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SERIES

Year Book
OF
UROLOGY

SCOTT

THE YEAR BOOK *of* UROLOGY

(1957-1958 YEAR BOOK Series)

EDITED BY

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THE YEAR BOOK PUBLISHERS

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THE PRACTICAL MEDICINE YEAR BOOKS

This volume is one of the 15 comprising the Practical Medicine Series of Year Books founded in 1900 by G. P. Head, M.D., and C. J. Head, and published continuously since then. The complete list follows:

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HORMONES AND DISSEMINATED PROSTATIC CANCER

ALTHOUGH ALMOST 17 years have elapsed since Huggins introduced castration-estrogen therapy for disseminated prostatic cancer, many questions regarding such treatment remain unanswered. For example: (1) When is the optimum time to begin endocrine therapy? (2) Should estrogen therapy be combined with castration? (3) If not, should castration precede or follow estrogen therapy? (4) Is one estrogen better than another? (5) Should large or small doses of estrogen be given? (6) Are there other steroids which are more effective than estrogens? (7) What is the best treatment we can offer the patient in relapse on castration-estrogen therapy? (8) What objective indices do we have to guide us in therapy?

Your editor is unable to provide definitive answers to these important questions. However, he is pleased to relate that at long last a co-operative study is under way which should provide some answers. A brief description of this study follows.

Late in 1956, Dr. Herbert Brendler, Associate Professor of Urology, New York University Post-Graduate Medical School, was asked to organize a co-operative study under the auspices of the National Cancer Chemotherapy Service Center, National Cancer Institute. This group, known as the Prostate Study Group, is one of several study groups organized for co-operative study of several human cancers, including, breast, leukemia, cervix and lung. For over a year now, this group, in collaboration with statisticians, has been working hard to develop a protocol. This is now complete, and the actual study should begin shortly. Initially, it will be conducted by 10 urologists and their associates in 10 medical institutions in the United States. As time goes by, it may be necessary to expand this group or, more likely, to form a

second prostate study group, as has been done in the study of breast cancer.

A word or two about the protocol: (1) a "statistical center" (the statisticians of which have participated in the development of the protocol) will be responsible for the design, printing and distribution of standard forms and records, allocation of experimental compounds, surveillance of collection of data, processing of study records and statistical evaluation of results; (2) patients admitted to the study must have had a positive tissue diagnosis, this to be confirmed by a consulting pathologist; (3) all criteria for admission to the study are made as uniform as possible; (4) treatment, consisting of the administration of a steroid or a placebo, is to be carried out according to the "double-blind" method.

Initially, in an effort to evaluate present-day indices of improvement, the effect of stilbestrol is to be compared with lactose, in patients with disseminated prostatic cancer who have been castrated at least 6 weeks before and who show evidence of active progression of their disease. Once begun, therapy is to be continued for a minimum of 4 weeks, unless the patient's condition deteriorates rapidly, in which case he is classed as a failure and other forms of therapy are instituted.

Criteria for measurement of effect, such as the size of the primary, the x-ray appearance of metastases, the level of the serum acid phosphatases, the patient's weight, his blood picture, his ambulatory status, the degree of his pain, etc., have all been standardized as well as can be. Statistical analysis of such data should permit an evaluation of the reliability of these indices which are being used at present for measurement of effect. Once reliable indices are found, they can be used to great advantage in the evaluation of other forms of therapy such as outlined earlier. Whereas it is too early to relate the order in which the various therapies will be evaluated, it should be possible within the year to evaluate a number of estrogens and to determine their optimum dosage. Evaluation of other steroids will follow.

Equally exciting to contemplate are the many other activities of the National Cancer Chemotherapy Service Center and its several Panels. Let us conclude with a brief account

of how this Center can provide invaluable aid to a co-operative study group such as the Prostate Study Group, assuming, let us say, that this group is interested in obtaining new steroids with special endocrine actions.

The Prostate Study Group can make their wishes known to a subcommittee of the NCCSC, whose chief function is to provide investigators with steroids. This subcommittee is guided by clinical requests, clinical results, available scientific literature, drug company lists with in-plant biologic data and a mass of biologic data on existing steroids already accumulated by the NCCSC. If the Prostate Study Group sees a compound which they think merits clinical trial, the Center can then provide data encompassing hormonal bioassay, tumor screening and toxicity measurement. The steroid together with an appropriate placebo is then prepared for clinical trial.

Already we can say that many steroids with important biologic actions are now available and a number should be given a clinical trial. With thought, hard work, co-operation —perhaps some luck—who knows but that the right one may be found.

GENERAL CONSIDERATIONS

Examination of the Urine

Identification and Clinical Significance of Casts are discussed by George E. Schreiner[1] (Georgetown Univ.). A fresh, clean-voided specimen should be examined, preferably concentrated and acidic. If the urine is alkaline, a few crystals of sodium chloride or some concentrated hydrochloric acid may prevent dissolution of the casts.

Casts are often found in urine, properly examined, from office and hospital patients. Identification can be valuable as a screening test and in the discovery of masked or asymptomatic renal disease. The casts are of specific diagnostic value, permit correlations with renal physiology and pathology and are helpful in treatment and prognosis. The examination should be one by the physician.

Hyaline casts are the gel of proteins which have presumably traversed the capillary membrane. Their formation depends on concentration of protein and other solutes and on acidification. Formed elements present at the time of gel formation are entrapped and are an indication of the condition in the nephron. When a significant number of hyaline casts are broad, loss of nephrons or obstruction with subsequent dilatation is inferred. The casts may be seen in small numbers in apparently normal urine and increase with exercise.

Red cells in a cast mean renal hematuria; they should always be considered pathologic. They may be the only manifestations of acute glomerulonephritis, subacute bacterial endocarditis, renal infarction or collagen kidney. When they increase, the cast appears orange-yellow. Addis considered the blood cast, which is homogeneous without distinguishable cell margins, pathognomonic of acute glomerulitis.

Leukocytes in casts are renal in origin. They may be seen in acute glomerulonephritis and nephrotic syndrome, but more often signal infection. Bacteria in casts are pathogno-

(1) A.M.A. Arch. Int. Med. 99:356-369, March, 1957.

monic of renal infection and are easily seen with phase-contrast microscopy or glitter cell stain. Granular inclusions may arise from degenerated cells, bacteria or unknown flotsam and jetsam in the nephron stream. Doubly refractile fat bodies (cholesterol esters) may be found free in casts, especially in intercapillary glomerulosclerosis with proteinuria. Fatty inclusions are found in the nephrotic syndrome, Kimmelstiel-Wilson disease, scleroderma kidney, lupus, periarteritis, miliary infarction and the recovery phase of acute renal insufficiency with tubular necrosis. Fat bodies are more numerous in the presence of hyperlipemia.

Epithelial casts are fused from desquamated tubular cells which form in rows of 2 or 3. An occasional renal epithelial cell or clump is not remarkable but many may indicate wholesale desquamation and sloughing. Degeneration of the discrete cellular cast into coarsely and finely granular material is a function of age and implies stasis in the nephron. Waxy casts represent the homogeneous degeneration of cells into a highly refractile, yellow cast seen frequently in chronic diseases with scar tissue and tubular dilatation. The most significant cellular cast is the broad renal failure cast, which is usually yellow and slightly granular and appears with increasing incidence in renal failure.

In addition to interpretation of individual casts, information may be obtained from the other elements in the urine. Red cell casts in a urine with a high percentage of broad casts suggest acute exacerbation of chronic glomerulonephritis or recent infarction of renal tissue. The so-called telescoped urine sediment may be seen in the kidney of subacute bacterial endocarditis, in collagen kidney in various states and with a combination of stages of glomerulonephritis. The components of this telescoped sediment are manifestation of acute glomerulonephritis (red cells, hyaline casts with red cell inclusions, blood casts and positive benzidine), the nephrotic syndrome (massive albuminuria, hyaline casts, cellular casts, oval fat bodies and doubly refractile fat bodies) and chronic glomerulonephritis (less albuminuria, pigmented granular casts, waxy casts and broad and renal failure casts).

► [There should be little disagreement with the view expressed by the au-

thor that examination of the urinary sediment should be made by the physician. So often we are content to rely on the report of a technician whose experience in such matters is much less than ours. It always does my heart good to visit a urologic clinic and see the urologist studying the sediment himself.—Ed.]

Reliability of Papanicolaou Technic When Cancer Cells Are Found in Urine. Samuel I. Roland and Victor F. Marshal[2] (New York Hosp.) examined the urine 6,740 times

SOURCES OF EXFOLIATED CANCER CELLS IN URINE OF 176 PATIENTS

	—No. of reports—		
Cases proved by biopsy	*Class IV*	*Class V*	*No. of patients*
Renal carcinoma			
Pelvic	4	11	6
Parenchymal	2	1	2
Ureteral carcinoma	0	1	1
Bladder carcinoma	120	219	123
Bladder leiomyosarcoma	1	0	1
Bladder papilloma (grade 1 carcinoma in some classifications)	7	7	6
Bladder papilloma with cystitis cystica	3	1	1
Prostatic carcinoma	22	14	16
Urethral carcinoma	2	5	2
Penile carcinoma	0	1	1
Penile melanosarcoma	0	1	1
Metastatic carcinoma to the urinary tract			
Adrenal to kidney	1	0	1
Stomach to kidney	0	1	1
Sigmoid to bladder	0	1	1
Ovaries to bladder	0	1	1
Rectum to bladder	3	0	2
Uterus to bladder	1	0	1
Pancreas with carcinomatosis	1	0	1
Cases unexplained by biopsy	8	3	8
Total	175	267	176

among 2,414 patients between August 1945 and June 1951 and noted malignant neoplastic cells in 176 (7.2%) patients. Sources of the exfoliated cancer cells in these 176 patients are shown in the table. Urine specimens that were classified as class IV gave fairly conclusive evidence of a malignant neoplasm; those classified as class V gave conclusive evidence of a malignant neoplasm. Among 8 unexplained cases, 2 patients died before lapse of the 5-year follow-up and autopsies were not obtained; 1 was not followed and 5 are alive 5 years later without urinary tract cancer.

(2) Surg., Gynec. & Obst. 104:41-44, January, 1957.

The study indicates that when cancer cells are shown in the urine there is cancer in the urinary tract in at least 95% of patients. An unexplained positive report warrants follow-up for an indefinite period. In reported cases, there have been many patients with positive Papanicolaou urine who did not show urinary tract cancer but who were found to have it on subsequent study.

► [In 1950, Drs. Marshall and Schmidlapp promised us this 5-year follow-up, and here it is (see New York J. Med. 50: 56, Jan. 1, 1950 and the 1950 YEAR BOOK, p. 22). It is only through a superb follow-up study such as this that the merit of any method of cancer detection can be determined.—Ed.]

Comparison of Dry Smear Technics with Wet Technics for Cytologic Study of Urine was made by Cyril Solomon, John M. Silberblatt and Richard M. Hyman[3] (New York City Dept. of Health), with the technical assistance of R. A. Bonime and Dorothy Schallert Fuller. The following new technics were compared with previously accepted methods of wet fixation.

METHOD.—*Dry smear with rehydration.*—Two drops of the initial sediment were placed on a frosted glass slide and then spread with the tip of a pipet, so as to form a rectangular smear. This was permitted to dry for 1-7 days. The sides were reconstituted by (*a*) immersion in Duponol C solution (sodium lauryl sulfate, USP), 2% for ½ minute; (*b*) rinsing in a mixture of equal parts of 95% alcohol and ether for 1 minute; (*c*) fixation by immersion in a mixture of 95% alcohol and ether for ½ hour; (*d*) routine staining (Papanicolaou).

"Wash-down" method and reconstitution.—After the first supernatant fluid was decanted from the centrifuge tubes and the original sediments removed, the walls of each tube were washed with a stream of physiologic saline solution, to 5 ml./tube. The resulting suspension of cells was centrifuged for 10 minutes and the supernatant fluid discarded. This sediment was then treated either by the usual method or by the preceding technic.

Slides prepared by a "wash-down" method were the most satisfactory. They contained the greatest amount of material with a preponderance of epithelial elements, and there was usually excellent clarity before drying. When treated by wet fixation, they were superior in content to slides prepared without "wash-down." This new technic results in recovery of material that would otherwise be lost.

► [According to our cytologist, it is extremely important that urine specimens for cytologic examination be fresh. He insists that urinary smears for cancer of the urinary tract be brought to the laboratory within a few

(3) Am. J. Clin. Path. 27:601-605, May, 1957.

minutes after collection. His instructions for urinary smears for cancer of the bladder are: (1) have patient drink 3 glasses of water/hour for 2-3 hours, then (2) have patient void or, if there is retention, catheterize patient and discard urine, (3) 1 hour later, telephone the laboratory that you are going to catheterize patient, (4) catheterize patient and immediately bring urine to the laboratory, within 3 minutes.—Ed.]

Diagnostic Value of Protein Excretion Pattern in Various Types of Proteinuria was investigated by D. Wolvius and J. C. M. Verschure[4] (Univ. Hosp., Utrecht), with the technical assistance of F. C. M. Hoefsmit. A microtechnic for paper electrophoresis was used in 83 analyses of serum and urine from 50 patients suffering from various types of proteinuria.

In the 81 diagrams made of urinary proteins all the major components of the serum appeared to be present. In none was a protein band without a counterpart in the serum found. Though certain differences could be found in the urine albumin-globulin ratios of the various types of proteinuria, no pathognomonic ratio appeared to exist. In each urine sample the clearance ratio of total globulins to albumins was determined. In this way more distinct differences could be observed between the various types of proteinuria, but no pathognomonic clearance ratios could be detected. The clearance ratio in 2 cases of pyelonephritis were distinctly higher than those in the other cases of organic renal diseases. This may be of clinical value. There proved to be a considerable difference in clearance ratio between postural proteinuria and continuous proteinuria. No correlation in general could be found between globulin-albumin clearance ratio and severity of the renal disorder causing proteinuria.

The protein excretion pattern in benign proteinuria resulting from physical exertion strongly resembled that seen in postural proteinuria. Globulin-albumin clearance ratios ranged from 0.3 to 1.7.

Clinical Studies on 267 Cases of Phosphaturia in Private Practice were made by I. Holmgren[5], who, for the purposes of the study, classed as phosphaturia cases of clear, faintly alkaline urine and those of a more strongly alkaline urine clouded with phosphate. Of the study patients, 67% were men and 33% women; 70.5% were 30 or over. About 77% of the patients had psychogenic and vegetative disturbances.

(4) J. Clin. Path. 10:80-83, February, 1957.
(5) Acta med. scandinav. 156:139-146, 1956.