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**Staff Meeting Bulletin  
Hospitals of the » » »  
University of Minnesota**



**Carcinoma of Prostate**

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during the school year, October to June, inclusive.

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William A. O'Brien, M.D.

I. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL  
 CALENDAR OF EVENTS  
 February 7 - 12, 1944

Visitors Welcome

Monday, February 7

- 9:00 - 10:00 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff, Todd Amphitheater, U. H.
- 9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Interns Quarters, U. H.
- 12:30 - 1:30 Pediatrics Seminar; Obesity; Alice Brill, W-205 U. H.
- 12:30 - 1:30 Pathology Seminar; The Pathology of Virus Disease of Plants; R. M. Marwin, 104 I. A.
- 7:30 - Cancer Biology Seminar; Genetics of Mammary Cancer in Mice; 116 M. H.

Tuesday, February 8

- 8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff, Main 515, U. H.
- 9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff, Eustis Amphitheater, U. H.
- 11:00 - 12:00 Urology Conference; C. D. Creevy and Staff, Main 515, U. H.
- 12:30 - 1:30 Pathology Conference; Autopsies. Pathology Staff, 104 I. A.
- 4:30 - 5:30 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Station 54, U. H.
- 4:00 - 5:00 Pediatrics; Grand Rounds; I. McQuarrie and Staff, W-205 U. H.
- 5:00 - 6:00 Roentgen Diagnosis Conference; L. Bixler, K. W. Stenstrom, M-515 U. H.

Wednesday, February 9

- 11:00 - 12:00 Pathology-Medicine-Surgery Conference; Myelogenous Leukemia, E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff, Todd Amphitheater, U. H.
- 12:30 - 1:30 Pharmacology Seminar; The Pharmacology of Phenarsine Hydrochloride; L. Fink, 105 M. H.
- 4:30 - 5:30 Neurophysiology Seminar; Sensitization to Acetylcholine and Sympathin Denervation; L. Thompson, 129 M. H.

Thursday, February 10

- 9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, Todd Amphitheater, U. H.
- 10:00 - 12:00 Medicine Rounds; C. J. Watson and Staff, East 214 U. H.
- 12:30 - 1:30 Poliomyelitis Seminar; Physiology of Muscle Pain and Tenderness, E. Gellhorn; Pain and Tenderness in Poliomyelitis, J. C. McKinley, 113 M. S.
- 12:30 - 1:30 Physiological Chemistry Seminar; Oral and Dental Biochemistry; W. D. Armstrong, 116 M. H.
- 5:00 - 6:00 Roentgenology Seminar; Review of Recent Radiologic Literature; Staff, M-515 U. H.
- 4:30 - 5:30 Bacteriology Seminar; Characteristics of Virus Diseases; R. G. Green, 129 M. H.

Friday, February 11

- 9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 8:30 - 10:00 Grand Rounds; I. McQuarrie and Staff.
- 10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; East 214 U. H.
- 11:45 - 1:15 University of Minnesota Hospitals General Staff Meeting; Hysteria in Children; A. D. Wert and R. A. Jensen, Powell Hall Recreation Room.
- 1:30 - 2:30 Medicine Case Presentation; C. J. Watson and Staff; Eustis Amphitheater.
- 1:00 - 2:30 Dermatology and Syphilology; Presentation of selected cases of the week; Henry E. Michelson and Staff; W-306 U. H.
- 1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff, Todd Amphitheater, U. H.

Saturday, February 12

- 10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff, E-214 U. H.

## II. TREATMENT OF CARCINOMA OF THE PROSTATE WITH STILBESTROL

A. C. Stahr  
F. X. Roach

Estrogens and castration have been used extensively in cases of carcinoma of the prostate since 1941, when Huggins described his experimental work and clinical results using these two methods of altering the hormonal system in laboratory animals and in men with carcinoma of the prostate. He demonstrated that either castration or estrogen administration in patients suffering from carcinoma of the prostate caused relief of urinary obstruction and of pain from metastases, improvement in the patient's general well-being, gain in weight, and softening and decrease toward normal in the size of the carcinomatous gland. Other workers had helped prepare the way for this discovery.

Kutscher and Wolbergs found the acid phosphatase content of the adult prostate to be very high, higher than in any other tissue of the human body. Phosphatases are dephosphorylating enzymes, i.e., they catalyze the breakdown of phosphoric esters with the resultant formation of phosphoric acid. Acid phosphatase is a phosphatase most active in an acid medium; alkaline phosphatase, an entirely different enzyme, is most active in an alkaline medium.

Gutman, Sproul, and Gutman found the acid phosphatase content of blood serum to be elevated in most cases of prostatic carcinoma which had metastasized to bone.

Serum alkaline phosphatase was found to be increased in carcinoma of the prostate with metastases to bone, but also in many other diseases of bone.

Huggins noted that after castration in patients with carcinoma, the serum acid phosphatase, if elevated, fell abruptly in those who were clinically improved, whereas the changes in the alkaline phosphatase level were more variable, usually rising after castration and then returning slowly toward pre-operative levels.

Carcinoma of the prostate is the only disease known to cause significant rises in serum acid phosphatase. It is not, however, elevated in all cases. Although it may be increased in those without demonstrable metastases, it is usually seen in patients with bony involvement. It is reported that 85 per cent of patients with metastasis of prostatic carcinoma to bone have elevated acid phosphatase levels.

The beneficial effects of castration are due to the removal of the interstitial cells of the testis which liberate the male sex hormone. Removal of this hormone causes atrophy of the carcinomatous prostate just as it causes atrophy of the normal adult prostate.

The mode of action of the estrogens is less certain. They may depress the pituitary, which normally stimulates the testes to form the male sex hormone; possibly they act directly on the male gonad in depressing the elaboration of androgen; they may act directly on the proliferation or metabolism of the neoplastic cells; or they may cause some shift in the androgen-estrogen balance. In any case, the patient on estrogen therapy for carcinoma of the prostate shows an improvement in all respects similar to that experienced by the castrated patient, except for the fact that his improvement is slower.

Some patients, whether treated by castration or by estrogens, who no change in their clinical course. The serum phosphatase levels and metastases on x-ray examination do not change, and the patients' disease takes the usual course, ending in cachexia, urinary obstructive symptoms, pain, and death.

The histologic changes in the carcinomatous prostate after castration or estrogen administration are interesting. In the untreated gland, the cells contain large vesicular nuclei, prominent nucleoli, and granular recicular cytoplasm. Some mitoses are visible. With regression in the size and with the softening of the gland clinically, the nuclei are seen to become smaller, and

the nuclear chromatin becomes more compact. No nucleoli or mitoses are seen, vacuoles appear in the cytoplasm and are located chiefly at the base of the cells. The regressive changes continue to an end stage, when the cell membranes rupture, the vacuoles coalesce, and the pyknotic nuclei lie free in the acinar spaces.

Since late in 1941, stilbestrol has been used in this hospital, alone, or frequently with other established methods of treatment in cases of carcinoma of the prostate. Sufficient time has elapsed for the accumulation of a fair number of cases of men suffering from this common malignancy, who have been treated by this means, and by the same token, sufficient time has elapsed so that an evaluation of the clinical results produced is warranted.

A study has been made of patients suffering from carcinoma of the prostate who have been treated for at least 6 months with stilbestrol. The diagnosis was made in the majority of cases by microscopic examination, but in a good many cases, the condition was diagnosed by the demonstration of bony metastases on x-ray examination or by the typical findings elicited on rectal examination. The usual patient has been seen several times a year in the Urology clinic since the diagnosis was originally made. Blood acid and alkaline phosphatase levels have been determined and x-rays of the pelvis taken at intervals.

Letters of inquiry were sent to all patients seen by the Division of Urology who had been taking stilbestrol for 6 months or longer. The patients were requested in these form letters to return to the Urology Out-Patient Department for an examination. If this was impossible, they were to answer a series of questions at the end of the letter concerning their present state of health, the regularity with which they had been taking stilbestrol, the side-effects of the drug, etc. Those who returned to the Out-Patient Department were examined by members of the Staff, special note being taken of the characteristics of the gland

on rectal examination, of complaints suggestive of metastases, and of the patients' answers to the above-mentioned series of questions. Acid and alkaline blood phosphatase determinations were run on each patient, and x-rays were taken of the pelvis or other areas suspected of being the site of metastasis. Private patients as well as clinic patients have been included in the series.

The usual dosage of stilbestrol has been 1 to 5 milligrams per day, taken orally.

Letters were sent to 74 patients. Answers have been received from 39 patients, and 15 are reported to have died - a total of 54 patients being accounted for. Several patients have moved and cannot be traced.

7 of the 15 patients who have died since the inception of stilbestrol therapy died of causes attributable to carcinoma of the prostate. Usually they were bedridden for months before death, suffering from metastases to the spine or pelvis, or from urosepsis. Only 1 of these patients was castrated, a year before death. He received little relief from pain due to metastases by this procedure, nor did subsequent therapy with stilbestrol seem to affect the clinical course.

The cause of death in the other 8 patients who have died is unknown or unrelated to this study.

9 of the 15 patients now dead experienced at least temporary benefit from complaints attributable to their disease. Some were relieved dramatically of their urinary difficulties. Their urinary frequency decreased, hematuria ceased, and they again voided with a good sized stream. Others were relieved of their pain due to metastases. 6 patients had metastases, 3 dying of carcinoma and 3 of other causes.

These pleasing results were transient, however, at least in those who died of carcinoma, and after periods of relief lasting up to 2 years in several cases,

the patient was again in a miserable state due to urinary obstruction by the carcinomatous gland or to bone and sciatic pain from metastases. The average duration of the disease in those who have died was 23.7 months.

The average duration of the disease in the 39 patients living is 23.9 months. 14 were found to have metastases at their first examination, and 1 has subsequently developed metastases to the pelvic bones. The average duration of the disease in these 15 with metastases is 24 months. Of the 15, ten have had pain, 8 were relieved by stilbestrol - 3 partially and 5 completely. However, 3 of these 5 with complete relief have had a recurrence of their pain. They should be subjected either to more vigorous stilbestrol therapy or to castration.

The chief complaint of many patients with carcinoma of the prostate is difficult urination. Although stilbestrol is effective in ameliorating the symptoms of urinary obstruction, some time is required for the gland to shrink. In order, then, to obviate the necessity of having the patient stay in the hospital with an indwelling catheter for a rather lengthy period of time, the obstructing tissue is frequently removed trans-urethraly. 19 of these 39 patients have had, within the last 2 years, prostatic surgery for removal of obstructing tissue. The other 20 have had no prostatic surgery, or surgery more than 2 years ago. The 2 year interval is chosen as the factor dividing the 2 groups merely because it would seem that if the carcinomatous tissue were to grow back and cause a recurrence of obstruction, it would do so within a 2 year period.

The relief from urinary symptoms obtained by each group was practically the same notwithstanding the fact that 1 group had the advantage of having had obstructing tissue removed within the last 2 years. In the group of 20 having had no surgery within this period of time, 10 obtained marked relief from urinary symptoms, 4 moderate relief, and 6 noted no relief. Of the group of 19 who had prostatic surgery recently, 10

obtained marked urinary relief with stilbestrol, 7 moderate relief, and 3 no relief.

Three of the total of 54 patients had elevated serum acid phosphatase values when first seen, and all had metastases to bone. They are still living. In each case the acid phosphatase value fell to normal after the inauguration of stilbestrol therapy. 12 patients had elevated alkaline phosphatase values when first seen. 7 of these 12 had bony metastases. The alkaline phosphatase values have not returned to normal in most cases as have the acid values.

The unpleasant side-effects of stilbestrol in this group have been the occurrence of tender enlarged breasts in 20 instances and nausea or epigastric distress in 10. All patients who took stilbestrol faithfully lost their potency.

Probably the greatest disadvantage in the treatment of carcinoma of the prostate with stilbestrol has been the tendency of the patients to quit taking the drug because they felt well after having taken stilbestrol for some time. It is interesting to note that some patients continued to get along well for as long as a year after they had stopped taking the drug. More frequently, however, the patients' symptoms returned if they stopped the stilbestrol. This was most apt to recur in those having pain from metastases. 11 of the 39 patients proved they could not be trusted to take stilbestrol faithfully. Obviously the solution of this problem is castration of these patients.

The effect of stilbestrol on the size and consistence of the carcinomatous prostate is less striking than the effect following castration. Frequently following castration the hard, nodular, enlarged gland recedes toward normal size and consistence. In several months, in fact, it may be impossible to tell that the gland is carcinomatous. After stilbestrol administration, the characteristics of the gland slowly approached

normal, but rarely is it impossible to determine that the malignant process is still present. Soft tissue metastases in 2 instances disappeared completely under the effect of the drug.

The changes in the bony metastases were quite variable. The usual osteoblastic lesion in some instances became denser and more sclerotic; in others it tended to disappear. It was not unusual to find that previous sites of metastasis had completely disappeared only to be supplanted by new sites. On the whole, the tendency of the metastases was to increase in size and number, whether the patient had pain or not.

The average duration of the disease in the living was the same in those with metastases and in those without metastases (24 months approximately). This demonstrates quite an improvement over the usual findings prior to hormonal therapy, when 2/3 of those with metastases could be expected to die within 9 months (Bumpus).

The fact that the average duration of the disease in those who died (23.7 mo.) is as great as the duration in those still living is at first disturbing, but one must remember that the dead include those who have died of other causes. Also the number of dead is small, making any comparison with this group rather hazardous.

Obviously the average duration of the disease to be calculated when all have died will reveal an appreciable rise in the time of survival when compared with that of those not treated by hormonal therapy (31 months in untreated - Bumpus).

It has not been determined definitely which method of treatment is the better - castration or estrogen therapy. The patients get a quicker response after castration and do not have to take any medication. On the other hand, when a patient becomes refractory to the beneficial effects of stilbestrol and has pain due to metastases, castration can be performed. Castration seems to relieve the pain of metastases more completely than does estrogen therapy. The logical

line of treatment would seem to be the administration of estrogen until painful metastases appeared, and then castration; thus the maximal amount of relief would be obtained from the one form of therapy before resort was had to the other.

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### III. GOSSIP

Fred Mears, Evrel Larson and Stanley Lundblad want us to know how much they appreciate our kindness and thoughtfulness at Christmas. They say: "Our boxes arrived in good shape and did much to contribute to as happy a Christmas as possible under the circumstances. It is pleasant to know that we share a part of the thoughts of former associates who are carrying on at home.

We had a pleasant Christmas Day. After completing morning rounds, all of us who could get away piled into a truck and spent the rest of the day swimming in a river near here. In the late afternoon we returned to a tasty turkey dinner which Uncle Sam served up for us, the memory of which still lingers on. The work continues on much the same as always, though we're not very busy these days. One of our chief problems is concerned with keeping reasonably cool; the weather is hot and humid and we all seem to be more bothered with it this year than last. I'm afraid it'll take quite an adjustment for us to become acclimated to Minnesota winters again. However, we're all more than willing to take a chance at it. The three of us had a Christmas tree this year which was really the duplicate of those we used to have at home. Unlike home, however, we cut it ourselves one noon when the temperature must have been at least 120° in the shade; it was a specie of pine that grows rather profusely on the island, in spite of the climate. We decorated it with ornaments which our wives had sent and then rigged up a spotlight so that it really glittered at night. This month we're scheduled to hold the monthly meeting of the "Island Medical Society." The occasion consists of a half day of ward rounds, presentation of medical and surgical papers, and finally a social hour and dinner. Since we first arrived, the society membership has grown and this - our third turn at playing host - will probably constitute the largest meeting to date. It is quite enlightening to exchange ideas with associates hailing not only from all parts of the U.S. but from different parts of the world.

Our very best to all of you. May your New Year be a happy one.....

At the annual staff dinner of the Eitel Hospital on January 27, 1944, this announcement was sent to the group:

"Le Menu  
Bar Americain  
\*\*\*  
Canapes  
appendices Vermiformis au pain rote  
\*  
Potage Jardinier  
Hors d' Oeurvres  
(celeri - olives - radis) - catouettes  
chaud ou Frois  
Cotes de Beuf a l' Anglaise  
de Quadratus lumbarum-cum myositis  
ossificans  
\*  
Hachi de pommes de terre. Bechamel  
Carottes & poix au beurre  
\*  
Laitue au fromage  
Petits Pains chauds - Condiments verts  
Cafe noir ou a la Creme  
\*  
Couronne macedoine au Cointreau

### PROGRAMME

Election des Officiers  
\*  
Un raconteur illustre  
Anecdotes suggestives, mais pas risquées  
\*  
Monsieur Francois et  
Madame Esther Blood (tres chic-  
Hbgn 100%)  
Virtuosos du violon et de l'accordeon -  
au radio

### KSTP

Programme Musical  
La danse des Ascaris Lumbricoides  
Menopause Blues  
Rhapsodie - Treponema Pallidum  
La Danse des Gametocytes  
Danse Macabre  
(Delirium Tremens du Violon)  
\*  
Cinema eu couleurs naturelles

Interpreter  
E. W. Bedford  
"Medicante"

- - -

John S. Grogan, Wadena Clinic writes to our superintendent: "May I at this time express my personal appreciation to you and the staff for the excellent service you have given the patients I have sent in. We out here in the country as well as your city doctors take too much for granted and accept the wonderful work and service you are rendering as a matter of course. My personal attitude has been different but like many others I have failed to acknowledge same. If this message could be conveyed to the staff, I would appreciate it.

Wishing you all a happy 1944 if such a thing is possible under the present strife. Again thanking you -"

And Thank you, John, whose son John is one of our recent medical graduates now in the service.....

DR. R. S. YLVISAKER

announced the removal of his office to 529 Medical Arts Building on Jan. 1, 1944. Tel. GE 9344.

J. M. HAYES, M. D.

Announces the opening of offices  
In Los Angeles: 2202 W. 3rd St., Bldg. #2, Medical Square, Tel. DRexel 3136.  
In Pasadena: 979 E. Washington Street, Tel. SYcamore 7-3334.  
Residence Telephone: Monrovia 5052.

Word has just been received from Ireland that it is Colonel Edward S. Murphy now, Murph went overseas as a Lt. Colonel, and now the little birds have come to roost. All of his friends join in sending congratulations and best wishes...T. R. McConnell, Associate Dean of the College of Science, Literature and the Arts, and Malcolm M. Willey, Vice-President, Academic Administration, University of Minnesota, are the editors of the January 1944 edition of "Higher Education and the War" in The Annals of the American Academy of Political and Social Science. Interpreters from the University of Minnesota include Roland S. Vaile, Harold S. Diehl, Everett Fraser, Wesley E. Peik, Russell A. Stevenson, W. S. Miller, J. M. Nolte, E. G. Williamson, Arthur R. Upgren and Drs. McConnell and Willey. In addition there are reports from other Universities. Every staff member interested in Post War Education should read this issue....The Center for

Continuation Course in Otolaryngology, February 7th to 11th will be held at the Curtis Hotel as the Center for Continuation Study building is not yet ready for occupancy. Advance registration in Otolaryngology indicates a large turnout. Visiting lecturers include Oscar A. Batson (Pennsylvania), Paul H. Holinger, (Illinois), John R. Lindsay (Chicago), and Theodore E. Walsh (Washington-St. Louis). The first medical course at the Center will be Clinical Dietetics for dietitians, February 21, 22, 23. Subjects will be recent clinical developments in which dietetics plays the role. ...Dr. and Mrs. E. J. Carey of Marquette are guests of the Hennepin County medical profession today. Mrs. Carey is President of the auxiliary of the American Medical Association. Dr. Carey is Dean of the medical school, as well as Professor of Anatomy. The women are entertaining Mrs. Carey, and the physicians have Dr. Carey as their guest. Tonight medical husbands and wives will meet at the society's rooms at 8:15 p.m. to hear Dr. Carey discuss present day medical problems. They are a famous pair and most delightful company. Dr. Carey was a guest of the University over last weekend when he presented his material on studies of the motor end plate in experimental and clinical poliomyelitis. Dr. Carey's work was presented before a special 3 day course for orthopedic surgeons who are studying the results of the Kenny technique... ..Do sick people really like visitors? If the illness is short, apparently they do not, if our survey of patient opinion is correct. One man said he disliked speaking from a prone position in bed. One woman said they always came at the wrong time. Most of the patients felt the visitors stayed too long. Baby mothers liked visitors after they began to feel better. Patients with chronic illness like visitors as a rule. The subject was aired on the Minnesota Hospital Association program and provoked considerable comment. Each month on this program a different hospital question is discussed. There is a story for the newspapers and each hospital superintendent invites 5 persons to listen and to comment on the program.....