

Interstitial Irradiation Therapy With a Solution of Au¹⁹⁸ as Part of Combination Therapy For Prostatic Carcinoma^{1,2}

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Prostatic carcinoma can be divided into four stages, as it is seen clinically. Stage O is a lesion which is completely limited to the prostate and is a relatively small lesion. Stage I is a lesion which invades the capsule and partially invades the areola tissue around the prostate itself and around the base of the seminal vesicles, with no evidence of lymph node or vascular metastasis. Stage II is a lesion which is larger than this with extensive invasion around the bladder neck and the base of the seminal vesicles, but again no evidence of distant metastasis. Stage III is a lesion which does have a vascular metastasis and lymph node metastasis. This clinical staging, it is to be emphasized, is subject to much correction in that recent studies indicate that approximately 5 per cent of Stage O lesions have either vascular or lymphatic lesions; that 45 per cent of Stage I and II lesions have lymphatic metastases and that 10 per cent of Stage I and II lesions have vascular metastases.

A clinical classification which has been found useful upon the basis of the study of approximately 4,000 patients with prostatic cancer is shown in Fig. 1. This emphasizes that Stage O, I and II groupings make up approximately 30 to 40 per cent of all patients who are seen clinically, although Stage O makes up 5 or less per cent of those who are seen clinically. Although those who fall into Stage O lend themselves very well to radical prostatectomy by either the perineal or retropubic approach, there are occasions when such radical surgery is not indicated and where less radical removal would be acceptable to the individual patient. Radical surgery, as usually carried out, is not successful in patients who have extension beyond the prostate itself; in other words, patients in Stage I and II in the above described classification. This is probably due to the fact that the line of dissection crosses local spread of cancer.

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During the past ten years we have had occasion to utilize interstitial irradiation as an adjunct to surgical destruction of the prostate in Stage I and II lesions and compare this with simple surgical removal of the lesion without the utilization of interstitial irradiation with Au¹⁹⁸ as adjunctive therapy. Our studies showed that such therapy is of no value in the treatment of disseminated lesions but is extremely useful in the treatment of the local lesion. It gives promise of results in about 50 per cent of Stage I and II lesions which are as good as those obtainable in Stage O lesions.

The details of the technic of administration of the interstitial irradiation have been previously described (1,2,3,4.). The methods for radiation protection described and standardized by Dr. Elkins, have worked satisfactorily in 976 patients and over 1,000 administrations of the material. The principles underlying the administration of the material are as follows: A total dosage of 100 millicuries or less is utilized to prevent local damage to adjacent tissues. A small volume, less than 2 cc, is necessary, otherwise local spread along fascial planes will lead to damage to the rectum or ureter. As the injection is carried out, one monitors the area by means of a small probe which can be sterilized or by the utilization of hypaque as the diluting material and following the distribution by x-ray films. The material may be injected either retropubically, transrectally, transperineally, or through an open perineal incision. Multiple sites of injection and repeated instillations at two-month intervals are useful to destroy residual tumor, Figs. 2-9 inclusive.

Limiting our study to the 2,864 patients with prostatic carcinoma studied prior to 1959 in order to obtain a five-year follow-up, the following results are of significance. In 57 patients who had a small, so-called "operable" lesion (Stage O), who were followed five years or more, no local recurrences were noted and apparent successful ablation of the tumor was present in 51, or 89 per cent, by radical perineal or retropubic surgery. On the other hand, in 13 patients with definite Stage II lesions, surgical removal alone, resulted in only one successful incident. On the contrary, in 44 patients with Stage II lesions who received a combination of surgery and interstitial irradiation with radioactive gold as an adjuvant, 26 apparent cures resulted. Of the 18 who had residual cancer, only two had this in the locally treated area, Table I (4). In general, addition of irra-

A. Local lesion limited to prostate, incidence, 5 to 20%

1. No node or marrow dissemination	90% of A
2. Positive nodes—no marrow	8% of A
3. Negative nodes—positive marrow	2% of A
4. Positive nodes and positive marrow	?% of A

B. Local lesion, extraprostatic invasion present, incidence, 80 to 95%

1. No node or marrow dissemination	20% of B
2. Positive nodes—no marrow	20% of B
3. Negative nodes—positive marrow	?% of B
4. Positive nodes and marrow	50% of B

Fig. 1. Suggested clinical classification as the result of lymph node and bone marrow findings. Incidence is a rough estimate. This is useful in estimating prognosis clinically.

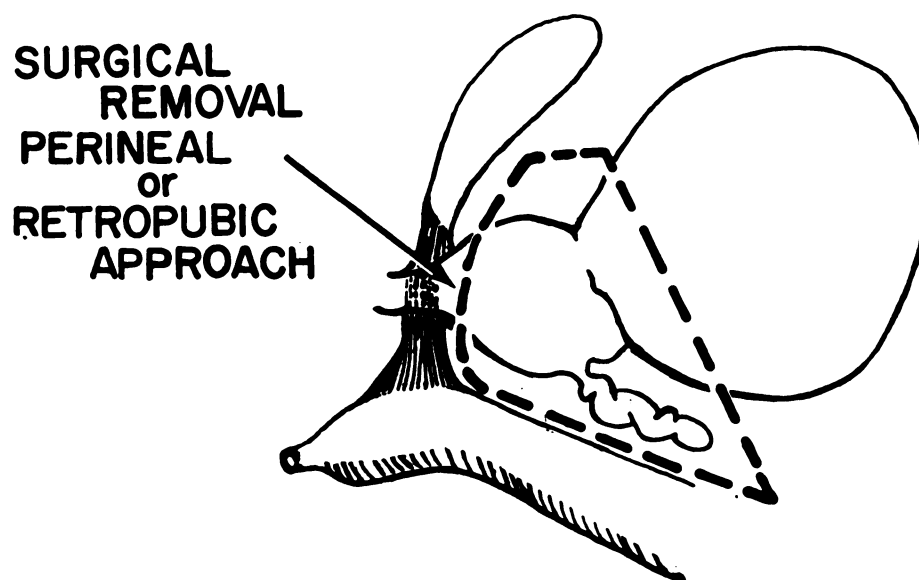


Fig. 2. There are five technics utilizing surgery, surgical cauterization with the high frequency current and interstitial irradiation that have been utilized in this series for destruction of the local lesion. These are illustrated diagrammatically as follows:

A. Classical prostateseminal-vesiculectomy through either the perineal or retropubic approach—good for very small lesions.

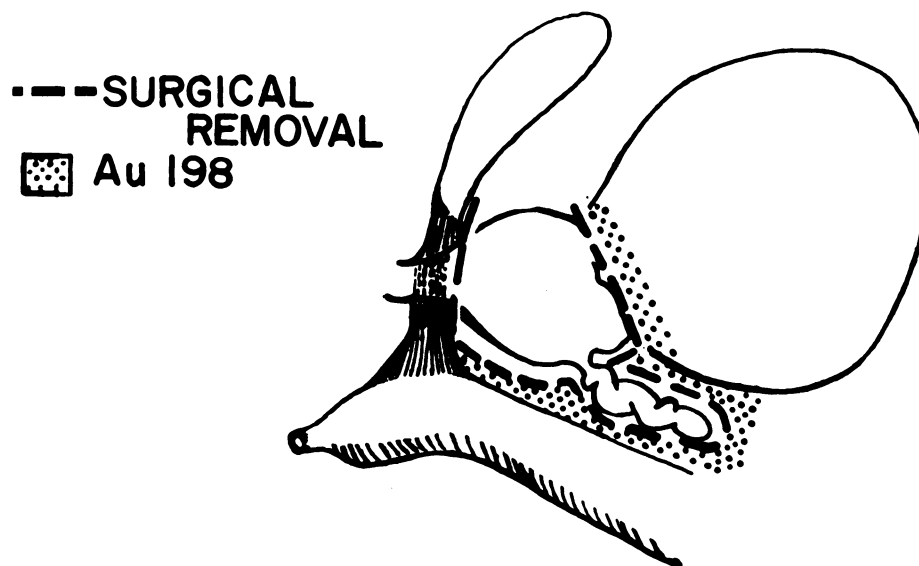


Fig. 2. B. Classical prostateseminal-vesiculectomy through the perineal or retropubic approach—Stage I or II lesion. Adjunctive use of Au^{198} decreased the incidence of local recurrence significantly.

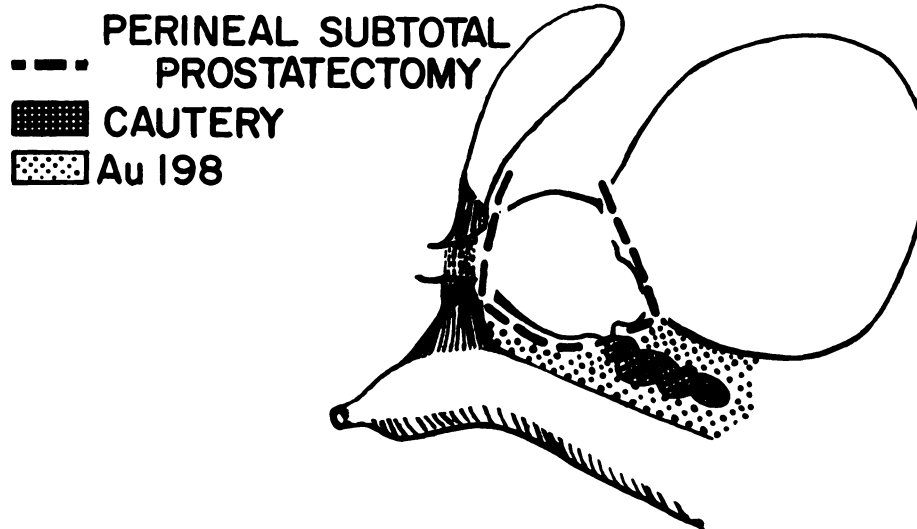


Fig. 2. C. Subtotal prostatectomy through perineal approach with adjunctive cauterization and Au¹⁹⁸—very useful in Stage II lesions with fixed seminal vesicles.

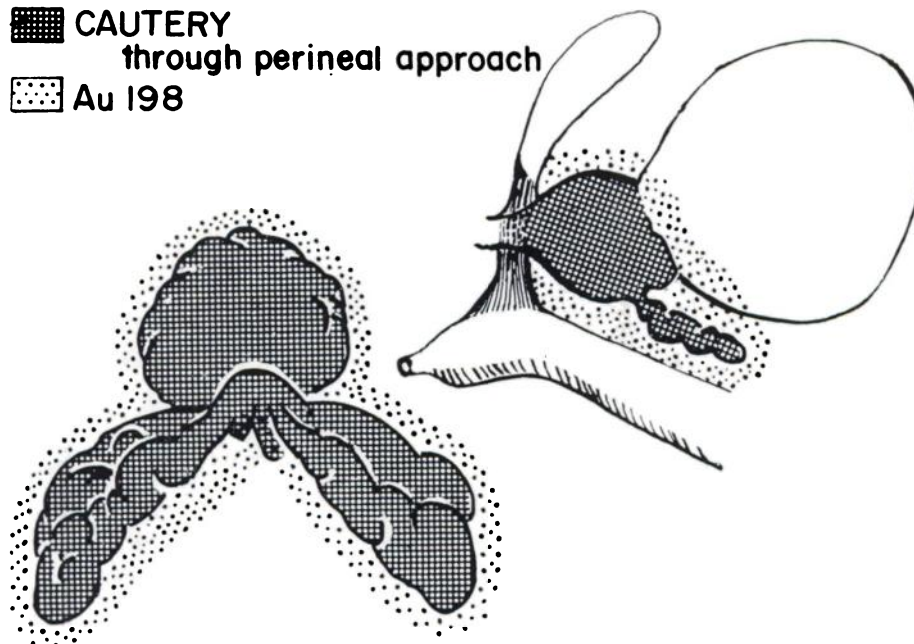


Fig. 2. D. Cauterization and adjunctive Au¹⁹⁸ in very fixed Stage II lesions—through perineal approach.

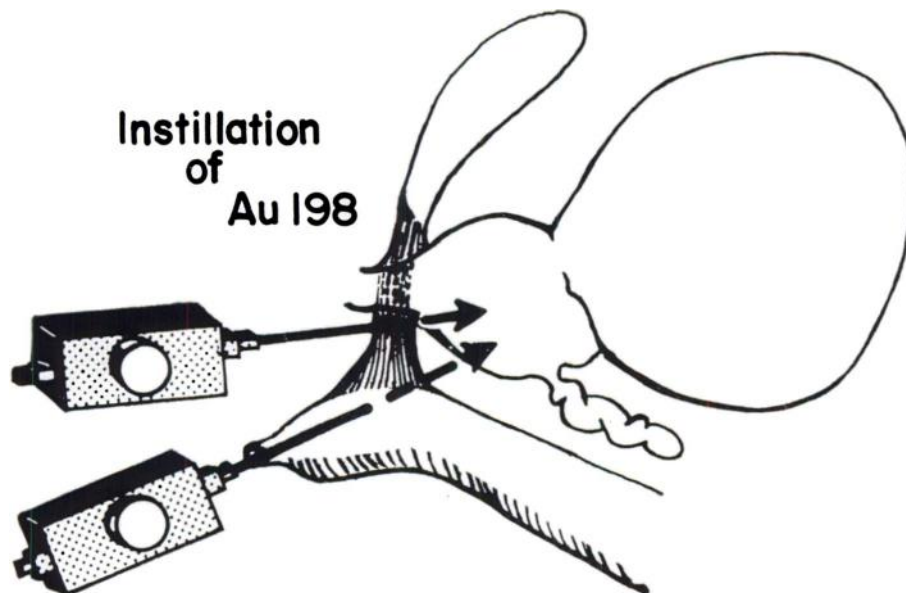


Fig. 2. E. In small but fixed lesions, Au^{198} alone utilizing either the transperineal or transrectal approach with repeat injections and radiographic control of distribution.



Fig. 3. Monitoring perineal injection by x-ray film of radiopaque material used as a diluent. Note good distribution except about nodule at base of prostate on left side. Such an area can be cauterized with high frequency current and remaining tumor can be destroyed by the combined effect of the Au^{198} emissions or more Au^{198} solution can be injected directly in the uninfiltated area.

diation therapy, altered the local lesion markedly and altered the life history of the lesions in the individual patient favorably. This is seen in Fig. 10, where 445 patients who had such combination therapy and had a five or more year follow-up are charted. During the past six years, since the above charts were compiled, 244 patients have been treated. Increasingly improved results have been obtained by the utilization of combination therapy. Complications from such radiation treatment were few and consisted essentially of delayed wound healing and occasional perineal fistula which might take many months to heal, and one case of ureteral fistula which required repair. The incidence of rectal damage was under 0.2 per cent in the last 500 patients who underwent such therapy, Table II.

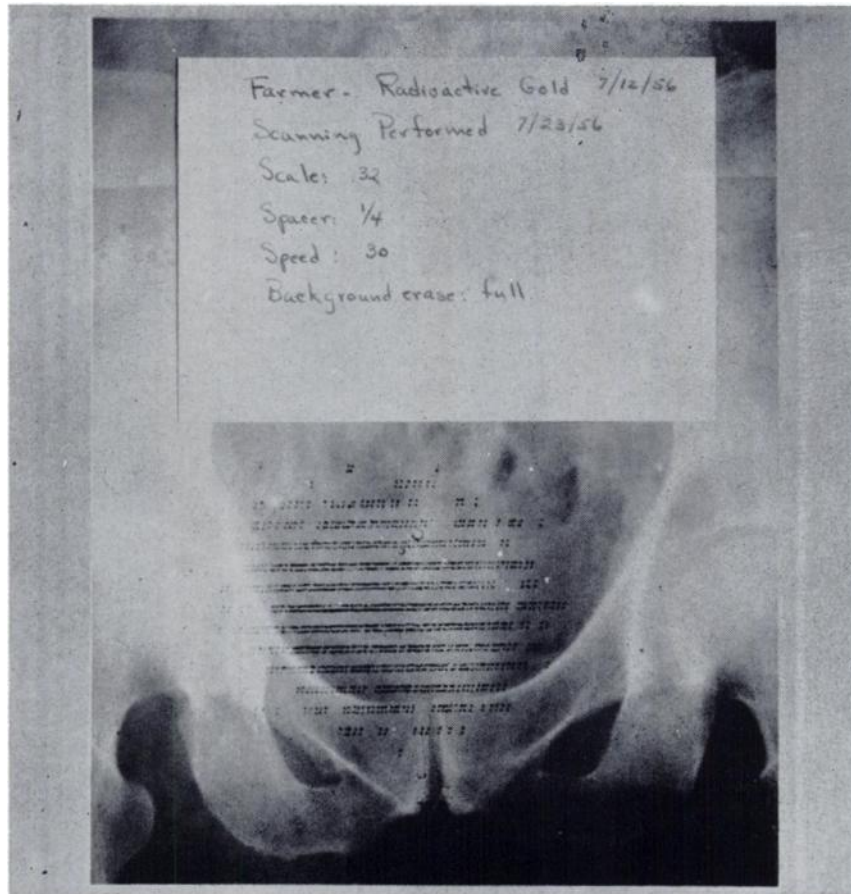
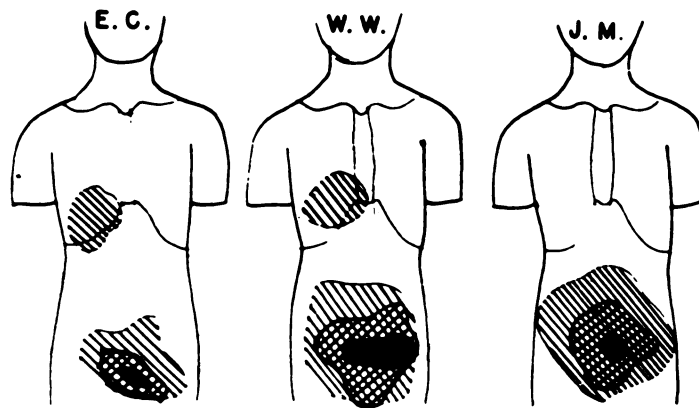


Fig. 4. Scan of prostatic area 11 days after injection of Au^{198} . Note that remaining material in local area is high.

DISTRIBUTION OF RADIOGOLD IN 3 CASES

A. After one day



B. After five days

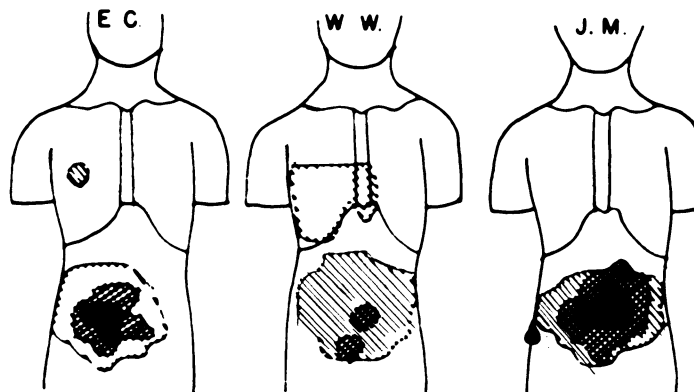


Fig. 5. Scanning studies in three patients illustrative of significant remaining irradiation in prostatic area. Black spots are the hottest areas. (Courtesy of Dr. T. Evans.)

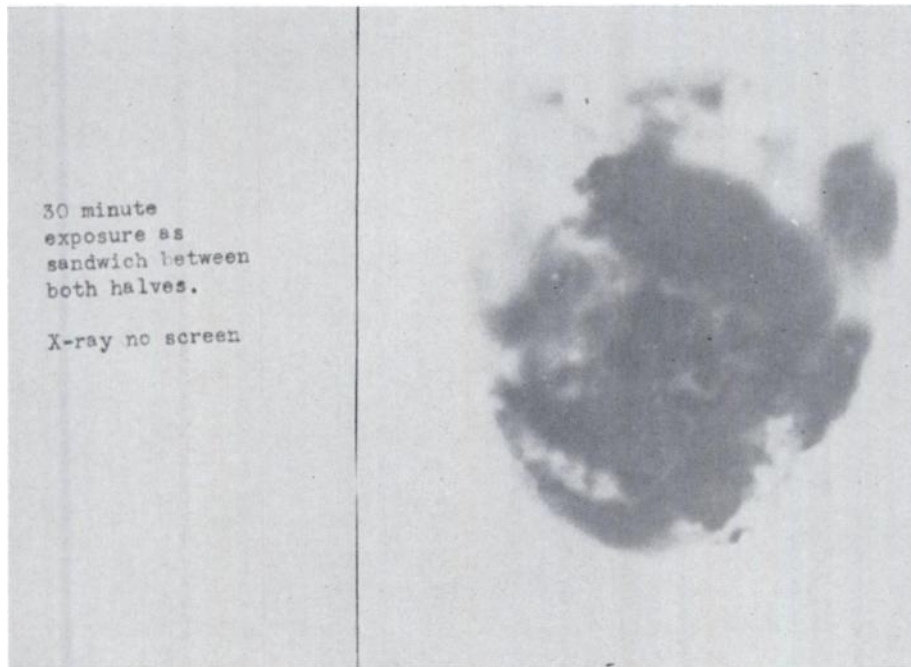


Fig. 6. Radioautograph of prostate removed after injection of 2 cc of Au^{198} solution containing 6 millicuries of Au^{198} . Note character of distribution—about 90 per cent of the activity was in the injected area. (Courtesy of Dr. T. Evans.)

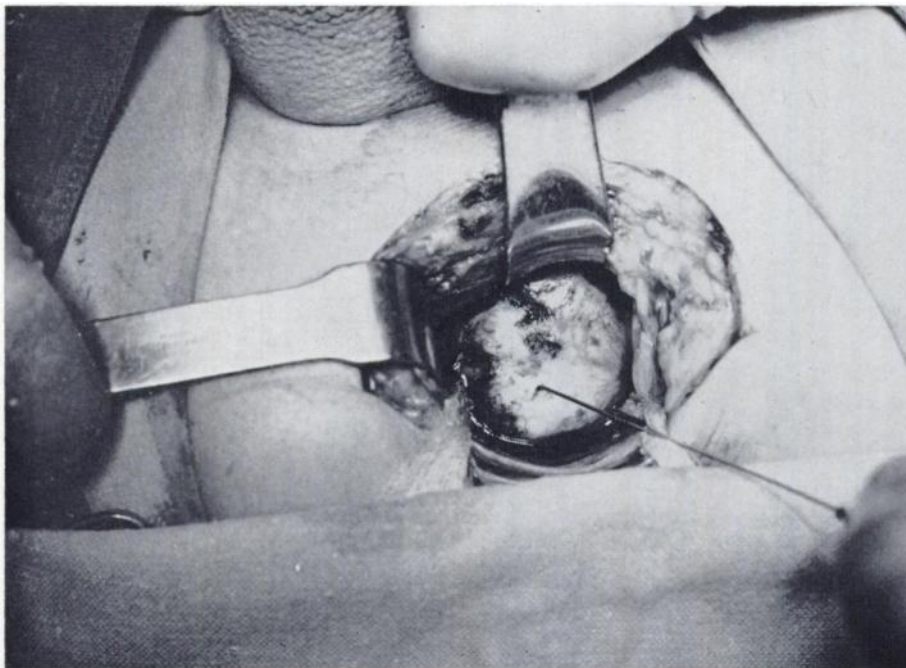


Fig. 7. Perineal exposure of prostatic cancer which is being infiltrated with Au^{198} solution.

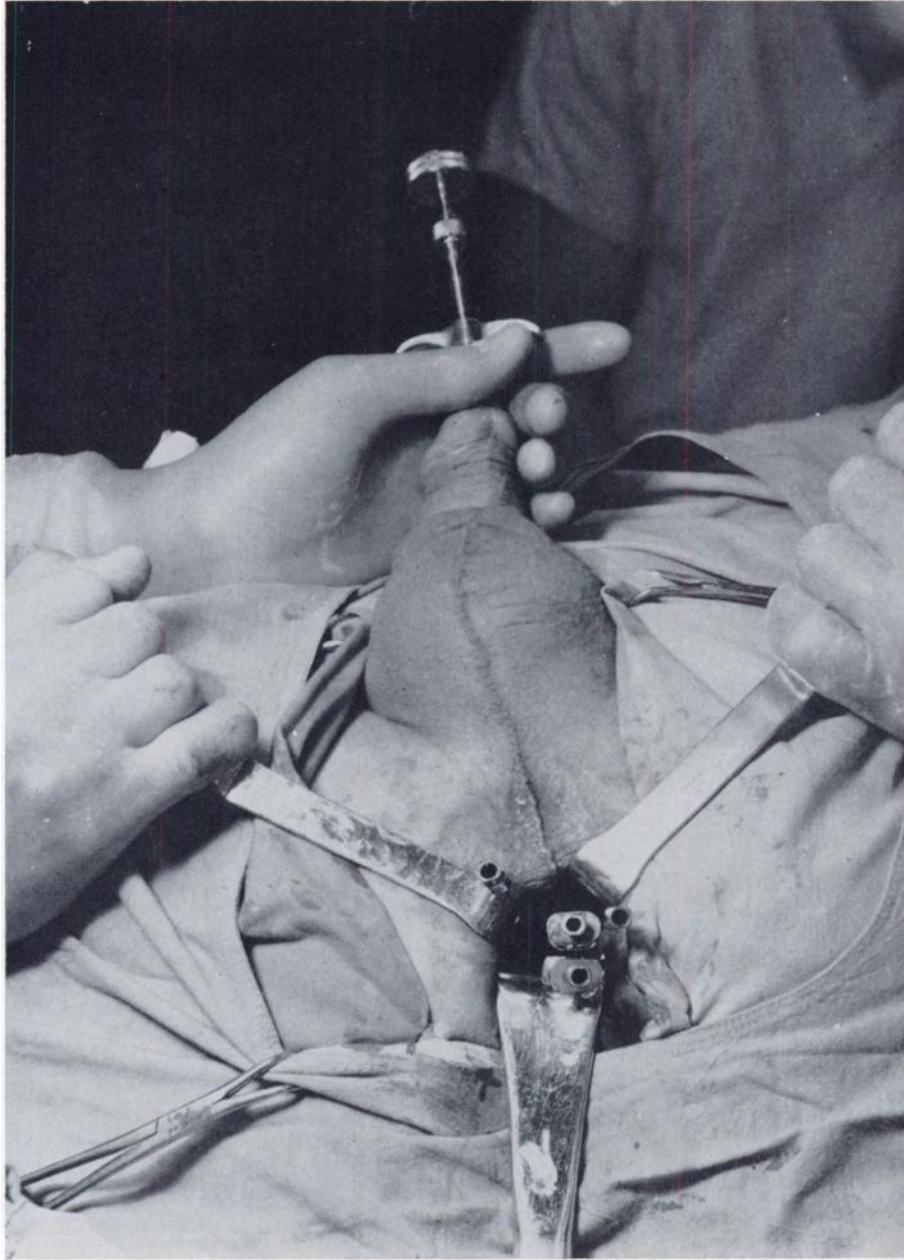


Fig. 8. Illustrative of transrectal infiltration of prostatic cancer with Au¹⁹⁸ solution. Patient is placed in the exaggerated lithotomy position and the anus dilated. Retractors in the rectum and the Lowsley tractor in the urethra bring the prostate into the field. Needles are appropriately placed to afford best injection of Au¹⁹⁸ solution.

Radical removal of pelvic lymph nodes was carried out in 44 patients with pelvic lymph node metastasis and no evidence of lymph node involvement above the bifurcation of the aorta. A ten-year follow-up in this group revealed eight patients still alive and apparently well, by a combination of radical surgery and infiltration of the entire area with Au^{198} as an adjuvant. The significance of these results needs further study.

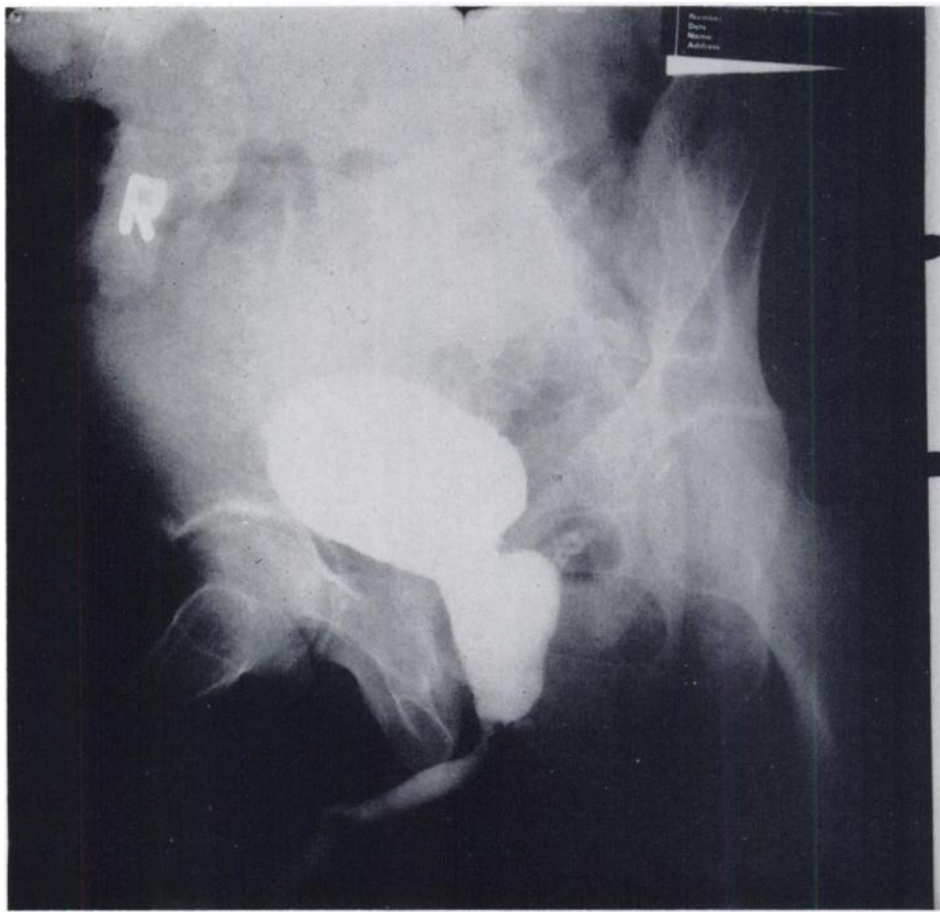


Fig. 9. Cystourethrogram of patient whose prostatic cancer had been treated by combination of cauterization and injection with 85 millicuries of Au^{198} . Note almost complete prostatectomy. Patient is well after two years. Completely continent.

The recent report of George, Carlton, Dykhuizen and Dillon (5) would seem to indicate that external irradiation of high energy, properly applied, is useful either alone or as an adjuvant in these patients. Our results were not as optimistic, Figs. 11, 12, 13. Our preliminary studies show that interstitial irradiation is more flexible and properly combined with surgery will probably give better results for the ablation of the local lesion. Judgment in the utilization of these modalities which are not mutually exclusive is necessary.

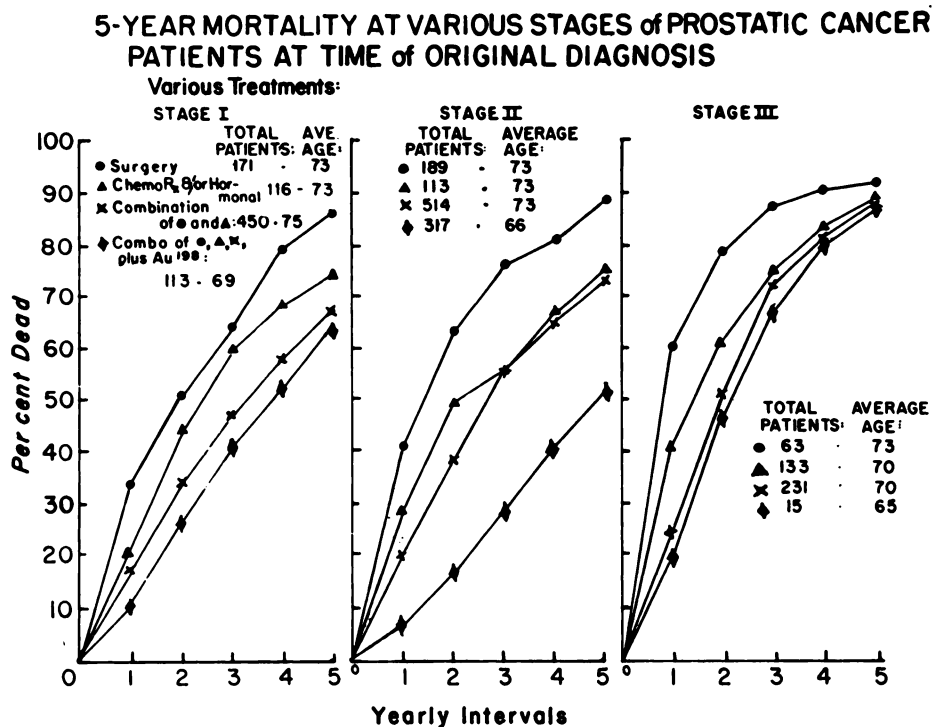


Fig. 10. Note the increased survival with the utilization of combination therapy including instillation of Au¹⁹⁸ solution. Increased survival was *not* present when metastasis were already present. A total of 850 patients in Stage I, 1,133 in Stage II and 442 in Stage III, followed for five years or more, are seen in chart. 445 of these patients received therapy with Au¹⁹⁸ all during the period 1951 to 1957 inclusive.

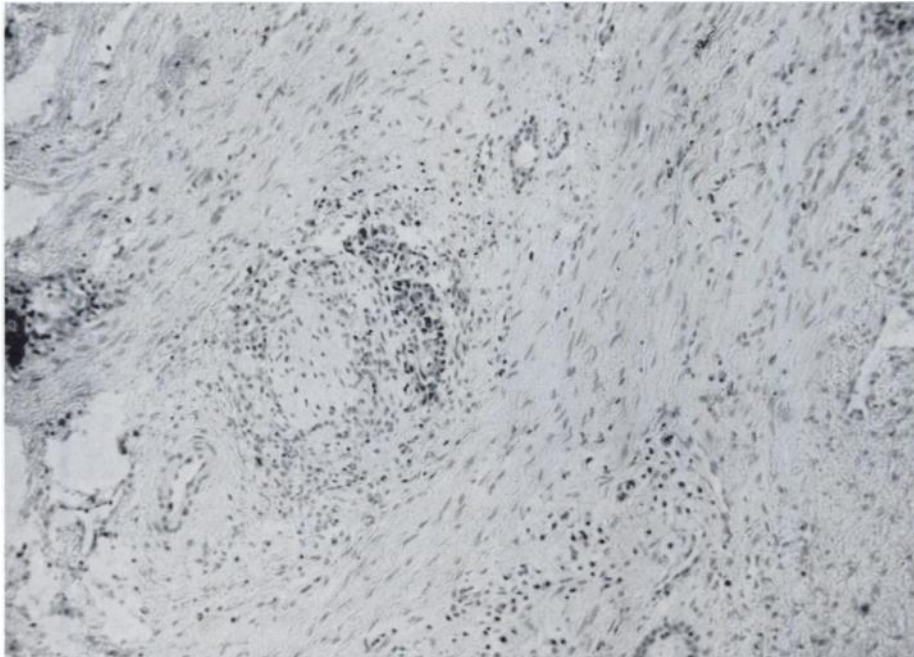


Fig. 11. The effect of cobalt therapy. 72-year-old white male with prostatic cancer. A appearance before therapy. B. appearance after 4,508 r Co_{60} therapy. No residual carcinoma seen.

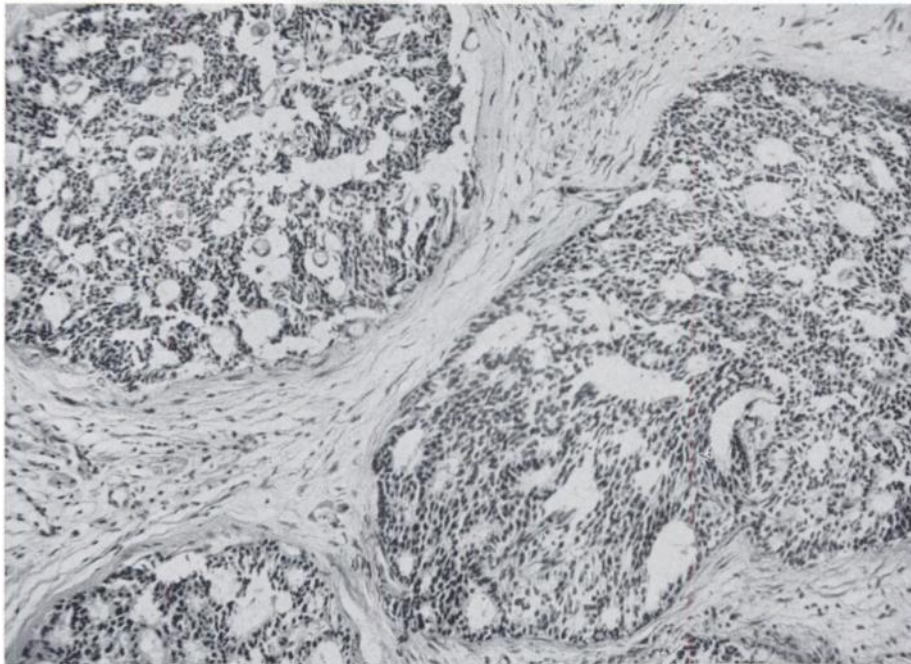


Fig. 12. The effect of cobalt therapy. A 71-year-old white male with prostatic cancer. 4,000 r Co₆₀ given in November, 1963. A—is microscopic appearance before therapy.

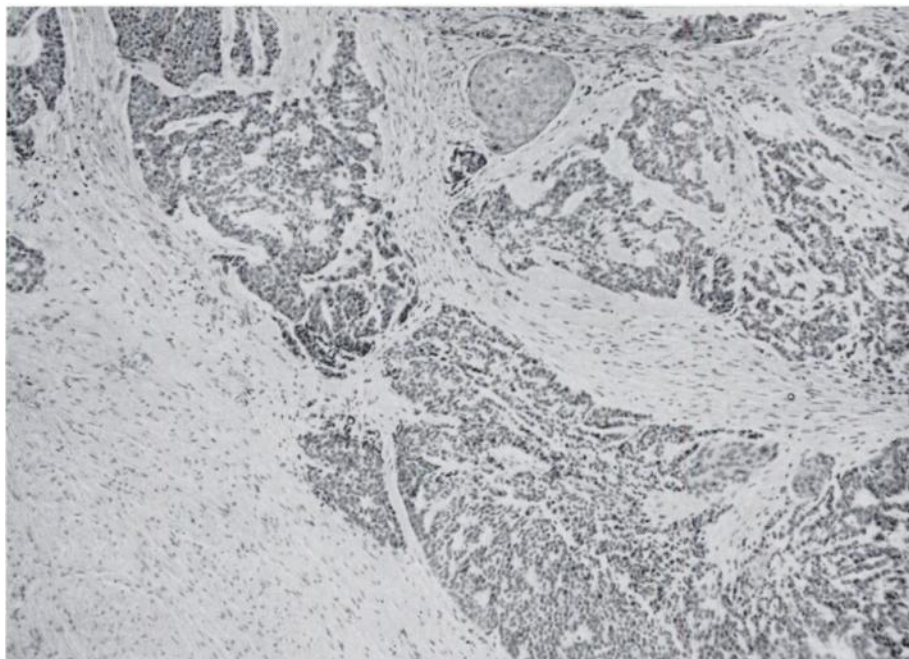


Fig. 12. B—is microscopic appearance after therapy—radical perineal prostatectomy in February, 1964. Note residual areas of cancer with much fibrosis interstitially. Only partial effect from therapy.



Fig. 13. The effect of cobalt therapy. 59-year-old white male given 4,499 r Co_{60} in December, 1963. Developed rectourethral fistula for which colostomy was done December 20, 1963. By March, 1964, local lesion had grown markedly and bulged in perineum. No effect from therapy.

In conclusion, in a total series of 976 patients with prostatic cancer, combinations of surgery plus interstitial instillation of Au¹⁹⁸ for destruction of the local lesion of prostatic cancer showed the following:

1. The methods for protection of personnel, et cetera, worked out by Dr. Elkins are satisfactory.
2. The complications—anemia, leucopenia, damage to the adjacent organs, delayed wound healing, are very minimal when the principles underlying the technics of administration are adhered to.
3. Significant improvement in the results of attempts to destroy the local lesions are obtained. This is in the order of magnitude of 55 per cent “cure” as compared to 8 per cent “cure”.

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Announcement

The Section of Therapeutic Radiology and the Section of Radiobiology, Department of Radiology, University of California School of Medicine, San Francisco, are now offering a four-year training program in radiation therapy under the auspices of the National Cancer Institute of the National Institutes of Health. Clinical and basic training will be well integrated. The program is conducted jointly by Dr. Franz Buschke and by Dr. Harvey Patt.

Those interested should write directly to the Training Director, Dr. Franz Buschke, Department of Radiology, University of California Medical Center, San Francisco, California 94122.