

# URINARY CHOLESTEROL EXCRETION IN MEN WITH BENIGN PROSTATIC HYPERPLASIA AND CARCINOMA OF THE PROSTATE

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Urinary excretion of nonesterified (NEC) and total cholesterol (TC) has been investigated in 79 patients with prostatic adenoma (BPH) and 48 patients with carcinoma of the prostate. Normal range of NEC was determined in 62 healthy individuals and was found to be 0.26–2.2 mg/24 hours (2 SD) with a mean value of 0.76 mg/24 hours. TC ranged from 0.3–2.9 mg/24 hours with a mean value of 0.92 mg/24 hours. In benign prostatic hyperplasia normal values for NEC and TC were determined in stages without residual urine. In contrast patients with BPH and residual urine showed elevated NEC in 42.1% and elevated TC in 61.4%. In prostatic carcinoma NEC hyperexcretion was present in 44.8% of stage A and B and in 52.6% of stage C and D. TC was elevated in 52.2% and 63.2%, respectively. Simultaneous determination of NEC and serum acid phosphatase (SAP) gave a pathologic result of at least one parameter in 51.7% of stage A and B and in 84.2% of stage C and D. If TC and serum acid phosphatase were combined, percentage of elevated values increases to 62.1 of stage A and B and was identical with 84.2 of stage C and D. If BPH with residual urine and other known conditions of urinary cholesterol hyperexcretion in males, pluripotential malignant testicular neoplasms and diseases of kidney and urinary tract, can be excluded with reasonable certainty, both parameters may be of value in diagnosis of prostatic cancer in even early clinical stages of the disease, especially in combination with the determination of SAP.

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**H**YPEREXCRETION OF URINARY NONESTERIFIED (NEC) or total cholesterol (TC) in prostatic cancer has been reported recently.<sup>3,11</sup> It was concluded that both parameters are valuable in the diagnosis of the disease. A comparative evaluation of NEC and TC has not yet been undertaken; in addition, the performed studies did not show the value of these parameters in diagnosis of early clinical stages. Other known common conditions of urinary cholesterol hyperexcretion in males are pluripotential testicular neoplasms, diseases of kidney and urinary tract and benign prostatic hyperplasia.<sup>3,12,13,16,19</sup> In regard to the frequency of BPH in comparison to prostatic carcinoma, it was additionally necessary

to investigate whether elevated levels of urinary cholesterol were present in all clinical stages of BPH or only in patients with BPH and residual urine with indication for surgical treatment.

## MATERIALS AND METHODS

Nonesterified and total urinary cholesterol were analyzed in 2 ml aliquots of 24-hour urine. After extraction with 6 ml ethyl acetate for 30 minutes in a rotating system, the urinary phase was removed. The ethyl acetate extract was purified with alkali (2 ml 0.1N NaOH) and water washings and dried under a stream of nitrogen. The residue was dissolved with 0.1 ml of the internal standard solution (10 mg 4-androstene-3, 17-dione/dl isoctane), followed by GLC on a 180 cm 1% XE 60 column, i.d. 2 mm, temp. const. 220 C. Quantitation was performed due to the peak height ratio, since alterations of cholesterol and 4-androstenedione concentration gave a linear response.

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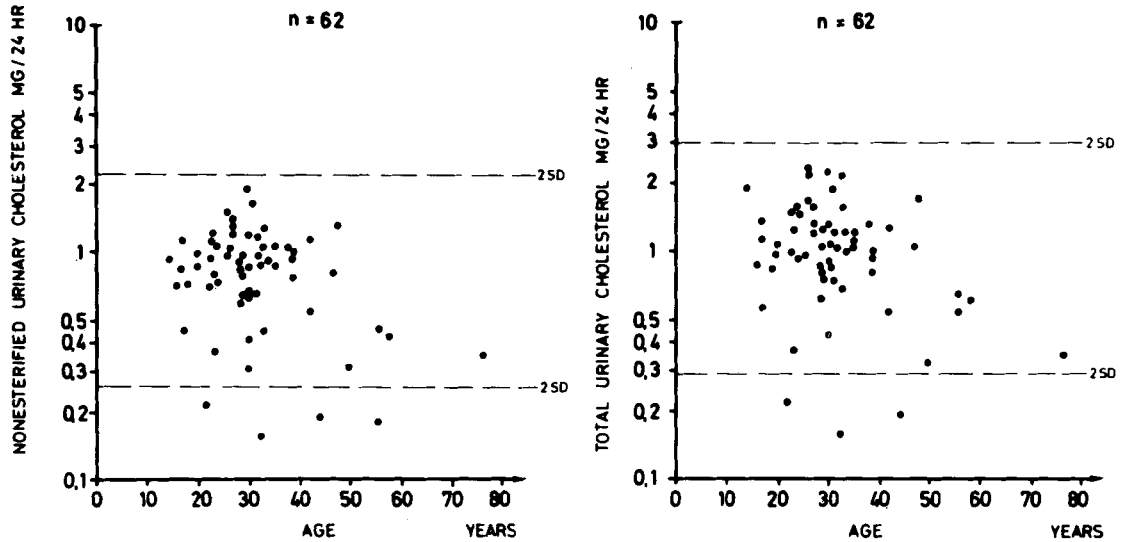


FIG. 1. Urinary excretion of nonesterified and total cholesterol in normal male individuals.

TC was measured as above including hydrolysis of the dried extract with 0.1 ml 3N KOH and 0.9 ml ethanol for 60 minutes at 60 C. NEC and TC were measured with an intraassay variance of 2.3% and 5.6% and an interassay variance of 11.2% and 10.9%, respectively. Specificity of the method was confirmed by simultaneous mass spectrographic analysis in selected samples.

### Clinical Material

The clinical material consisted of patients with histopathologically proven prostatic neoplasms, which were divided in clinical stages A–D according to Flocks. 11 patients were found to have a palpable prostatic nodule (stage A); in 18 patients the prostatic cancer was not nodular but confirmed to one lobe of the gland (stage B). 5 patients showed local extension outside of prostate (stage C); in 14 cases metastasis in pelvis, other bones or lung were present. When urinary cholesterol determinations were performed, patients did not receive any treatment. A diagnosis of prostatic cancer had been established in most cases at the time of the investigation.

22 patients with BPH were diagnosed by rectal examination; they were without any symptoms (stage 0) or showed pollakiuria and impaired urinary stream (stage 1). Residual urine was excluded in all these cases. In 57 patients with BPH diagnosis was histopathologically proven after transurethral resection. In all these patients residual urine was pres-

ent (stage 2); in some combined with urinary incontinence or secondary kidney damage (stage 3).

The normal range for NEC and TC excretion was calculated using standard procedures and was obtained from a group of clinically healthy and biochemically normal individuals.

## RESULTS

### Normals

This group comprised 62 clinically healthy, asymptomatic and biochemically normal male individuals covering an age range of 14 to 76 years.

The excretion values for NEC and TC are illustrated in Fig. 1. Statistical analysis of the results obtained gave a mean excretion of 0.76 mg/24 hours NEC and 0.92 mg/24 hours TC. The range for normal values was calculated as the mean  $\pm$  2 SD including 95% of the population. On the basis of these results, the upper normal limit of the urinary excretion of NEC was considered to be 2.2 mg/24 hours and for TC to be 2.9 mg/24 hours. Hyperexcretion in the male, therefore, was defined as any result exceeding this value. It is important to note that the values of excretion of this group presented a log normal distribution.

### Prostatic Hyperplasia

The results obtained in the study of 79 patients with a diagnosis of adenomatous pros-

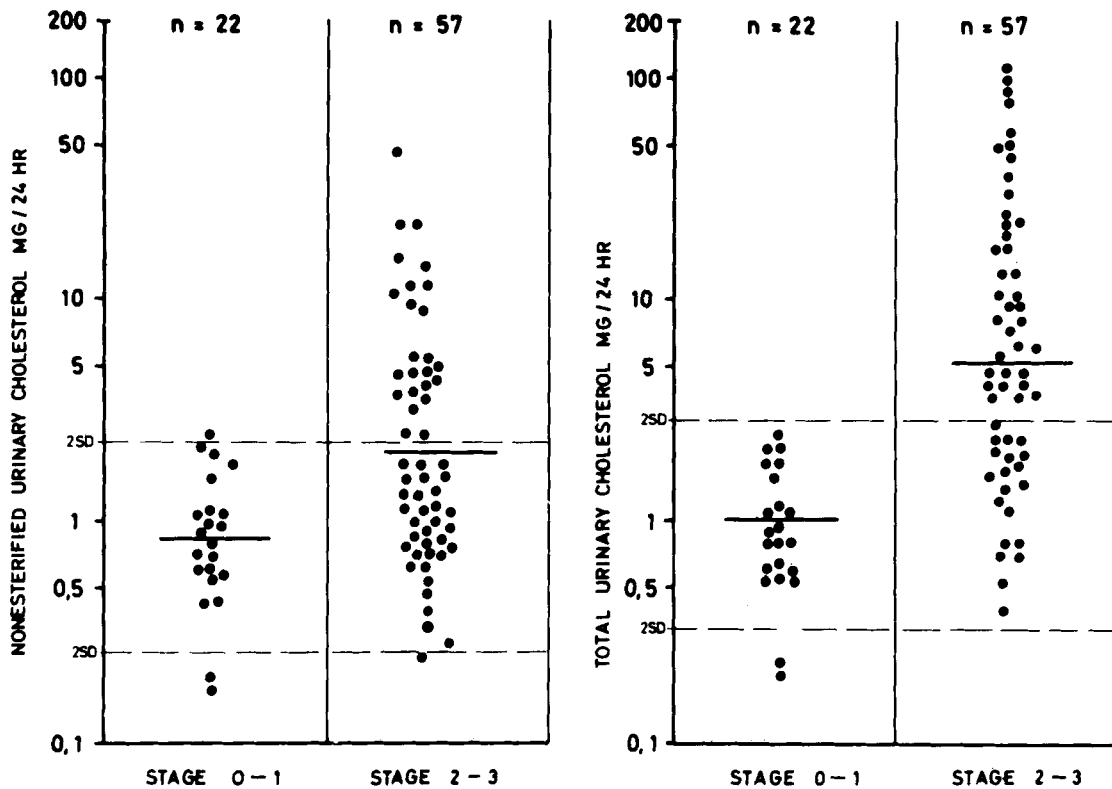


FIG. 2. Urinary excretion of nonesterified and total cholesterol in patients with a diagnosis of adenomatous prostatic hyperplasia.

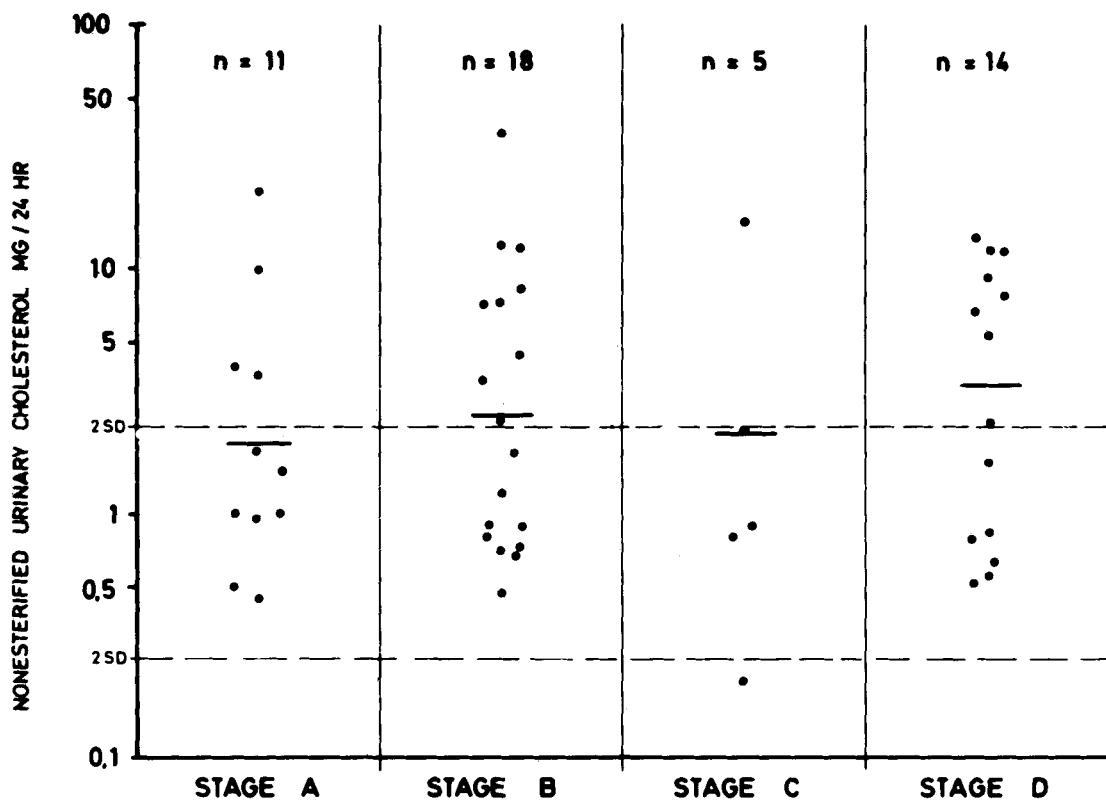


FIG. 3. Urinary excretion of nonesterified cholesterol in patients with prostatic carcinoma stage A-D.

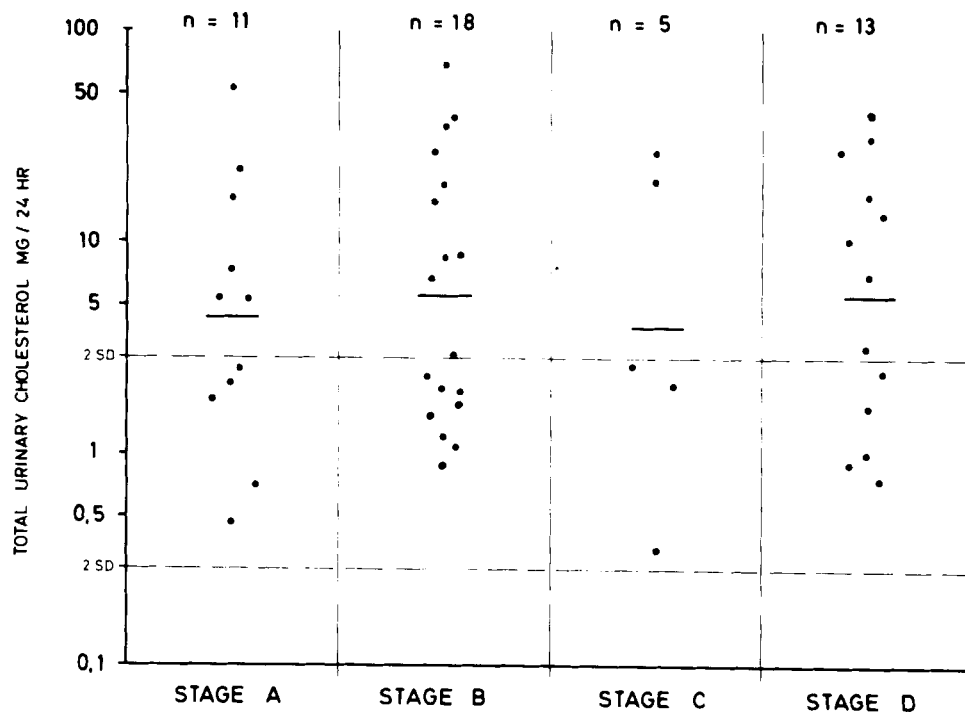


FIG. 4. Urinary excretion of total cholesterol in patients with prostatic carcinoma stage A-D.

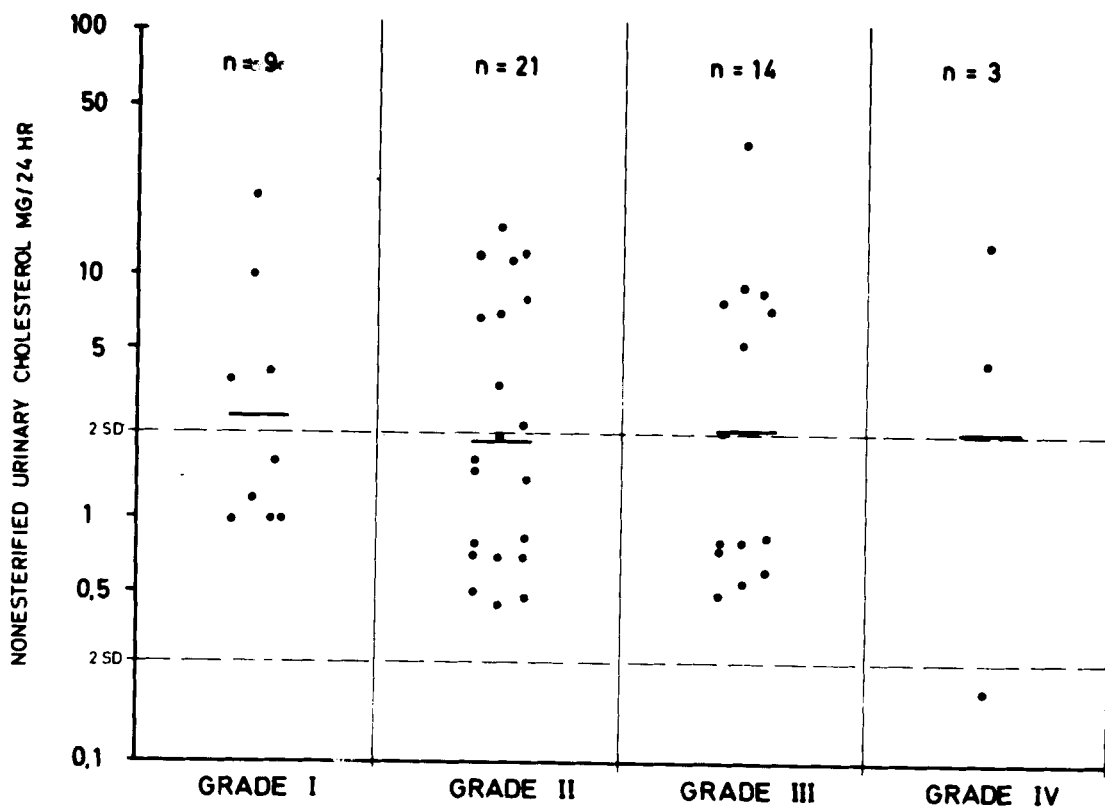


FIG. 5. Urinary excretion of nonesterified cholesterol in patients with prostatic carcinoma histological grade I-IV.

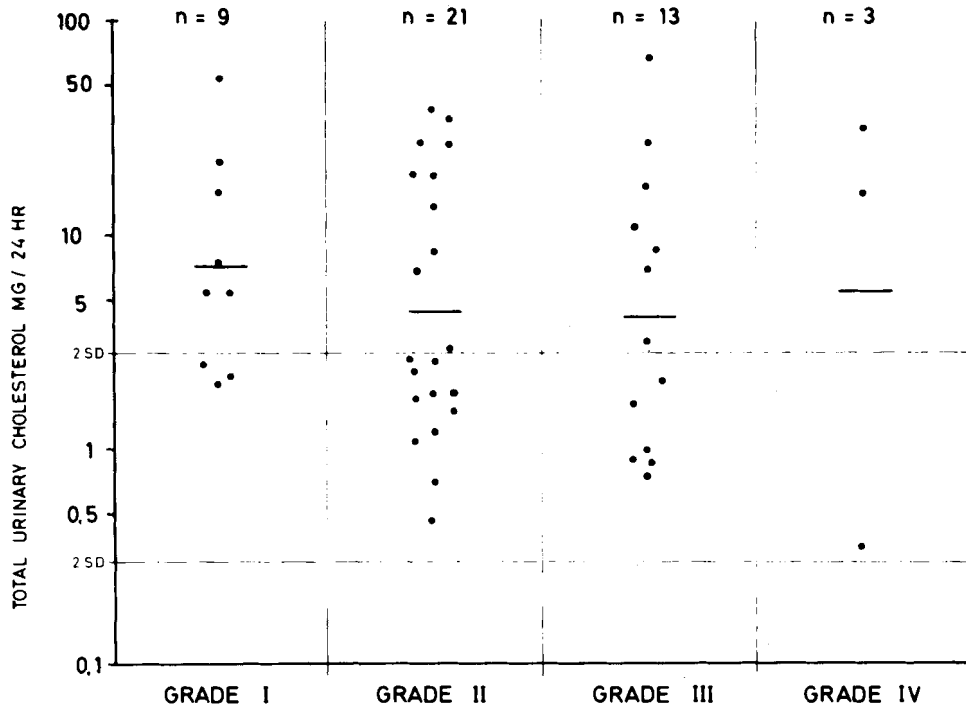


FIG. 6. Urinary excretion of total cholesterol in patients with prostatic carcinoma histological grade I-IV.

tatic hyperplasia are presented in Fig. 2. It is remarkable that in the 22 patients with stage 0-1 NEC and TC values were normal in contrast to the 57 patients with stage 2-3 who revealed elevated NEC in 42.1% and elevated TC in 61.4%.

#### Adenocarcinoma of the Prostate

The NEC and TC values of 48 patients with prostatic carcinoma are illustrated in Figs. 3-6. The diagnosis was made on tissue obtained by needle biopsy or after resection. The group was divided in clinical stage A-D according to Flocks (Figs. 3, 4) and based on the histologic examination in grade I-IV (Figs. 5, 6). Hyperexcretion of NEC was present in 44.8% of stage A and B and in 52.6% of stage C and D; elevated TC values were detected in 52.2% and 63.2% respectively.

Both parameters did not show any correlation to histological findings. It was remarkable that even in stage A NEC and TC hyperexcretion occurred; in all of these patients levels of serum acid phosphatase were normal.

Simultaneous determination of NEC and serum acid phosphatase gave a pathological result of at least one parameter in 51.7% of stage A and B and in 84.2% of stage C and D

(Fig. 7). If TC and serum acid phosphatase were combined, percentage of elevated values increased to 62.1 of stage A and B and was identical with 84.2 in stage C and D (Fig. 8).

#### DISCUSSION

The association of enhanced serum acid phosphatase activity with prostatic neoplasms is well known; unfortunately, it is not suitable for detection of early clinical stages.<sup>12,14</sup> Elevation of urinary nonesterified cholesterol in patients with prostatic cancer was first reported by Acevedo *et al.*<sup>2</sup> In a series of 32 patients, in 29 (91%) hyperexcretion of NEC was observed based on an upper normal limit of 1.2 mg/24 hours. Nonesterified cholesterol seemed to be the major component, representing about 70% of total urinary cholesterol, but only in a few cases have NEC and TC been determined simultaneously. In a comparative evaluation of serum acid phosphatase and total urinary cholesterol in prostatic cancer, Chu *et al.*<sup>9</sup> found pathologic values of serum acid phosphatase (SAP) in 67% and of urinary cholesterol in 62%. When a combined determination of these two assays was performed, in 86% of the patients with prostatic cancer at least one parameter was elevated.

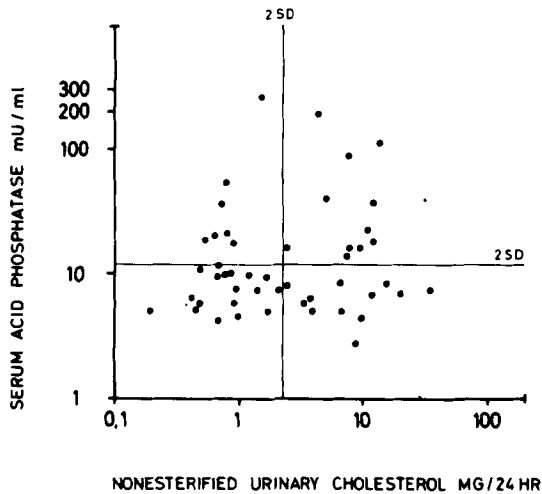


FIG. 7. Comparable evaluation of serum acid phosphatase and nonesterified urinary cholesterol in prostatic carcinoma.

It was concluded that a simultaneous determination of these parameters is valuable in diagnosing patients with prostatic neoplasia. However, it has to be mentioned that all patients except one had stage D carcinoma with diffuse osseous metastasis.

The percentage of pathologic results is dependent on the upper normal limit of an assay. For urinary nonesterified cholesterol we classified all values below 2.2 mg/24 hours as normal. The higher percentage of elevated NEC values in prostatic carcinoma described by Acevedo *et al.*<sup>2</sup> is caused by the lower upper

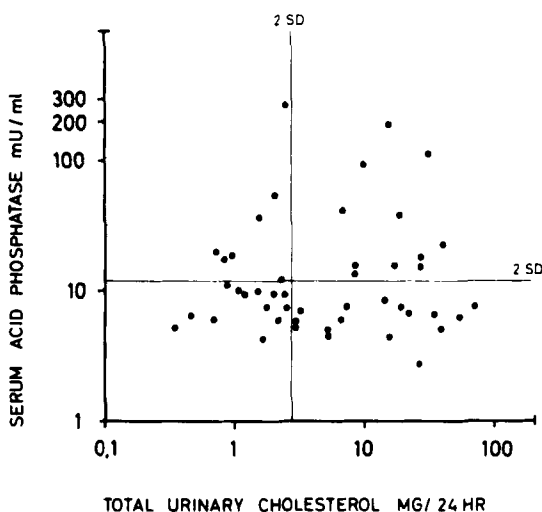


FIG. 8. Comparable evaluation of serum acid phosphatase and total urinary cholesterol in prostatic carcinoma.

normal limit of 1.2 mg/24 hours, which might be due to methodological differences. The rate of pathological urinary total cholesterol values in prostatic neoplasms reported by Chu *et al.*<sup>9</sup> was very similar to those for stage C and D presented in this study, due to the nearly identical upper normal limit of 2.6 mg/24 hours in comparison to 2.9 mg/24 hours. Consequently we found in stage C and D a nearly identical rate of elevated values for simultaneous determination of SAP and total urinary cholesterol.

In benign prostatic hyperplasia stage 0-1, urinary cholesterol values were normal. However, the presence of residual urine in BPH was associated in a considerable percentage with pathologic NEC and TC levels. In all the latter patients the diagnosis was done from tissue obtained by TUR, there was no evidence of cancer in the samples examined. The possibility of "occult" prostatic carcinoma being at least in part responsible for the observed pathologic urinary cholesterol levels could be not completely excluded, since such a diagnosis is done at autopsy and the complete gland has to be studied.

In discussing the clinical value of the NEC and TC test in the diagnosis of prostatic cancer, one has to consider that elevated urinary cholesterol levels had been detected in other diseases too, although the scientific value of older studies is limited due to the inadequate analytical techniques, as well as in some cases, to gross deficiency in patient selection.<sup>2,4,5,6,7,8,9,10,12,17,18</sup> Hyperexcretion of urinary cholesterol in males occurred in patients with pluripotential malignant testicular neoplasms and benign or malign diseases of kidney and urinary tract.<sup>3,12,13,18,19</sup> If these diseases and BPH with residual urine can be excluded with reasonable certainty, NEC or TC determinations may be valuable in the diagnosis of prostatic cancer even in the early clinical stages of the disease, especially when in combination with serum acid phosphatase.

The physiologic mechanisms of urinary cholesterol excretion are not known; Acevedo *et al.* suggested an excretion as a protein bound complex.<sup>1</sup> Hyperexcretion in nephrotic syndrome is possibly caused by increased glomerular filtration of plasma lipoproteins especially HDL fraction.<sup>15</sup> If elevated urinary cholesterol is present without incidence of disease in the kidney and urinary tract, as in the case of prostatic carcinoma, higher production of specific lipoproteins by the malign-

nant cells may be discussed. In patients with prostatic adenoma, the presence of residual urine could be responsible for the observed elevated urinary cholesterol values.

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