

Intraprostatic Injections of Various Antitumoral Compounds into Rats

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Summary. The local effects of seven antitumoral compounds injected into the prostates of old male CR rats were studied. - The acute and sub-acute histopathological patterns found give rise to the hypothesis of a direct biological or chemical action of some of the tested drugs on the glandular epithelium of the rat prostates.

Key words: Intraprostatic injections, local effect of antitumoral compounds, acute and subacute effects, histological findings

Introduction

Lower and Johnston (2) in 1930, described their experiments designed to reduce the size of the prostate in dogs and rats. They tried local intraprostatic injections of various chemical reagents, such as silver nitrate 5-10%, sodium hydroxide 10%, Lugol's solution, and 95% alcohol. Of the animals that survived, prostates were reduced in size due to fibroblastic replacement.

O'Connor and Ladd (4) reported in 1936-37 on the effect of injecting mercurochrome 2%, silvol 5%, electrargol and metaphen tincture 1/5000% into the prostates of dogs, as well as distilled water and normal saline or simple needling of the prostate. They concluded from histological studies on the sacrificed animals, that the local prostatic changes resulting from such procedures do not depend on the specific effect of the chemical agent used but on a fibrotic reaction common to all.

Similar experimental observations were reported later.

Ritter and Lippow (6) in 1938, after injecting electrargol into guinea pigs' prostates, found that the resultant early inflammatory reactions were replaced a month later by fibrotic tissue which reabsorbed itself to the point of disappearance in the course of time.

Emmett, Lovelace and Mann (1) reported in the same year the results of their experimental study on eight dogs, into whose prostates sylnasol was

injected in one lobe only, reserving the second for control. A marked reduction in the size of the injected lobe was finally found, this being the result of a reduction in the size and number of the glandular acini and an increase of the connective stroma.

Riba, Milligan and Queen (5) in 1940, following Townsend's (7) observation that substances diffuse from one point throughout the gland, performed injections in one area of the dogs' prostates, using 1% mercurochrome, normal saline and simple puncture. Gross and microscopic examination revealed no definite distinction in the prostates of the variously treated animals from those of the control dogs, an inflammatory reaction with fibrosis being present in the injected animals that was also discernible in the untreated prostates of experimental animals.

Neal et al. (3) in 1972, reported the results of intraprostatic injections in twelve dogs, using methotrexate. At autopsy they observed chronic inflammatory changes and some reduction in the prostatic size due to fibrosis.

The above-quoted works were involved, in the main, with chronic effects of the reagents tested. The purpose of the present work was to examine, histopathologically, the acute and sub-acute effects on rat prostate of seven different antitumoral drugs injected intra-prostatically.

Material and Methods

Ten-week-old male CR rats were injected in the prostate after performing laparotomy. Seven different drugs were tested, each of which was injected into ten animals. A control group of ten rats was injected with saline.

Five animals from each group were sacrificed one week after injection and the remaining five one

week later. Histological examinations were performed on the following organs: prostates, testes and epididymis, bladder, liver, kidneys, adrenals and heart. The sections were stained with haematoxylin-eosin-phosphomolybdic acid - light green stain, after Bouin fixation.

The following drugs were tested:

1. Epodyl: Triethyleneglycol diglycidyl ether (I.C.I. 32865). 0.02 c.c.

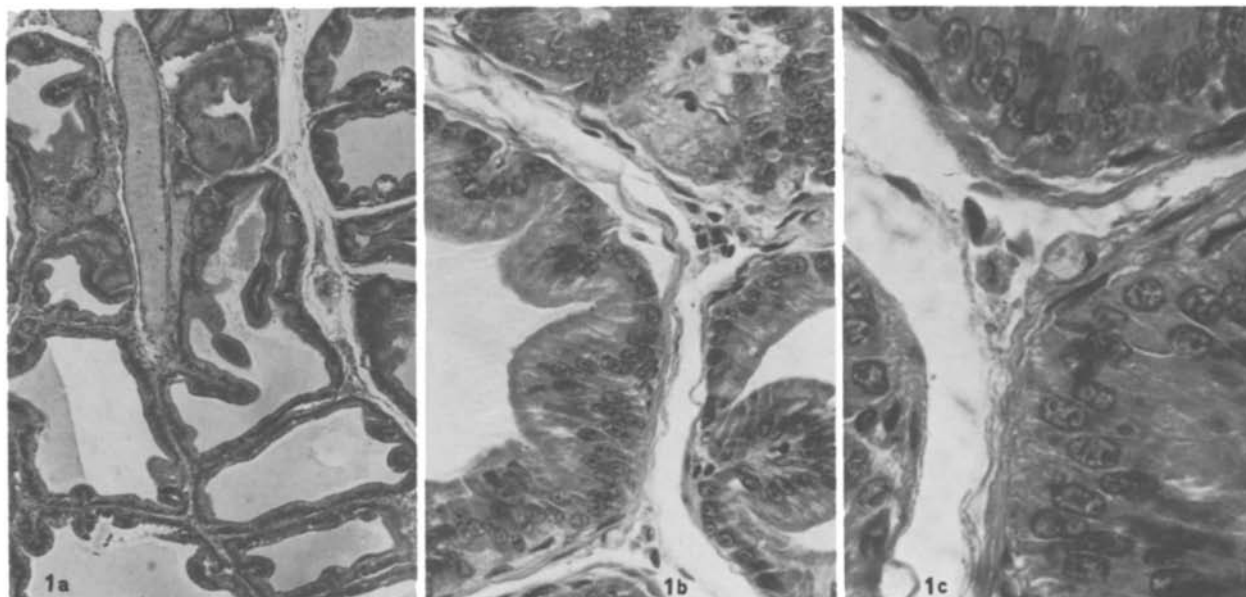


Fig. 1. Prostate, CR rat, 12 weeks old, H.E. + L.G. a) x 120, b) x 200, c) x 500

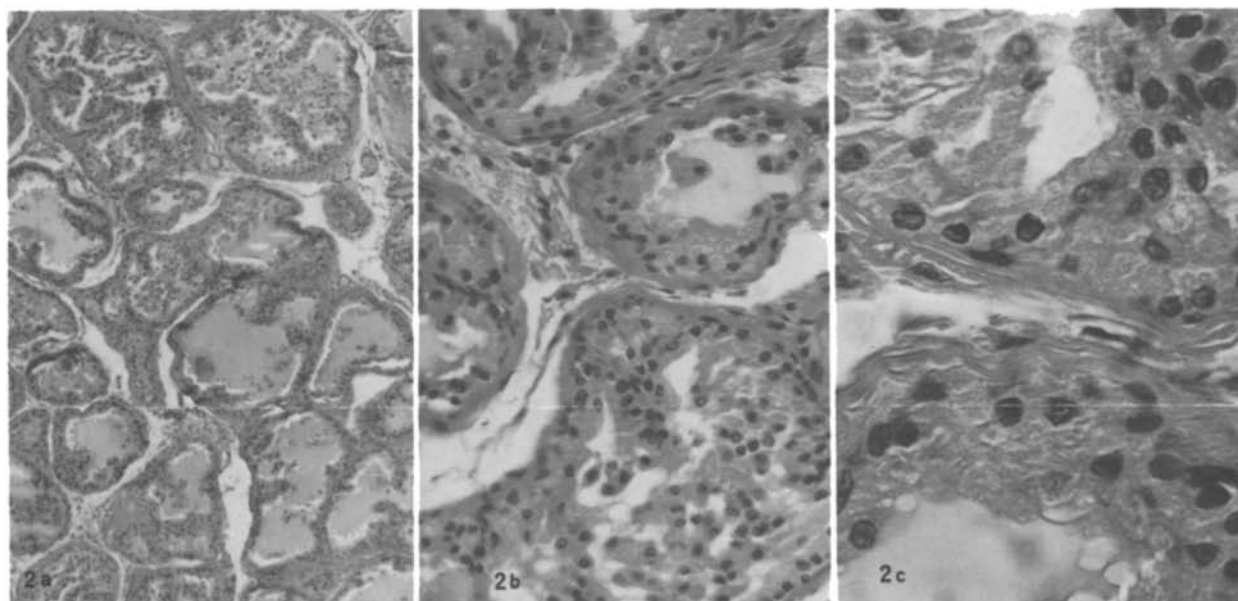


Fig. 2. Epodyl treated prostate: necrotic and necrobiotic changes of glandular epithelium H.E. + L.G. a) x 120, b) x 200, c) x 500

2. Thiotepa; U.S.P. Tris (1-azyridinyl) phosphine Sulfide. 0.06 mg.
3. Mitomycin-C (Kyowa). 0.01 mg.
4. Actinomycin D.: (Dactinomycin - Cosmogen Lyovac M.S.D.). 0.01 mg.
5. Fluoro-uracil; I.S.P. - 5-Fluor-uracil. 0.01 mg.
6. Methotrexate; 4-Amino - N¹⁰ - Methyl Pteroylglutamic Acid. 0.1 mg.
7. Proresid: (SP-I/SP-G), Podophyllinic acid 2-ethylhydrazide. 4 mg.
8. Normal saline (control group). 0.02 c.c.

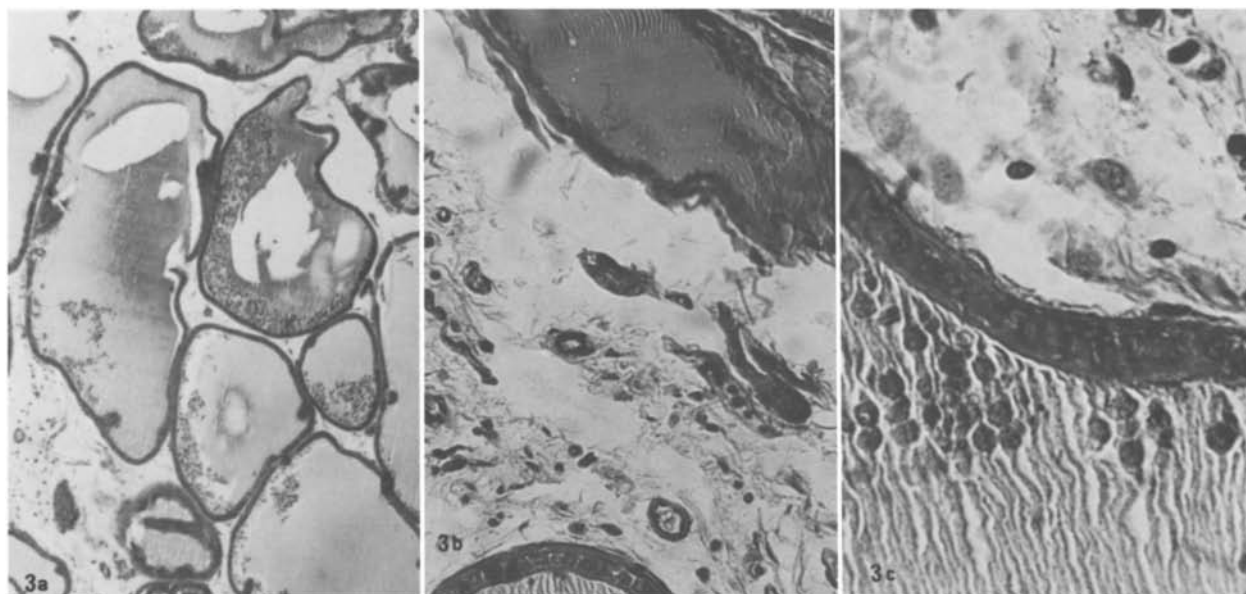


Fig. 3. Thiotepa treated prostate: Flattening and desquamation of the glandular epithelium. H.E. + L.G. a) x 120, b) x 200, c) x 500

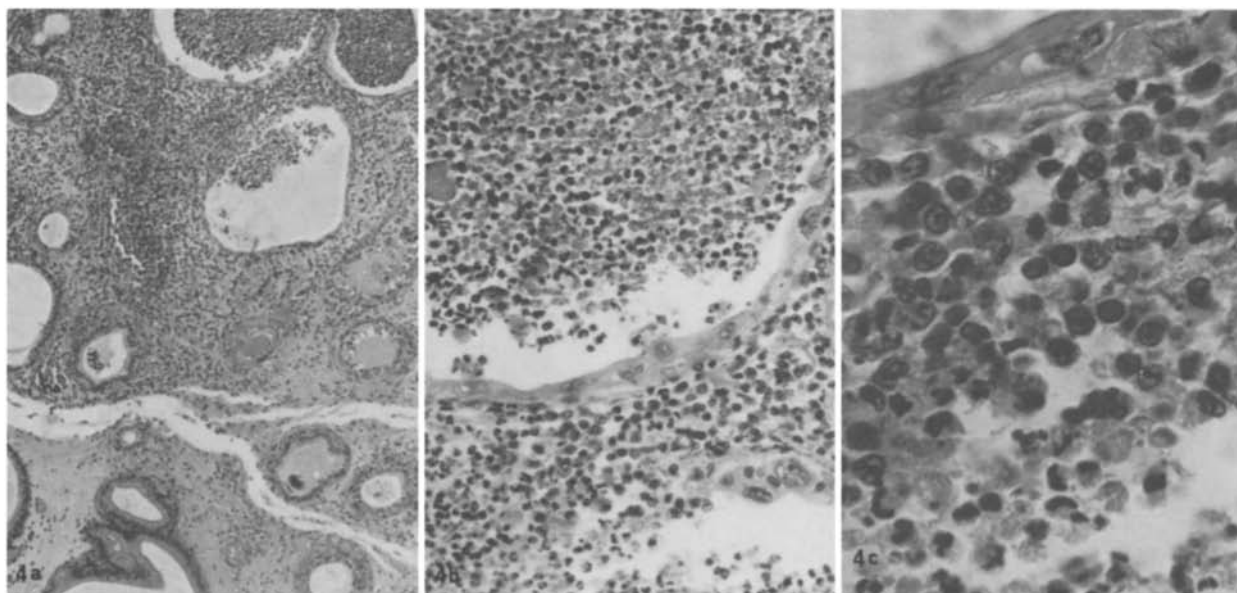


Fig. 4. Mitomycin C treated prostate, Abscesses formation. H.E. + L.G. a) x 120, b) x 200, c) x 500

Results

The prostate itself was the only organ showing abnormal pathology following local injection of the antitumoral agents, except in the cases specifically mentioned below.

The histopathological findings were as follows:

1. Epodyl group (Fig. 2.: a, b and c): severe damage of the prostate mainly in the form of abscesses and necrosis of injected areas; clear

necrobiotic changes of the glandular epithelium. Toxic lesions were observed in the liver (vacuolar and fatty degeneration of the centro-lobular cells). Three animals died within the first week after injection, presenting the same histological picture.

2. Thiotepa group (Fig. 3.: a, b and c): flattening and partial desquamation of the glandular epithelium. Although all the animals were clinically normal, mild toxic changes were found in the liver.

3. Mitomycin C group (Fig. 4.: a, b and c):

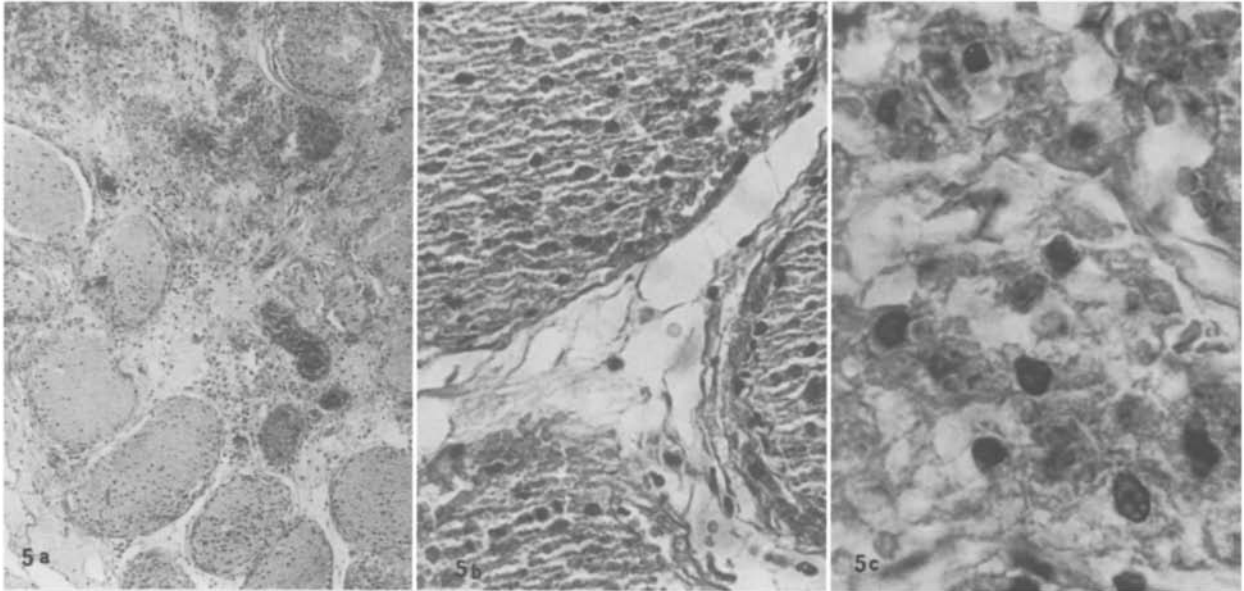


Fig. 5. Actinomycin D treated prostate: Diffuse necrosis of the gland. H.E. + L.G. a) x 120, b) x 200, c) x 500

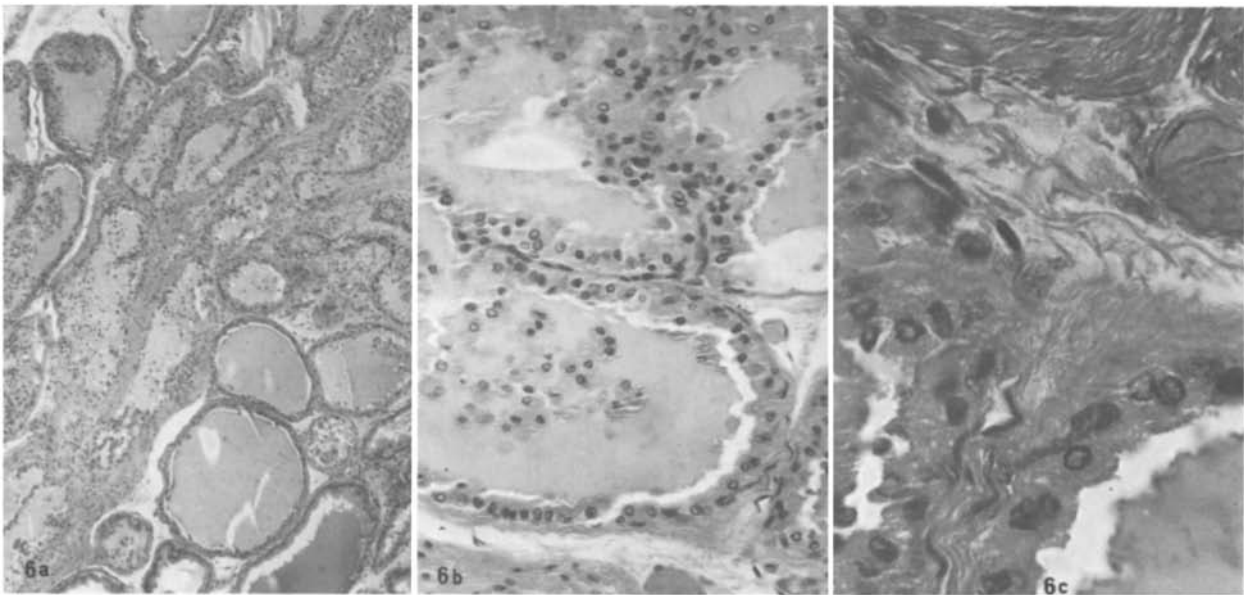


Fig. 6. Fluoro-uracil treated prostate: Massive epithelial desquamation and necrobiotic changes. No cellular inflammatory reaction. H.E. + L.G. a) x 120, b) x 200, c) x 500

Interstitial inflammatory reaction with formation of abscesses. No pathological changes in other organs or clinical symptoms were found.

4. Actinomycin D group (Fig. 5.: a, b and c): Interstitial inflammatory and severe epithelial necrosis of the prostates were found, other organs being normal. The animals of this group were apathetic and weak.

5. Fluorouracil group (Fig. 6.: a, b and c): Flattening and massive epithelial desquamation

with necrobiotic changes and very mild interstitial cellular reaction. No clinical symptoms could be observed.

6. Methotrexate group (Fig. 7.: a, b and c): The majority of the prostates were normal except for minute regions where flattening and slight desquamation of the glandular epithelium were seen.

7. Proresid group (Fig. 8.: a, b and c): This drug was found to be extremely toxic to the rats,

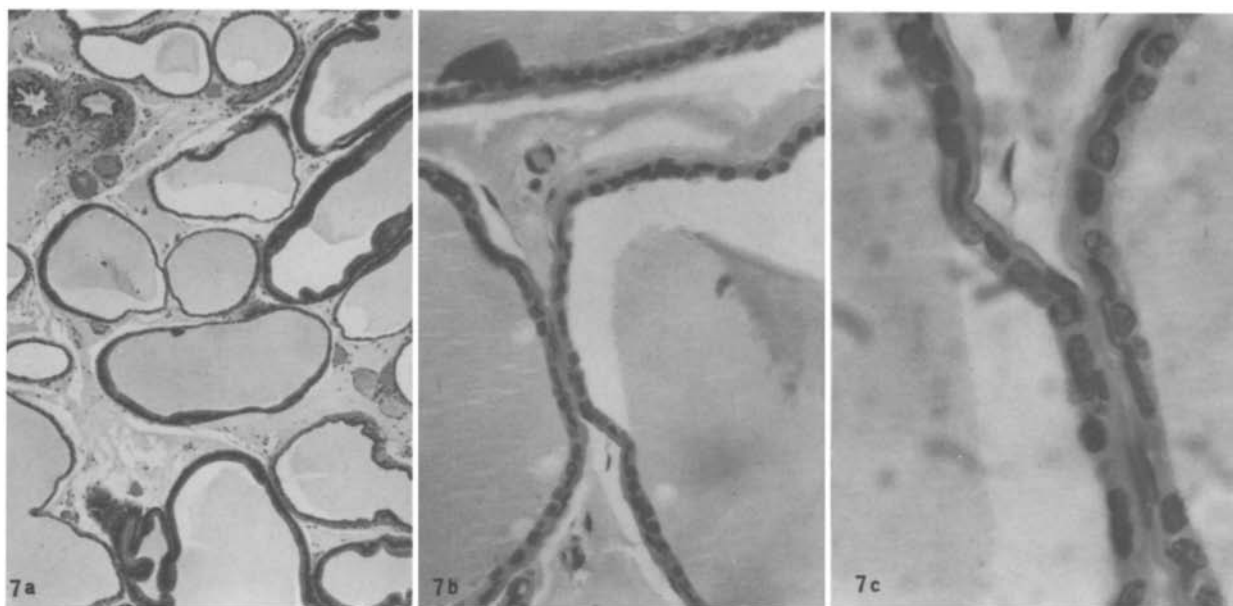


Fig. 7. Methotrexate sodium treated prostate. Flattening of the epithelium and a mild inflammatory reaction. H.E. + L.G. a) x 120, b) x 200, c) x 500

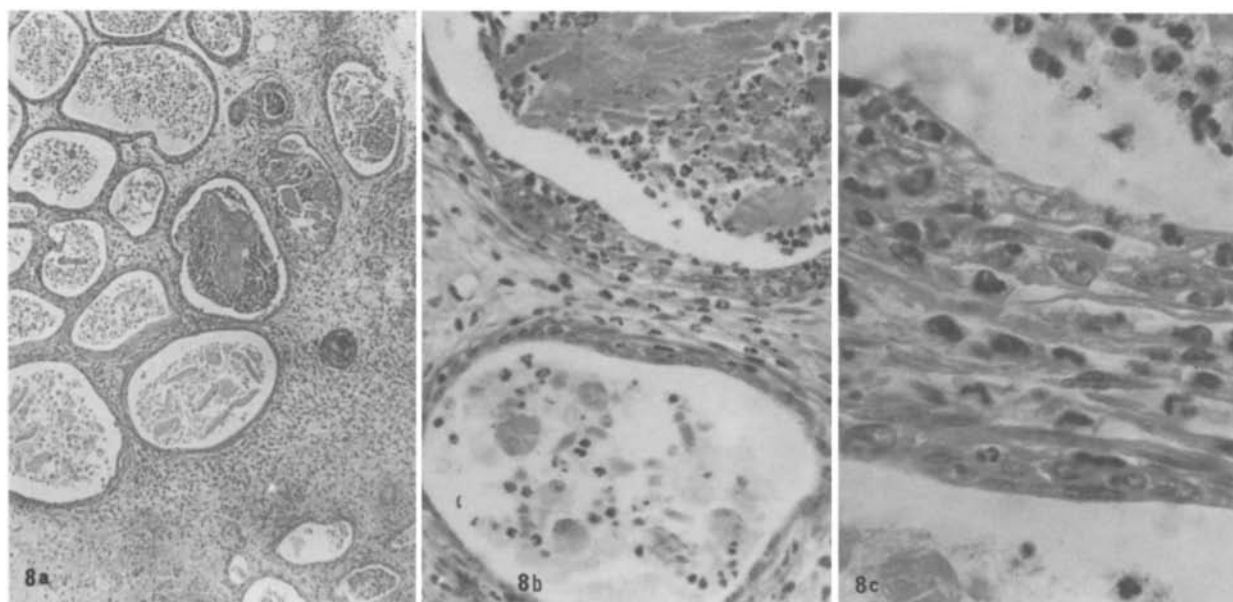


Fig. 8. Proresid treated prostate: Abscesses formation and necrotic changes. H.E. + L.G. a) x 120, b) x 200, c) x 500

seven out of ten animals dying within ten days following injection. The prostates showed diffuse abscesses and severe epithelial necrotic changes. Similar lesions were observed in the urinary bladder and in the coagulating glands.

Discussion

Seven groups of ten rats each received intraprostatic injections of seven different antitumoral compounds. One test group was injected with saline only (Fig. 1: a, b and c, showing normal histology).

The acute and sub-acute histological findings in the rat prostates show reactions in the glandular epithelium and interstitium that suggest a special local effect and not a non-specific tissue reaction.

Although each of the drugs tested shows a dissimilar local effect, the main histological changes can be divided into two groups:

Group A. Clear and constant flattening of the glandular epithelium with a mild interstitial reaction. This histological pattern was observed in the rat prostates treated with Thiotepa and Fluorouracil. The Methotrexate treated group showed only minute histological changes of the same nature.

Group B. Severe local damage: sterile abscesses and necrotic foci. These lesions were present in the rats injected with Epodyl, Mitomycin C, Actinomycin D and Proresid.

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