

✓

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

**Estrogens and Carcinoma  
of the Prostate**

INDEX

	<u>PAGE</u>
I. LAST WEEK . . . . .	180
II. MEETINGS	
1. ANATOMY SEMINAR . . . . .	180
2. PHYSIOLOGY-PHARMACOLOGY SEMINAR . . . . .	180
3. BACTERIOLOGY SEMINAR . . . . .	180
4. E. STARR JUDD LECTURESHIP . . . . .	180
III. ESTROGENS AND CARCINOMA OF THE PROSTATE . . . . .	
. . . . . C. D. Creevy . . . . .	181 - 190
IV. GOSSIP . . . . .	191

---

Published for the General Staff Meeting each week  
during the school year, October to June, inclusive.

Financed by the Citizens Aid Society,  
Alumni and Friends.

William A. O'Brien, M.D.

I. LAST WEEKDate: February 5, 1943Place: Recreation Room,  
Powell HallTime: 12:15 - 1:10 p.m.Program: "Ophthalmostopic Aspects of  
Some Local and Systemic Vas-  
cular Diseases (Lantern Demon-  
stration) - Ferdinand L. P.  
Koch.Attendance: 111Gertrude Gunn,  
Record Librarian

- - -

3. BACTERIOLOGY SEMINARThursday, February 18 at 4:30 in  
214 Millard Hall.

Microbial Symbiosis.

Franziska Melzer

- - -

4. E. STARR JUDD LECTURESHIPThursday, March 11 at 8:15 p.m. in the  
auditorium of the Museum of Natural  
History.Traumatic Shock with Particular Refer-  
ence to War Injuries.

Alfred Blalock

II. MEETINGS1. ANATOMY SEMINARSaturday, February 13, at 11:30 a.m. in  
room 226 Institute of Anatomy.Age Incidence of Leukemia in Pure Strain  
and Hybrid Mice.

Arthur Kirschbaum

Relationship between Plasma Cells and  
Hyperglobulinemia.

Fred Kolouch

- - -

2. PHYSIOLOGY-PHARMACOLOGY SEMINARTuesday, February 16 at 12:30 in 214  
Millard Hall.

Harold N. Wright.

Subject to be announced.

- - -

### III. ESTROGENS AND CARCINOMA OF THE PROSTATE

C. D. Creevy

Carcinoma of the prostate is a deadly disease. It accounts for one-fifth of obstructions at the vesical neck (Young) and has become much commoner in recent years. Thus, while there were but 83 cases recorded in the literature up to 1899, Duff found that it increased as a cause of death from 0.8 per 100,000 in 1917 to 3.7 in 1928. Moore has recently demonstrated carcinoma of the prostate at autopsy in 21 per cent of a considerable series of males past forty. It seems likely that the incidence of the disease at necropsy depends both upon the care with which it is sought, and upon the investigator's interpretation of certain rather common changes in the gland. Baron and Angrist, making a very painstaking search, have recently identified "occult" carcinoma of the prostate in 46 per cent of 50 consecutive autopsies on men past 50 years of age who died of other diseases!

The increased frequency of prostatic cancer seems to be due, not to heightened individual susceptibility, but to increased longevity. Life expectancy at birth among the industrial policyholders of the Metropolitan Life Insurance Company increased from 46.6 years in 1911 to 63.4 years in 1941; and the number of males more than 65 years old doubled in the United States between 1911 and 1935. Since the average age at which carcinoma of the prostate is discovered is above 60, the disease becomes evident clinically in many more men than formerly.

To summarize: A man of 65 today is no more likely to have the disease than was his great grandfather at the same age, whereas a male child born today is far more likely to die of a prostatic cancer than was his great grandfather, because of his greater chances of surviving to old age. In any case, the physician of today has to recognize and treat a great many carcinomas of the prostate.

One of the most unfortunate aspects of prostatic neoplasm is that it is usually discovered late in its course. Barringer found but 4.5 per cent of 351 prostatic carcinomas localized in and about the gland itself, while Young (reported by Colston and Lewis) regarded only 3.4 per cent of 1040 cases as suited to a radical operation aimed at cure. Further evidence is found in the fact that metastases to bone were seen in the X-ray at the first visit in 25 per cent of a large series of patients by Bumpus, and in 58 per cent of a smaller series by Barney and Gilbert.

This late discovery is attributable to several factors: The tumor causes no symptoms until it becomes large enough to produce obstruction at the vesical neck, or until it involves other structures and causes pain. It grows so slowly that the detrusor muscle has plenty of time for hypertrophy which compensates for the obstruction, thus delaying the onset of symptoms. Moreover, three-fourths of prostatic neoplasms originates in the posterior lamella of the gland, at a relatively great distance from the urethral lumen, and so cause obstruction late in their course. Further, the symptoms of obstruction are indistinguishable from those due to benign hypertrophy, and patients are likely to regard them as normal accompaniments of old age, and to defer consultation until they become intolerable, which usually takes a long time. Adding to these difficulties is the fact that about one-fourth are concealed from the examining finger by surrounding or intervening benign hypertrophy, and hence cannot be identified until far advanced.

Thus we see that, at present, only about three to four per cent are even potentially curable by operation. While this percentage can be increased somewhat by educating patients to consult their physicians at the first sign of obstruction to urination, the most serious problem at present is that of the 96 to 97 per cent of patients who have waited until local extension or metastasis has made cure impossible. In the recent past,

the treatment of these people has been based upon the degree of obstruction. When it is absent or mild in character, irradiation, both interstitial and external, has been helpful in causing regression of the growth and amelioration of symptoms. Its by-effects are unpleasant, and it frequently fails to give satisfactory relief. Pain from metastases which have resisted irradiation sometimes yields to the subarachnoid injection of alcohol or to cordotomy, but these measures do not retard the progress of the tumor and its metastases. Troublesome obstruction is unusually dealt with by transurethral resection.

By combining these methods, one can promise the average patient a year or so of comfort, and can hope that a few will secure relief for several years. This is, of course, not a pleasant picture.

It has long been known that the prostate is dependent for development and maintenance upon the secretions of other glands. Since Berthold suspected it in 1849, quite a number of investigators, among them Tandler and Grosz, have demonstrated that castration of the immature male prevents or arrests the normal development of the prostate and other accessory sex organs, and that, in the mature male, it is followed by simple atrophy of the prostate.

It is also known that the secretion of male hormone by the testis depends upon a functioning anterior pituitary. Many authors (Cushing, Moore, Wells and Overholser, Moore and Price, Smith) have reported atrophy of the testes and accessory sex organs after hypophysectomy, and it has been shown that this atrophy, whether from castration or from hypophysectomy, may be prevented or corrected by the administration of natural or of synthetic male hormones such as testosterone propionate (Moore and Gallagher, Moore and Price).

It has also been observed that, after castration, the anterior lobe of the pituitary becomes hyperplastic, and that the excretion of prolans in the urine is measurably increased (Evans and Simpson,

Engle).

There is a considerable literature upon the production of prostatic hypertrophy in the experimental animal by the administration of various hormones, but to discuss it here would take too much time. Suffice it to say that the experimental hypertrophies differ strikingly on microscopic examination from the clinical types, and that the cause of this condition in man remains to be determined. Since castration causes simple atrophy of the normal prostate, it is tempting to assume that it will have the same effect upon benign hypertrophy, but this idea was proved incorrect after an extensive clinical trial in the nineties by many surgeons. Nevertheless, Huggins has recently shown that castration may exert a profound influence upon cancer of the prostate. It may well be that the effect of castration upon cancer differs from that upon benign hypertrophy because cancer develops from the true prostatic glands, while benign hypertrophy originates, as suggested years ago by Motz and Pereaudeau, not from the prostate itself, but from the periurethral glands which spring from the urethral mucosa, and, strictly speaking, are not "prostatic" at all.

That there is a close relationship between the cells of the normal prostate and those of the carcinomatous gland is strongly suggested, as pointed out by Huggins, by the behaviour of the enzymes called "phosphatases." These enzymes have the ability to split phosphoric acid off from organic phosphoric esters, and appear to be important in the formation and destruction of bone, glycolysis, etc. Kutscher and Wolbergs found these substances in much larger amounts in the normal adult prostate than in any other tissue of the human body, although the significance of this observation is not known. They are not present in appreciable amounts in the prepuberal prostate, unless it is first stimulated by the injection of testosterone propionate, when adult levels are attained. The phosphatases are elaborated by the acinar epithelium of the prostate, (Gomori) and occur in large amounts in the prostatic

fluid (Dmochowski).

The Gutmans and Sproul found them in high concentration in the carcinomatous prostate, and in metastases therefrom; Gutman, Barringer and Woodard, and Huggins all found the phosphatases of the blood serum increased in the presence of metastases to bone from the prostate, although not in every case. It is customary to distinguish "acid" from "alkaline" phosphatases, according to the pH of the medium on which the enzymes are most active. It has been found that the increase of the "acid" phosphatase is most constant and most significant in the serum of patients with metastases from prostatic cancer. Dean believes that the serum acid phosphatase does not increase until the carcinoma has broken through the prostatic capsule. For practical purposes, one may regard a definite and sustained elevation of the acid serum phosphatase as diagnostic of prostatic carcinoma with metastases.

The "alkaline" phosphatases also are usually increased in prostatic cancer, but may vary with other diseases of bone. Woodard and her coworkers state that alkaline phosphatase is produced in excess by bone as part of a defense mechanism, which is evoked by a variety of stimuli, such as deficiencies of calcium and phosphorus (rickets), increased excretion thereof (hyperparathyroidism), or by injury from primary or metastatic tumors.

The serum phosphatase levels are normal in benign hypertrophy of the prostate, and in normal adult males, Sullivan and the Gutmans have recently reviewed their experience with the phosphatases and have concluded that a rise of the acid component of the enzyme above four modified Bodansky units\* is highly suggestive of

\*The laboratory of the University Hospitals reports the phosphatases in terms of King-Armstrong units, the upper limit of normal being 4 for the acid and 8 for the alkaline component.

the presence of metastatic carcinoma of the prostate, while Huggins regards levels above ten King-Armstrong units as practically diagnostic. At present, however, it is advisable to regard minor alterations in the level of the acid phosphatase merely as interesting and suggestive unless coupled with other unmistakable evidence, such as definite metastases to bone in the X-ray, or a positive biopsy. They are especially helpful in the presence of suspected prostatic carcinoma with doubtful changes in the bones on X-ray. One must remember that the phosphatase level may be normal in the presence of carcinoma of the prostate with metastases (15 per cent of 130 cases - Sullivan and the Gutmans). Presumably the individual cells in these cases are anaplastic and do not form phosphatase. In such cases, when there is doubt as to the diagnosis, the same authors have seen the acid phosphatase rise rapidly after the administration of 25 milligrams of testosterone propionate daily for five days. They have designated this a "provocative test," and have suggested that it may be helpful, since testosterone does not cause a rise of serum phosphatase in the normal adult male.

Impressed by the resemblance between the normal and the cancerous prostatic cells as evidence by phosphatase formation, and mindful of the effect of castration upon the normal cell (simple atrophy), Huggins tried the effect of castration upon carcinoma of the prostate. Of his first 19 cases 71 per cent experienced striking improvement in the form of relief of pain from metastases, amelioration of urinary symptoms, softening and shrinkage of the prostate itself, and a return toward normal of the phosphatase levels, especially of the acid component. These beneficial effects had, at last reports, been sustained for as long as thirty months in some instances. In all successful cases, there was a gain in weight and a distinct improvement in general condition. A few had hot flashes and edema of the ankles of uncertain origin. Metastases to bone at first became denser

and more conspicuous, then tended, in some patients, to fade. Compression myelitis from metastases to the spinal cord has disappeared. Alyea and Henderson, Nesbit and Cummings, Herbst, Chute, Sullivan and the Gutmans, Huggins, and Neuswanger have reported similar results. Dean and his coworkers, however, have observed recurrence of pain in the majority of cases after a variable number of months and Randall, who castrated five patients with carcinoma of the prostate between 1933 and 1935, was not much impressed by the resulting benefits.

The administration of testosterone propionate caused, in untreated patients, an aggravation of the signs and symptoms, and in patients previously relieved of pain by castration, a prompt recurrence. Huggins also found that effects similar to those of castration could be produced by the administration of estrogens such as alpha estradiol or stilbestrol and that, in some cases in which the acid phosphatase had been but little reduced by castration, a fall followed the administration of estrogens.

Since, in patients who were not relieved by castration, the acid phosphatase either did not fall or at least did not return to normal, Huggins concluded that the failure to obtain relief was due to the formation of male hormones (or of closely allied compounds), by extragenital foci, such as the adrenal glands.

Satterthwaite and his coworkers have noted that the fall in the urinary excretion of the 17 ketosteroids\* after castration was greatest in the successful, and least in the unsuccessful cases.

\*The 17 ketosteroids are steroids which have the ketone or oxygen group in the 17 position, and which exhibit androgenic activity. Some doubtless come from the adrenal, others from the testis. It is, at present, impossible to make any definite statements concerning their origin, nor concerning the significance of variations in their excretion.

Dean found that the urinary prolans usually increased after castration of patients with carcinoma of the prostate, while the excretion of the 17 ketosteroids was variable; they rose in 11 of 17 cases castrated. He also found, interestingly enough, that the administration of estrogens to intact patients with prostatic cancer suppressed the excretion both of the prolans and of the 17 ketosteroids. This is in line with the experimental observations of Moore and Price, and of Myers, Leonard, and Risaw.

If Dean's observations are verified by other workers, they may be interpreted liberally to mean that no patient should be castrated for carcinoma of the prostate until the estrogens have been given a thorough trial, since their failure to stimulate the hypophysis may conceivably prevent that elaboration of male hormones by extragenital foci which Huggins believed to be responsible for failure in certain cases. Another possible inference is that the patient should be given estrogens until the acid phosphatase falls, then castrated, the therapy with estrogens then being continued indefinitely in the hope of preventing stimulation of the adrenals by preventing the overactivity of the hypophysis which ordinarily follows castration. Additional studies on the excretion of prolans and the male sex hormones after castration, estrogen administration, and combinations thereof, are needed. Selye's observation that estrogen given to male rats caused hyperplasia of the adrenals suggests the possibility that estrogen administration may, in the long run, defeat itself as a therapeutic measure.

Munger has thought that heavy irradiation of the testicles produces beneficial effects similar to those of castration and of estrogen administration, but this seems a roundabout and uncertain method when compared to the other two.

Herbst, Kearns and his coworkers, Chute, Weller, Wishard, and Dean have reported their results from the treatment

of prostatic cancer with estrogens. Although, except for Dean and Chute, they have not made experimental studies comparable with Huggins', their clinical results have been good, both with estradiol, alpha estradiol, ethinyl estradiol, and with stilbestrol. Chute believes that the administration of estrogens following castration hastens the disappearance of symptoms.

Therapy with the estrogens in the male is a form of non-surgical castration. It is not entirely clear whether it works by "neutralizing" the male hormone or by suppressing the anterior pituitary so that the testes simply stop secreting androgens. Dean's evidence favors the latter view, as do the experimental observations previously cited, that estrogens suppress the activity of the anterior lobe. Impotence regularly occurs with sufficient doses, and Heckel has reported the disappearance of sperm from the semen, and of spermatogenesis as evidenced by aspirator biopsy of the testes. The enlargement and tenderness of the breast and nipple which often occurs is well known, and Herbst has excised such a breast and has described hypertrophy and hyperplasia of the glandular and erectile tissue, so that the whole structure closely resembles that of the female organ. While it is true that estrogens have some carcinogenic potency in huge doses in the experimental animal, this does not seem important if one confines their use to frankly inoperable prostatic cancer, more especially since the effective clinical dose is minute compared to the experimental carcinogenic dose.

The changes which follow the administration of estrogens to patients with carcinoma of the prostate resemble those which result from castration both as to the patient's general state, relief of pain, regression of metastases, fall in the serum acid phosphatase, and softening and shrinkage of the prostate. This last effect appears very slowly, and is often inconspicuous, at least in the first year. Heckel and Kretschmer, and Shenken, Burns, Kahle have taken tissue from the carcinomatous prostate before and some time after prolonged treatment with stilbestrol, and

have demonstrated very striking degenerative changes in the malignant cells. Herbst observed a case in which diabetes improved so much during treatment of prostatic carcinoma with stilbestrol that insulin, although previously necessary, could be discontinued.

Estrogen therapy has an advantage over castration in that it produces no feeling of loss comparable with that which follows castration. So many old men object to losing their testicles that several surgeons (Huggins, Chute et al, Hess) have resorted to intracapsular orchidectomy, which leaves the tunica albuginea and the tunica vaginalis. Patients are told that "a part of each testicle" is to be removed. The resulting scar and hydrocele give a false impression to their possessor. The use of estrogens, and particularly of stilbestrol by mouth, removes the necessity for any deception. Moreover, the stilbestrol is cheap and, unlike alpha estradiol, does not need to be administered by a second person.

Many women are unable to take stilbestrol because of nausea, which is apparently of central origin. Men are less sensitive, and most patients experience little or no discomfort if they take the drug in a single dose at bedtime.

The average effective dose is three milligrams, the extremes being one-half to ten. Once the desired effect has been secured, it seems wise to reduce the dose to the lowest level which keeps the patient comfortable. Chute observed a rapid effect, with relief of urinary retention in 9 of 12 cases, from 10 milligrams a day for ten days, after which 3 milligrams are given daily.

For those who cannot tolerate oral stilbestrol or who forget to take it, alpha estradiol or stilbestrol may be given intramuscularly in oil, although the need for a weekly or twice weekly injection throughout life is very objectionable. Here one should consider castration unless the sterile 10 milligram pellets of alpha estradiol advocated by Kearns become commercially available.



Forty milligrams inserted beneath the skin with Kearns' implant cause no disability, and the effect will last for from four to six weeks. Kearns has also reported success from ethinyl estradiol 0.2 milligrams daily by mouth in patients who are intolerant to stilbestrol.

One real disadvantage of oral therapy with stilbestrol is that the patient may discontinue the drug when his symptoms have disappeared, and then fail to return until they have again become severe.

If obstruction to urination is conspicuous, transurethral resection should precede castration or stilbestrol because their effect upon the prostate is very slow and often quite incomplete; resection will save the patient much discomfort and inconvenience.

- - -

### Case Reports

Case 1.                      aged 70, was admitted in May 1941 with complete urinary retention due to an obvious carcinoma of the prostate. Complete relief followed transurethral resection. In October, he returned with pain in the right groin and a large, hard, spherical tumor in the right upper thigh. Aspiration biopsy demonstrated that this had the same structure as the original tumor in the prostate. Urinary symptoms were absent.

The subarachnoid injection of alcohol was without effect. Cordotomy was followed by retention of urine, and transurethral resection had to be repeated. The patient left the hospital on November 15, 1941, still having pain in the groin, and feeling very weak.

Stilbestrol, 3 milligrams daily was started at my request by his physician, Dr. A. P. Goblirsch, on December 15, 1941. Improvement was rapid. On December 1, 1942, urinary symptoms were absent. The patient had no pain except on exertion, and this was not sufficient to require even aspirin. The general condition was excellent. The tumor in the

thigh was scarcely palpable. The prostate was small, smooth, and hard. Future developments are awaited with great interest.

Case 2.                      aged 57, had become incapacitated by severe pain in the distribution of the left sciatic nerve. It had come on gradually over many months, and was associated with weight loss, weakness, mild obstruction to urination, and severe constipation. The prostate was enlarged grade 2, hard, nodular, and fixed. A large infiltration of the seminal vesicles almost closed the rectum. X-ray disclosed multiple metastases in the pelvis. The acid serum phosphatase on November 22, 1941 was 27, and the alkaline 22.5.

On November 22, 1941 stilbestrol, 3 milligrams daily by mouth was started, and was supplemented by 10 milligrams intramuscularly twice weekly for two weeks. Improvement was gradual but very gratifying; first the constipation and then the pain disappeared. The acid phosphatase on January 23, 1942 was 9.6 and the alkaline 18.4.

When last seen in November 1942, one year after treatment was started, the patient had long since regained his lost weight, and pain was absent except when he leaned too far out the second story window in putting on the storm windows. Urinary symptoms were minimal. The prostate and seminal vesicles were much smaller but still hard. The acid phosphatase was 2.3 and the alkaline 12.7. X-ray of the pelvis showed unmistakable regression of the metastases.

Case 3.                      , aged 66, was first seen in the outpatient clinic in February 1942 complaining of mild obstruction to urination and rather severe pain in the sacroiliac and sciatic areas. The general state was good. The prostate was small, smooth, and hard. X-rays of the lumbar spine and pelvis were negative for metastases. The acid serum phosphatase was 96 and the alkaline 68.

For some obscure reason the patient went home, and was not seen again until December 17, 1942, when he was admitted because of urinary retention which followed profuse bleeding. He was emaciated and uremic, and the serum phosphatase values were: acid 185; alkaline 102. X-ray revealed extensive osteoblastic metastases in the spine and pelvis, a fact which, when coupled with the acid phosphatase level of February 1942, suggests that metastases to bone were present but not recognizable at that time.

Catheter drainage was instituted, fluids were forced, and stilbestrol was given in daily 5 milligram doses. Forty milligrams of alpha estradiol were inserted on December 21, 1942 with Kearns' implanter. The following table shows the rapid and striking effect of the estrogens upon the serum phosphatase.

Date	Acid	Alkaline
12-18-42	185.0	-
12-21-42	60.0	-
12-28-42	4.9	102.0
12-30-42	9.3	91.0
1-4-43	4.4	54.2
1-8-43	2.92	54.7
1-10-43	4.0	56.0
1-13-43	3.5	48.3
1-15-43	4.1	41.0
1-18-43	3.8	43.6
1-20-43	4.0	34.0
1-22-43	2.2	34.0
1-25-43	3.4	35.8
1-27-43	2.6	33.2

Retention of urine persisted and, since the general state was poor, trocar cystostomy was done on December 30th. He improved so rapidly thereafter that trans-urethral resection was done on January 18, 1943 (unwisely as it turned out). The patient died on January 29, and autopsy revealed an extensive, if unsuspected, bronchopneumonia as the cause of death.

This case is cited simply as an example of the rate at which the serum phosphatase may fall under the influence of the estrogens.

### Comment

These three patients have been selected from seventy-five who have been or are under treatment. The results have, in the main, been excellent in that pain has been alleviated or has disappeared, urinary obstruction of mild degree has diminished and the general state has improved strikingly in most cases. The behaviour of the phosphatase has resembled that seen following castration. The prostate itself has been slow to shrink and soften, and I have yet to see a patient in which its consistency has become normal. It is, of course, too soon (and the series of cases too small) to permit one to say how many patients with carcinoma of the prostate can be made comfortable, and for how long a time, by the administration of estrogens, but enough evidence has accumulated to permit one to say very definitely that the method is a great boon to large numbers of old men, and that too much credit cannot be given to its originator, C. B. Higgins, of the University of Chicago.

My own experience has been such as to make me wonder whether, as experience accumulates, there will not be an increasing tendency to abandon castration in favor of estrogens. Time and observation alone will tell.

### Summary and Conclusions

1. Carcinoma of the prostate is increasing in frequency due to aging of the population.
2. Under present conditions, only three to four per cent are amenable to cure by Young's radical perineal prostatectomy.
3. Striking palliation can be had in many cases, particularly in relieving pain and causing regression of the neoplasm; from castration and from the administration of estrogens.
4. The administration of estrogens constitutes non-surgical and reversible castration, and is not followed by

the psychic disturbances which castration may produce.

5. One is justified in suspecting that the results of estrogen therapy are at least as good as those of castration, and may even prove to be better in some respects.

6. More investigation is needed.

#### Bibliography

1. Alyea, E. P. and Henderson, A. F.  
Carcinoma of the prostate; immediate response to bilateral orchidectomy.  
J.A.M.A. 120:1099-1102, '42.
2. Baron, E. and Angrist, A.  
Incidence of occult adenocarcinoma of prostate after fifty years of age.  
Arch. Path. 32:787-793, '41.
3. Barringer, B. S.  
Prostatic carcinoma.  
J. Urol., 33:616-620, '35.
4. Barringer, B. S. and Woodard, H. Q.  
Prostatic carcinoma with extensive intraprostatic calcification.  
Tr. Am. Assn. G.U. Surg., 21:363, '38.
5. Berthold, A. A.  
Transplantation der Hoden.  
Arch. f. Anat. u. Physiol. 1840, p.42.
6. Bumpus, H. C.  
Clinical study of 1000 cases of carcinoma of the prostate.  
Surg., Gynec., & Obst. 43:150-155, '26.
7. Carcinoma of the prostate.  
(Editorial) J.A.M.A. 119:950-951, '42.
8. Chute, R., Willetts, A. T. and Gens, J.P.  
Experiences in treatment of carcinoma of the prostate by castration and stilbestrol.  
J. Urol. 48:682-692, '43.
9. Colston, J. A. C. and Lewis, L. G.  
Carcinoma of the prostate, a clinical and pathological study.  
South. M. J. 25:696-700, '32.
10. Dean, A. L., Woodard, H. Q., and Twombly, G. H.  
The endocrine treatment of cancers of the prostate.  
J. Urol., 49:108-117, '43.
11. Dmochowski, A.  
Siers les phosphatases, d l'urine.  
Compt. read. Soc. de biol., 113: 956-957, '33.
12. Duff, J.  
Cancer mortality, bladder, kidney, and prostate, 1917-1928.  
J. Urol., 32:346-353, '34.
13. Engle, E. T.  
The effect of daily transplants of anterior lobe from gonadectomized rats on immature test animals.  
Am.J.Physiol., 88:101, '29.
14. Evans, H. M., and Simpson, M. E.  
Comparison of hypophyseal implants from normal and gonadectomized animals.  
Am.J.Physiol., 89:371, '29.
15. Gomori, G.  
Distribution of acid phosphatase in the tissues.  
Arch. Path., 32:189-199, '41.
16. Gutman, A. B. and Gutman, E. B.  
An "acid" phosphatase occurring in the serum of patients with metastasizing carcinoma of the prostate gland.  
J. Clin. Invest., 17:473, '38.
17. Gutman, E. B., Sproul, E. E. and Gutman, A. B.  
Significance of increased phosphatase activity of bone at site of osteoblastic metastases secondary to carcinoma of prostate gland.  
Am.J.Cancer 28:485, '36.
18. Gutman, A. B.  
Serum "acid" phosphatase in patients with carcinoma of the prostate gland.  
J.A.M.A., 120:1112-16, '42.

19. Heckel, N. J. and Steinmetz, C. R.  
The effect of female sex hormone on  
the function of the human testes.  
J. Urol., 116:319-321, '41.
20. Herbst, W. P.  
The effect of estradiol dipropionate  
and diethylstilbestrol on malignant  
prostatic tissue.  
Tr. Am. Assn. G.U. Surg., 35:195-202,  
'41.
21. Herbst, W. P.  
Biochemical therapeutics in carcinoma  
of the prostate gland.  
J.A.M.A. 120:1116-1120, '42.
22. Herger, C. C. and Sauer, H. R.  
Further observations on the serum  
acid phosphatase activity in car-  
cinoma of the prostate.  
J. Urol., 46:286-302, Aug. '41.
23. Hess, E.  
Technique for castration in carcinoma  
of the prostate.  
J. Urol., 48:703-705, '43.
24. Higgins, C. C., and Gosse, C. L.  
Present status of castration for  
carcinoma of the prostate.  
Cleveland Clin. Quart., 9:80-86,  
April '42.
25. Huggins, C. B. and Hodges, C. V.  
Studies in prostatic cancer.  
Cancer Res., 1:293-297, '41.
26. Huggins, C. B. and Stevens, R. E.  
The effects of castration on ad-  
vanced cancer of the prostate gland.  
Arch. Surg., 43:209-223, '41.
27. Huggins, C., Scott, W. W. and  
Hodges, C. V.  
Studies on prostatic cancer III.  
J. Urol., 46:997-1006, '41.
28. Kearns, W. A., Bruskewitz, H. W., and  
Flaherty, W. A.  
Treatment of carcinoma of the pro-  
state with estrogens.  
Wis. M. J., 41:575-581, July '42.
29. Kutscher, W., and Wolbergs, H.  
Prostataphosphatase.  
Ztschr.f.physiol.chem.236-237, '35.
30. Meyer, R. K., Leonard, S. L.,  
Hisaw, F. L. and Martin, S. J.  
The influence of estrin on the  
gonad stimulating complex of the  
anterior pituitary of castrated  
male and female rats.  
Endocrinol., 16:655, '32.
31. Moore, C. R.  
The testis hormone, in Glandular  
Physiology and Therapy.  
A.M.A. Press, Chicago, '32.
32. Moore, R. A.  
Morphology of small prostatic  
carcinoma.  
J. Urol. 33:224, '35.
33. Moore, C. R., and Gallagher, T. F.  
On the prevention of castration  
effects in mammals by testis ex-  
tract injection.  
Am.J.Physiol. 89:388, '29.
34. Moore, C. R. and Price, D.  
Gonad hormone functions and the  
reciprocal influence between gonads  
and hypophysis.  
Am.J.Anat., 50:13-71, '32.
35. Motz, B., and Perearnau  
Contribution a l'etude de L'revolu-  
tion de l'hypertrophie de la pro-  
state.  
Ann. d. mal. des org. g.u., 33:  
1521-1548, '05.
36. Munger, A. D.  
Experiences in the treatment of car-  
cinoma of the prostate with irradia-  
tion of the testicles.  
J. Urol., 46:1007-1011, '41.
37. Nesbit, R. M. and Cummings, R. H.  
Prostatic carcinoma treated by  
orchidectomy.  
J.A.M.A., 120:1109-1111, '42.
38. Neuswanger, C. H.  
Discussion. J. Urol., 48:594-597,  
'43.
39. Randall, A.  
Eight year results of castration for  
carcinoma of the prostate.  
J. Urol., 48:706-709, '43.

40. Satterthwaite, R. W., Hill, J. H., and Packard, E. F.  
Experimental and clinical evidence of the role of the 17 ketosteroids in prostatic carcinoma.  
J. Urol., 46:1149-1154, '41.
41. Selye, H.  
Compensatory atrophy of the adrenals.  
J.A.M.A., 115:2246-2252, '40.
42. Shenken, J. R., Burns, E. L., and Kahle, P. J.  
The effect of diethylstilbestrol and diethylstilbestrol dipropionate on carcinoma of the prostate. II. Cytological changes following treatment.  
J. Urol., 48:99-112, July '42.
43. Smith, P. E.  
The effect upon the reproductive system of ablation and implantation of the anterior hypophysis, in "Sex and the Internal Secretions," Williams and Wilkins, Baltimore, '34, p. 748.
44. Sullivan, T. J., Gutman, A. B., and Gutman, E. B.  
Theory and application of serum "acid" phosphatase determination in metastasizing prostatic carcinoma.  
J. Urol., 48:426-458, '42.
45. Tandler, J. and Grosz, S.  
Ueber den Einfluss der Kastration auf den Organismus.  
Arch. f. Entwicklungsmech d. Organ., 30:236, '08.
46. Weller, C. G.  
Discussion.  
J. Urol., 48:699-700, '43.
47. Wells, L. J. and Overholser, M. D.  
Sperm formation and growth of accessory reproductive organs in hypophysectomized ground squirrels.  
Anat. Rec., 72:231-243, '38.
48. Wishard, W. N. Jr.  
The clinical use of stilbestrol in the treatment of carcinoma of the prostate.  
Quart. Bull. Indiana Univ. Med. Center, 4:5-9, '42.
49. Woodard, H. Q. and Craver, L. F.  
Serum phosphatase in the lymphomatoid diseases.  
J. Clin. Invest., 19:1-7, '40.
50. Woodard, H. Q., and Kenney, J. M.  
The relation of phosphatase activity in bone tumors to the deposition of radioactive phosphorus.  
Am. J. Roent. & Rad. Therapy, 47:227-242, '42.
51. Young, H. H.  
The radical cure of cancer of the prostate.  
Surg., Gynec., and Obst., 64:472-84, '37.

IV. GOSSIP

The bulletin of the Hennepin County Medical Society has a startling account of the needs of the armed forces for physicians during the present year. The editor points out that most of the men will be obtained from the Twin Cities as the other sections of the state cannot spare many more men. Minnesota will not be asked to carry any other state's burden so that there will be no opportunity for relief from some other sector. In a word, if every available physician under 45 went into service the number would be inadequate. A certain number have been declared essential at our places and in other institutions. Physical defects account for more who cannot go. The only way the deficit can be made up is by taking older men. The demand for nurses is equally great and all recruiting will now be done through the medium of the American Red Cross. They are asking Minnesota for 900 nurses which means that Minneapolis will have to supply about 40 a month. As all the student nurses are already in the enlisted reserve the number must come from graduates. Inactive nurses must return to duty and more nurses' aids must be trained. These lay volunteers replace nurses in the ratio of 8 volunteers for every nurse, which gives you some idea of how much the program will have to be stepped up. Final word as to the fate of the medical students has been received. They will resign their commissions and go into service. They will be assigned here and their expenses paid by Uncle Sam. They will not be compelled to live in dormitories or other public buildings unless they are already doing so. This is the last word which has been received but it may be changed. This is meeting week in Chicago. Every hospital, medical, and public health organization is having organization meetings at this time. The council on medical education and hospitals will meet on Monday of next week. In every instance military and civilian problems are up for discussion. Sunday, February 14, the national conference on medical service will hold its 17th annual meeting. Discussion will be concerned with an analysis of current trends in the control of medicine and medicine in the post-war era. This meeting is the

outgrowth of a conference which started in Minnesota. It was held here annually and attracted such wide attention that it was decided to make it a central gathering and hold it in Chicago. One of the subjects of special interest will be the return of the medical officer to private practice. In World War #1 this was accompanied by many aches and pains. Out of it grew an enormous interest in graduate training and places were at a premium. Medical men contemplating graduate training at some distant date should make application now. Most people see greater increase in benefits to war veterans, extension of social security, and expansion of public health. Control of medical education in post-war days is also an interesting subject for speculation. W. L. Burnap, of Fergus Falls, is secretary of the national council on medical service. An interesting letter came from Alex Blumstein, now in the army. One half of the page was letter and one half was p.s. As a psychiatrist he should know the significance of a long p.s. He states "no special news. I do the same kind of work I have always done, - minus the female customers, but this will soon be remedied for the WAACs are coming." He wishes to be remembered to everyone. Alex has been missed. He was one of the most helpful staff men to patients and other staff men that this institution has ever had. Unofficial news channels tell us that his present commanding officer feels the same way about him. A letter just came in asking for a physical examination. This man states he is prepared to pay cash for the procedure. Any offers? This is rheumatic fever month. The University is cooperating with the Minnesota State Medical Association in observing the same. Rheumatic fever has become an important disease. The Metropolitan Life Insurance Company is interested in seeing what can be done through public education. They will supply each physician with special material concerning the disease and some to give to his patients. The University will offer a special course for public health nurses February 22, 23, 24, 1943. The radio talks this month will be on rheumatic fever. There will be a special hospital program on rheumatic fever. Many parents, physicians, and teachers have difficulty recognizing the disease....