

# TETRACYCLINE ULTRAVIOLET FLUORESCENCE IN BLADDER CARCINOMA

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**F**LUORESCENCE IN TUMORS VIEWED UNDER ultraviolet light following the administration of tetracycline was first reported by Rall and co-workers<sup>9</sup> in 1957 and since then has been observed in a variety of human and experimental tumors. Although the initial studies suggested that tetracycline (Achromycin V) ultraviolet fluorescence might be specific for histologically malignant lesions,<sup>6-8</sup> the observation of such fluorescence in a variety of non-neoplastic conditions<sup>1, 12</sup> has indicated that the factors responsible for its localization are apparently not specific for tumors and are certainly poorly understood.

The present observations concern the occurrence of tetracycline ultraviolet fluorescence in bladder carcinoma.

## MATERIALS AND METHODS

The bladders of 21 patients with bladder carcinoma were studied between September, 1962, and April, 1964, at Memorial Hospital for Cancer and Allied Diseases and James Ewing Hospital prior to and following total cystectomy.

The patients were given tetracycline orally, 250 mg. every 6 hours for 2 to 6 days, the drug being discontinued 12 to 72 hours before observations regarding fluorescence were made. Patients were examined endoscopically with incandescent and, when feasible, with ultraviolet light, utilizing conventional incandescent endoscopes and a specially designed ultraviolet quartz rod endoscope respectively.

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American Cystoscope Makers, Inc., generously designed and made the instrument available for this study.

The examinations by ultraviolet microscopy were made by Dr. Stephen Sternberg and Dr. Myron Melamed of the Department of Pathology of Memorial Hospital.

Received for publication Aug. 6, 1964.

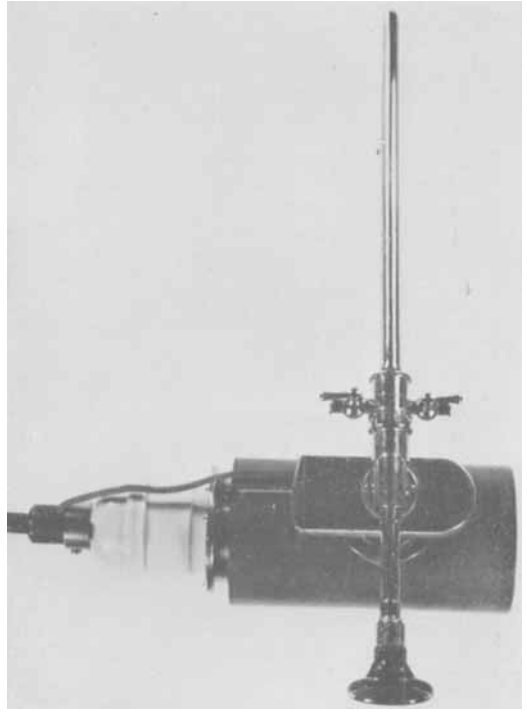


FIG. 1. Ultraviolet-light endoscope.

The special instrument (Fig. 1) consists of an open-end panendoscope sheath, size 28 French, with a bayonet lock and water irrigation at the distal end. The telescope consists of a foroblique system and is mounted in a cone that supports a quartz rod placed immediately under the telescope and angled at the distal end. The field of vision of the foroblique telescope is adjusted to cover the illuminated field. The ultraviolet light source contains a 100-watt mercury arc, which is placed in a reflecting light shield surrounded by an insulated micarta case. Heat ventilation is by convection only. The light from this bulb passes through 2 quartz condensers and through a quartz prism via the proximal end of a 1/8-in. diameter quartz rod. The quartz rod is approximately 8 in. long. There are 2 filters that may be placed in the light beam before it reaches the proximal end of the

quartz rod. A clear filter, Corning no. 1-59, is used to remove the infrared radiation and allows the surgeon to see a normal visual field. The ultraviolet filter, Corning no. 7-51, is ground thin so that it transmits more than 90% of the light at 3,660 Å, 40% at 4,000 Å, and 0% at 4,300 Å. The filters are mounted on a slide that may be conveniently moved in and out of position.

Immediately prior to cystectomy, the bladder of each patient was first viewed with incandescent light, and all abnormal-appearing areas were noted and grossly characterized. Each bladder was also examined with the ultraviolet endoscope either at the time of incandescent-light endoscopy or immediately following cystectomy. In some patients, the urethra would not accommodate the 28-French ultraviolet instrument, and in these instances the unopened cystectomy specimen was examined with this instrument immediately after operation. In each patient the opened cystectomy specimen was also examined under ordinary incandescent light and under 4-watt, 3,660-Å ultraviolet light.

Areas in the bladder that revealed bright greenish-yellow (tetracycline) fluorescence with ultraviolet light, either endoscopically or upon examination of the opened specimen, were

suitably marked for subsequent histological study. It is of note that there was no gross discrepancy in size, distribution, or number between the fluorescent lesions noted endoscopically and those noted upon examination of the opened specimen.

## RESULTS

In 6 bladders (Table 1), a total of 9 carcinomas was identified as a result of tetracycline ultraviolet fluorescence in bladder mucosa that appeared normal by incandescent light. Five of the 9 lesions were early invasive epidermoid carcinomas and 4 were in situ carcinomas. No observations were made relating the specific size of the fluorescing area to the specific size of the tumor. Tetracycline ultraviolet fluorescence was observed in 2 areas that on subsequent histological examination did not reveal cancer. In this case (case 2) 4 fluorescent spots were observed in close proximity over an area on the vesical trigone. Two of these spots revealed infiltrating epidermoid carcinoma; the other 2 showed no apparent microscopic abnormality. None of the areas of fluorescence observed in bladder mucosa that appeared normal by incandescent light exceeded 1 cm. in greatest diameter.

TABLE 1  
ULTRAVIOLET TETRACYCLINE FLUORESCENCE IN BLADDER CARCINOMA

Case no. Hosp. no.	Sex Age	Previous treatment*	Tetra- cycline dose, gm.†	Endoscopy & incandescent- light inspection	Endoscopy & ultraviolet-light inspection	Microscopic diagnosis
1 25-19-67	M 64	Segmental resection; radon seed im- plantation; TUR (4×); Co <sup>60</sup>	3.5	No tumor visible	Fluorescent area at lt. ureteral orifice	Invasive epidermoid carcinoma
2 26-13-04	F 43	Segmental resection; TUR; Cs <sup>137</sup>	2.0	No tumor visible	4 fluorescent spots over area on vesical trigone	Two of the 4 areas revealed invasive epidermoid carcinoma
3 23-16-85	M 67	TUR (2×)	3.0	Nodular tumor at dome	Fluorescence around rt. ureteral orifice	Invasive epidermoid carcinoma at dome; in situ carcinoma at rt. ureteral orifice
4 24-70-11	M 55	TUR; Co <sup>60</sup>	4.5	Ulceration behind rt. ureteral orifice	3 fluorescent areas visible: ulceration behind rt. ureteral orifice; posterior wall; lt. ureteral orifice	Invasive epidermoid carcinoma of ulcer behind rt. orifice; invasive epidermoid carcinoma of posterior wall; in situ carcinoma in left ureteral orifice
5 24-70-43	M 52	Fulguration (4×); TUR (2×); pelvic perfusion; Co <sup>60</sup>	3.0	No tumor visible	2 fluorescent areas on posterior wall	Both areas revealed in situ carcinoma
6 21-17-84	M 51	TUR; Co <sup>60</sup>	4.0	Superficial ulceration at site of previous trigone biopsy	1 fluorescent area on lateral wall	Both areas revealed irradiated superficial epidermoid carcinoma

\*TUR = transurethral resection.

†Given as 2 gm. per day.

Thirteen of 17 grossly visible bladder carcinomas (Table 2) revealed definite tetracycline ultraviolet fluorescence, 2 demonstrated questionable fluorescence, and 2 showed no fluorescence whatever.

#### DISCUSSION

The possibility that a bladder neoplasm may have a preclinical phase has been overshadowed by the facts that recognized bladder neoplasms are usually symptomatic and that bladder cancer is rarely reported as an incidental autopsy finding. The utilization of the Papanicolaou technique for examination of the urinary sediment and the urologic evaluation of patients with positive urinary cytological findings have indicated that a bladder neoplasm may apparently exist for months or even years before the precise site becomes manifest.

TABLE 2  
TETRACYCLINE ULTRAVIOLET  
FLUORESCENCE IN GROSSLY VISIBLE  
BLADDER CARCINOMA

No. tumors	Fluorescence		
	Positive	Questionable	Negative
17	13	2	2

Although testing for tetracycline ultraviolet fluorescence was suggested as a potentially useful adjunct in the diagnosis of cancer by Rall and co-workers<sup>9</sup> in 1957, most studies have been performed on washings<sup>11, 13</sup> from areas that were not easily accessible to biopsy under direct vision. Work in progress at this institution concerning the usefulness of urinary tetracycline ultraviolet fluorescence in the identification of patients with bladder cancer has been disappointing. A study of such fluorescence in the urine samples from approximately 200 control and bladder cancer patients has revealed that both groups shed fluorescing cells in the urine, apparently equally, for up to 10 days following discontinuation of tetracycline; efforts to locate the carrier of the fluorescing material in the urinary sediment have been unrewarding to date.<sup>4</sup>

In the present study it was a primary objective to evaluate direct visualization of tetracycline ultraviolet fluorescence as a means of earlier detection of bladder cancer. Observations on patients with established blad-

der carcinoma treated by cystectomy without prior tetracycline therapy have inconsistently demonstrated a faint ultraviolet autofluorescence in the tumor as well as in the normal bladder mucosa, but not the bright greenish-yellow fluorescence of tetracycline. In 6 bladders, a total of 9 carcinomas was identified by tetracycline ultraviolet fluorescence in bladder mucosa that appeared normal by incandescent light. The possibility that other bladder cancers existed and were overlooked both by incandescent and by ultraviolet light examination in this group of patients has not, of course, been eliminated and gains support from the fact that tetracycline ultraviolet fluorescence was absent or questionable in 4 of 17 grossly evident cancers. However, the relative tetracycline ultraviolet fluorescence potential of early in contrast to grossly evident lesions has not been established by this or by any other study to date, and it is conceivable that such fluorescence may be a more consistent characteristic of early than of advanced neoplasms. Although false positive tetracycline ultraviolet fluorescence was observed only 2 times, and then in close association with 2 other fluorescing areas in which early invasive cancer was found, these studies do not establish a specificity of tetracycline fluorescence for bladder cancer and emphasize the need for histological study of suspicious areas.

In none of the 9 instances in which cancer was discovered by the use of tetracycline ultraviolet fluorescence in mucosas that appeared normal to incandescent light was there evidence of necrosis, but necrosis was evident in some of the grossly visible tumors in which such fluorescence was observed. No systematic attempts have yet been made to correlate the occurrence of tetracycline ultraviolet fluorescence with such factors as tumor size, location, necrosis, and ulceration, but the fact that such fluorescence was observed in scattered areas of in situ carcinoma and of early invasive carcinoma in 6 patients in whom the involved areas of mucosa appeared normal with incandescent light suggests that such factors are not critical to the occurrence of such fluorescence. In the present study, 6 sections of tetracycline ultraviolet fluorescent carcinomas of the bladder were examined by ultraviolet microscopy and no specific areas of fluorescence were identified in tumor cells. The complete absence of fluorescence in 2 cases of grossly evident cancer and its equivocal character in

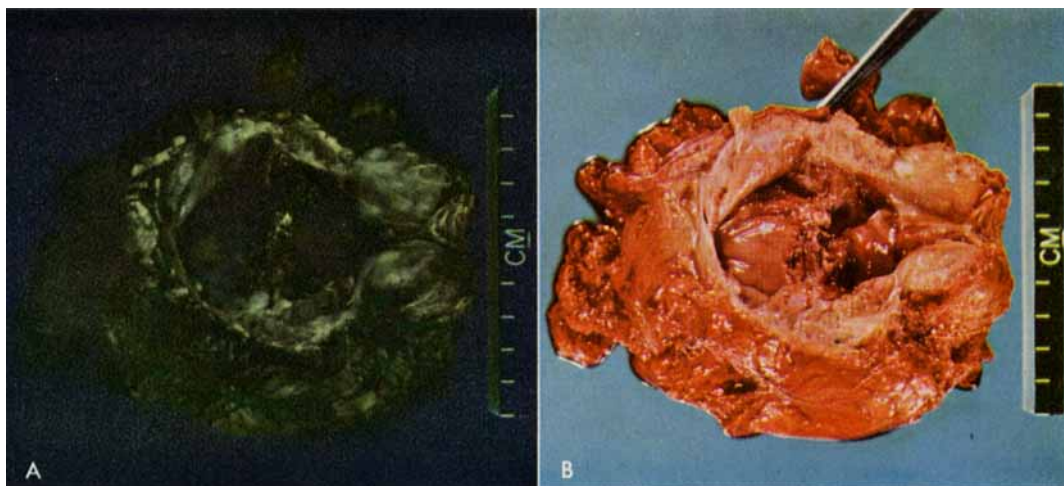


FIG. 2. A, Tetracycline ultraviolet fluorescence in a grossly visible bladder carcinoma. Mucosal surface of tumor shows ultraviolet tetracycline fluorescence; bladder and prostate urethral mucosa show autofluorescence. B, Same specimen seen in incandescent light.

2 other such cases emphasize current ignorance regarding the mechanism for localization and persistence of tetracycline fluorescence.

The fact that ultraviolet endoscopic examination of the intact bladder proved as effective in detecting fluorescent areas as did examination of the opened cystectomy specimen under ultraviolet light is important in establishing the reliability of the endoscopic method of examination. With improvements in ultraviolet optical systems, instruments permitting studies of the value of ultraviolet fluorescence in the earlier diagnosis of neoplasms in a wide variety of areas may be anticipated. Although it would be unjustifiable from present evidence to imply that ultraviolet endoscopy will solve the problems involved in the earlier detection of bladder

neoplasms, the results suggest that such ultraviolet visualization may prove a useful adjunct to presently utilized methods of diagnosis and simultaneously emphasize limitations in conventional diagnostic techniques by pointing out some failures of incandescent-light visualization.

#### SUMMARY

Tetracycline ultraviolet fluorescence was studied in the bladders of 21 patients with bladder cancer before and after cystectomy. Nine cancers, not detected during examinations of the bladders with incandescent light, were identified in 6 bladders by this technique. Possible applications to the earlier diagnosis of bladder cancer are briefly discussed.

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## TO OUR ADVISERS AND CONSULTANTS

We wish to thank our Editorial Advisory Board and the following individuals for their kind assistance in the evaluation of manuscripts received during 1963 and 1964.

Arnold Berrett, Salvatore Castro, Paul Clapp, Bayard D. Clarkson, George O. Clifford, Eugene E. Clifton, Sidney Cutler, Edwin R. Fisher, Philip Gallagher, William Geller, Ernest Greenberg, Étienne de Harven, William Haenszel, Ulrich Henschke, Frank L. Horsfall, Jr., Robert V. P. Hutter, Leopold G. Koss, Allyn B. Ley, Philip H. Lieberman.

Also, Averill A. Liebow, Ian MacDonald, A. R. Mackenzie, Rene C. Mastrovito, Klaus Mayer, Myron R. Melamed, Daniel G. Miller, Basil Morson, Rulon W. Rawson, Morton K. Schwartz, Robert S. Sherman, Maurice E. Shils, William W. Shingleton, Fredrick H. Shipkey, Chester Southam, Parker Vanamee, Willet F. Whitmore, Jr., and Ernest L. Wynder.

There were many others whom we consulted on a less formal basis and for their help we are also most grateful—John W. Berg, *Editor*; Walter Lawrence, Jr., *Assistant Editor*; Fred W. Stewart, *Editor Emeritus*.