial Union Main Ballroom.

Ancker Hospital

8:30 - 10:00 Tuberculosis and Chest Conference; Auditorium.

2:00 - 3:00 Surgery Journal Club; Classroom.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Medicine Rounds; Thomas Lowry; Sta. F.

11:00 - Orthopedic and Fracture Rounds; Drs. John Moe and Arthur Zierold; Sta. A.

11:00 - Pediatric Rounds; Erling Platou; Station K.

Monday, November 16 (Cont.)

Minneapolis General Hospital (Cont.)

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. A.

1:30 - 2:30 Tuberculosis Conference; J. A. Myers; Sta. M.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Veterans Administration Hospital

1:30 - Cardiac Conference; Drs. Berman, Weisbart, and Smith; Rounds Immediately following conference.

Tuesday, November 17

Medical School and University Hospitals

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

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:30 Physiology 114C -- Respiration; E. B. Brown; 129 Millard Hall.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - 1:30 Bacteriology Seminar; Isolation and Cultivation of Animal Cells; Armand Eiring; Conditioned Hemagglutinations in Bacterial Products; Richard Berk; 214 Millard Hall.

3:30 - Pediatric Seminar; Encephalitis; Brian Kiely; Sixth Floor, U. H.

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

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 X-ray Conference; Presentation of Cases by University Hospitals Staff; Eustis Amphitheater, U. H.

* 8:00 p.m. Minnesota Pathological Society Meeting; "Management of Pathological Fractures of the Long Bones"; Dr. Edwin F. Cave, Chief of Fracture Service, Massachusetts General Hospital, Boston; Owre Amphitheater.

Ancker Hospital

9:00 - 10:00 Medical X-ray Conference; Auditorium.

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

11:30 - 12:30 Neurology-Neurosurgery Conference; Classroom, Sta. M.

12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.

12:30 - ECG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Tumor Clinic; Drs. Eder, Coe, and Lipschultz; Classroom.

1:00 - Psychiatry Grand Rounds; J. C. Michael and Staff.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

Tuesday, November 17 (Cont.)

Veterans Administration Hospital (Cont.)

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:30 - Infectious Disease Rounds; Drs. Hall, Zinneman, and Brown.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery-Tumor Conference; L. J. Hay, J. Jorgens and Donn Mosser; Conference Room, Bldg. I.

1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

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

2:30 - 4:00 Psychosomatic Conference; C. K. Aldrich; Conference Room, Bldg. I.

4:00 - Thoracic Surgery Problems; Conference Room, Bldg. I.

Wednesday, November 18

Medical School and University Hospitals

8:00 - 9:00 Roentgenology Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.

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

12:30 - 1:30 Physiology 114B -- Transport Seminar; Nathan Lifson and M. B. Visscher; 214 Millard Hall.

12:30 - 1:30 Radioisotope Seminar; Measurement Methods for the Clinical Laboratory; Sol Sandhaus; 12 Owre Hall.

1:00 - 2:00 Dermatology Clinical Seminar; 300 North Clinic.

1:30 - 3:00 Pediatric Allergy Clinic; Albert V. Stoesser and Lloyd Nelson; W-211, U. H.

3:30 - 4:30 Dermatology Pharmacology Seminar; J. D. Krafchuk; 3rd Floor Conference Room, Heart Hospital.

4:00 - Medicine-Physiology Cardiovascular Conference; Discussion of a Cardiovascular Case Problem; Maurice B. Visscher; Heart Hospital Theater.

4:30 - 5:50 Dermatology Infectious Disease Seminar; J. D. Krafchuk; 3rd Floor Conference Room, Heart Hospital.

4:30 - ECG Reading Conference; Staff Room, Heart Hospital.

5:00 - 6:00 Residents Lecture; Cardiac Disease; Joseph Jorgens; Todd Amphitheater, U. H.

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

5:30 - 7:30 Dermatology Journal Club and Discussion Group; Hospital Dining Room.

7:30 - 9:30 Dermatology Pathology Seminar; Review of Interesting Slides of the Week; Robert W. Goltz; Todd Amphitheater, U. H.

Wednesday, November 18 (Cont.)

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

12:30 - 1:30 Medical Journal Club; Library.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Max Seham; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.

11:00 - Pediatric Rounds; Erling S. Platou; Station K.

12:00 - Surgery-Physiology Conference; Arthur Zierold and E. B. Brown; Classroom.

12:15 - Pediatric Staff Meeting; Classroom, Station I.

1:30 - Visiting Pediatric Staff Case Presentation; Classroom, Station I.

2:00 - 4:00 Infectious Disease Rounds; Station D.

4:00 - 5:00 Infectious Disease Conference; Wesley W. Spink; Classroom.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room; Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Zieve, Hay, Brakel and Nesbitt.

12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.

4:00 - Combined Medical Surgical Conference; Drs. Flink and Hay; Conference Room, Bldg. I.

5:00 - Medical Journal Club; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, November 19

Medical School and University Hospitals

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

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

12:00 - 1:00 Medical Journal Club; BCG; Don Mattson; 116 Millard Hall.

12:30 - Physiological Chemistry Seminar; Glutamic Acid Metabolism in Brain; John Logothetis; 214 Millard Hall.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 Radiology Seminar; Tumors of the Duodenum; Vincent Paciotti; Eustis Amphitheater, U. H.

Thursday, November 19 (Cont.)

Medical School and University Hospitals (Cont.)

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Ancker Hospital

8:00 - 10:00 Medical Grand Rounds; Auditorium.

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station I.

10:00 - Pediatric Rounds; Spencer F. Brown; Station K.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.

12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

1:00 - House Staff Conference; Station I.

Veterans Administration Hospital

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

1:00 - 3:00 Metabolic Disease Conference; Drs. Flink, Heller and Hoseth.

Friday, November 20

Medical School and University Hospitals

8:00 - 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.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 1:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Out-Patient Department, Heart Hospital.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Advanced Malignant Disease of the Upper Respiratory Tract; Jerome A. Hilger; Powell Hall Amphitheater.

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

1:30 - 2:30 Dermatology Grand Rounds; Presentation of Cases from Grouped Hospitals (University, Ancker, General and Veterans) and Private Offices; H. E. Michelson and Staff; Skin Clinic; W-312, U. H.

2:30 - 4:00 Dermatology Hospital Rounds; H. E. Michelson and Staff; Begin at Dermatology Histopathology Room, M-434, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

Friday, November 20 (Cont.)

Medical School and University Hospitals (Cont.)

4:00 - 5:00 124 Advanced Neurophysiology Lecture; Werner Koella and Ernst Gellhorn; 111 Owre Hall.
4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.
4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital
5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.
10:30 - Pediatric Surgery Conference; Oswald Wyatt; Tague Chisholm; Station I, Classroom.
12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.
1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.
1:15 - Pediatric X-ray Conference; Oscar Lipschultz; Classroom, Main Bldg.
2:00 - Pediatrics Rounds; Robert Ulstrom; Stations I and J.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.
1:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.
2:00 - Autopsy Conference; E. T. Bell and Donald Gleason, Conference Room, Bldg. I.

Saturday, November 21

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.
9:00 - 10:00 Infertility Conference; Louis L. Friedman, David I. Seibel, and Obstetrics Staff; Eustis Amphitheater, U. H.
9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.
9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.
10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.
10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.
11:30 - Anatomy Seminar; Invertebrate Blood; S. O. Cornwell; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.
11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry and Staff; Main Classroom.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.
8:30 - 11:15 Hematology Rounds; Drs. Hagen and Sherman.
11:15 - 12:00 Morphology . . . . Dr. Aufderheide; Conference Room.

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* Indicates special meeting. All other meetings occur regularly each week at the same time on the same day. Meeting place may vary from week to week for some conferences.