

The Acute Effects of Various Cytotoxic Compounds Injected into the Prostate Glands of Dogs

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Summary. The acute effects of direct injections with various cytotoxic compounds into the prostates of adult dogs were studied microscopically. The effects remained localised to the site of injection, with no diffusion of the agents into other areas of the prostate. No systemic effects were observed despite the high concentrations used. The main histological changes consisted of focal aseptic necrosis at the injection site surrounded by atrophy of the acinar epithelium.

Key words: Intraprostatic injections - Cytotoxic compounds - Local acute effects.

The gross architecture and microscopic structure of the adult canine prostate make it a suitable model for studying the effects of locally injected therapeutic agents. Several such studies have been reported with local injections of silver nitrate, sodium hydroxide, Lugol's solution and 95 % alcohol (3); mercurochrome, silvol, electrargol and metaphen tincture (5); sylnasol (1); mercurochrome and normal saline (6); and methotrexate (4). All of the reported histological changes were those of early inflammatory reactions followed by fibrosis. These effects were considered to be a non-specific response to the irritating chemical agents.

The aim of our study is to test a group of different anti-tumour compounds injected into the dog prostate and to describe the local acute histopathological findings.

MATERIALS AND METHODS

Sixteen adult male Mongrel dogs weighing from 25 to 40 kg were used. All animals were anaesthetised with intravenous Nembutal. The prostate was approached suprapubically and

extraperitoneally and exposed beneath the symphysis after reflection of the periprostatic fat. The right side was always the side injected with the cytotoxic compound and a biopsy was taken from the left lobe to act as control.

In all cases the post operative course was uneventful and the animals were sacrificed and autopsied after one week. Material for histopathological study was obtained and prepared from the prostate, lung, liver and kidneys; the sections were stained with haematoxylin-eosin and light green.

The following drugs were tested:

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|------------------------------|--|
| 1. Fluorouracil:
(n = 2) | 5-Fluoro-1, 2, 3, 4-tetrahydropyrimidine
75 mg (1.5 ml) |
| 2. Thiotepa:
(n = 2) | Triaziridin-1-ylphosphine
sulphide 15 mg (2 ml) |
| 3. Mitomycin-C
(n = 2) | 2 mg (2 ml) (Kyowa) |
| 4. Actinomycin D:
(n = 2) | (Dactinomycin, Cosmogen)
0.5 mg (2 ml) |
| 5. Etoglucid
(n = 2) | (Epodyl, ICI 32865)
1.13 mg (5 ml) |
| 6. Methotrexate:
(n = 2) | 4-Amino-N ¹⁰ -methyl
pteroylglutamic acid
2.5 mg (1 ml) |

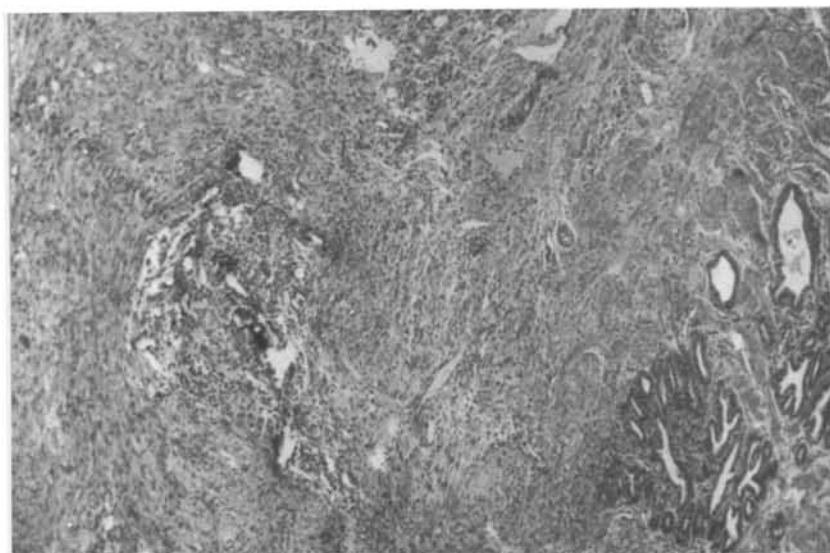


Fig. 1. Fluoro-Uracil:
HE-LG x 90

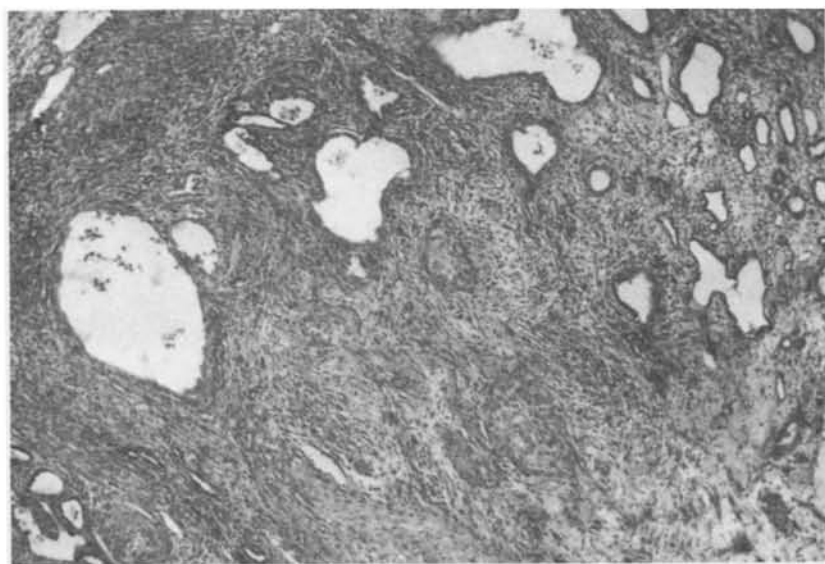


Fig. 2. Thiotepa:
HE-LG x 90

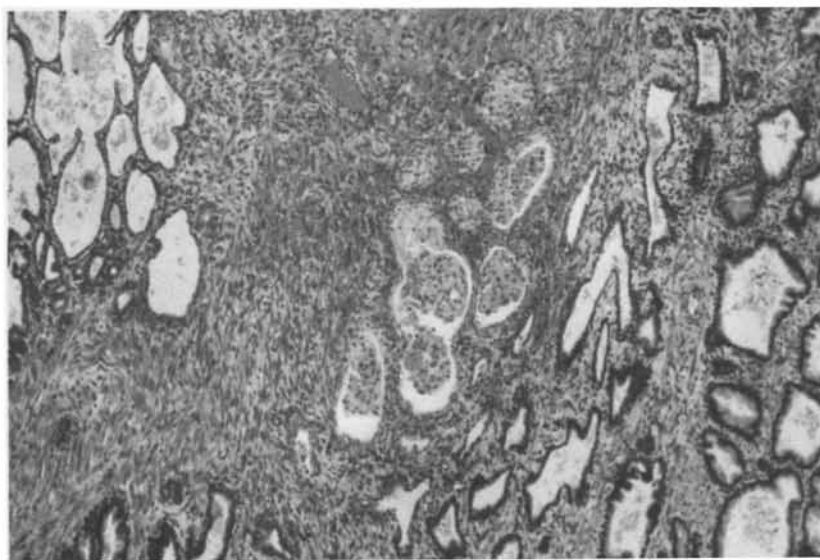


Fig. 3. Mitomycin-C:
HE-LG x 90

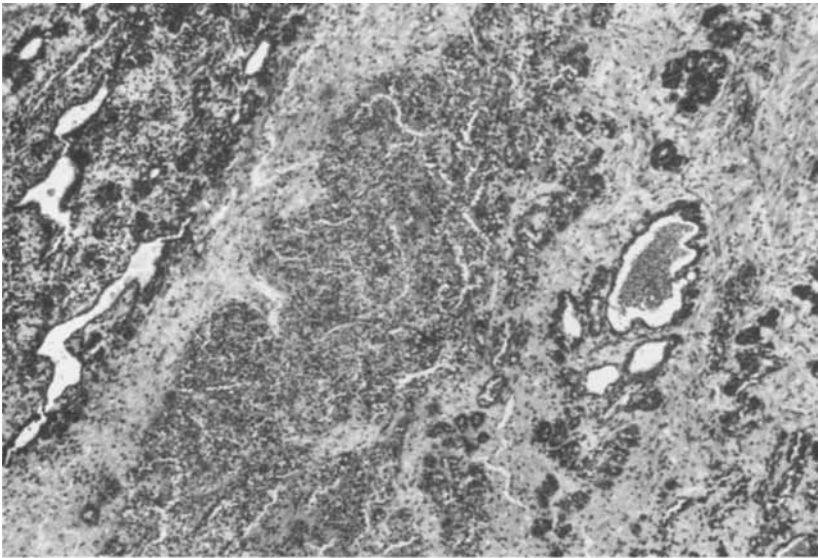


Fig. 4. Actinomycin D:
HE-LG x 90

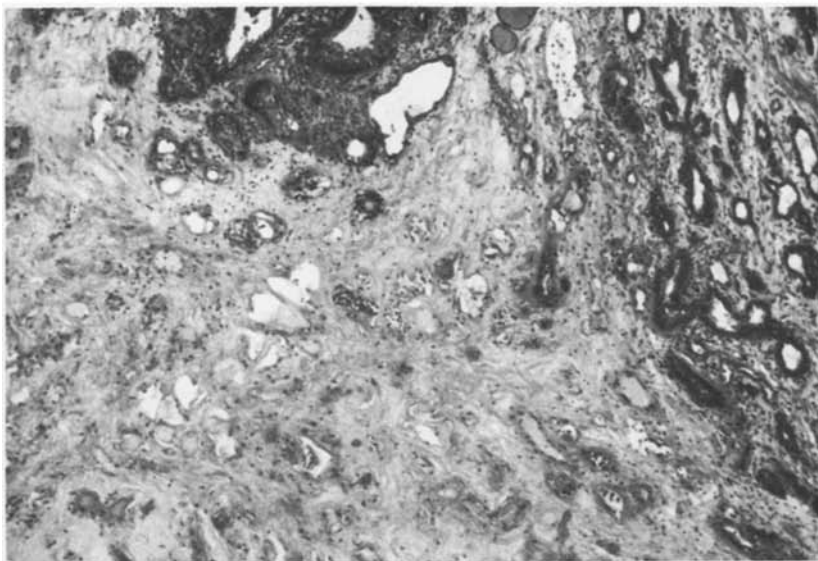


Fig. 5. Epodyl: HE-LG x 90

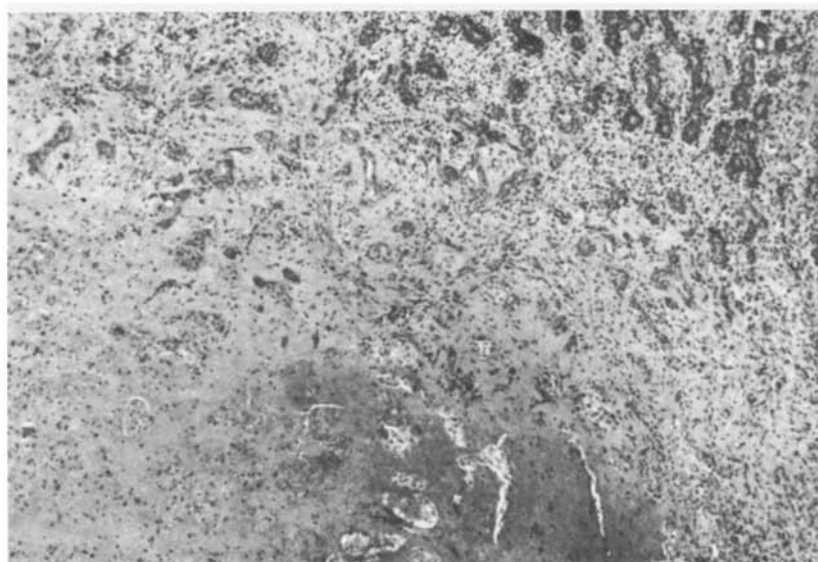


Fig. 6. Methotrexate:
HE-LG x 90

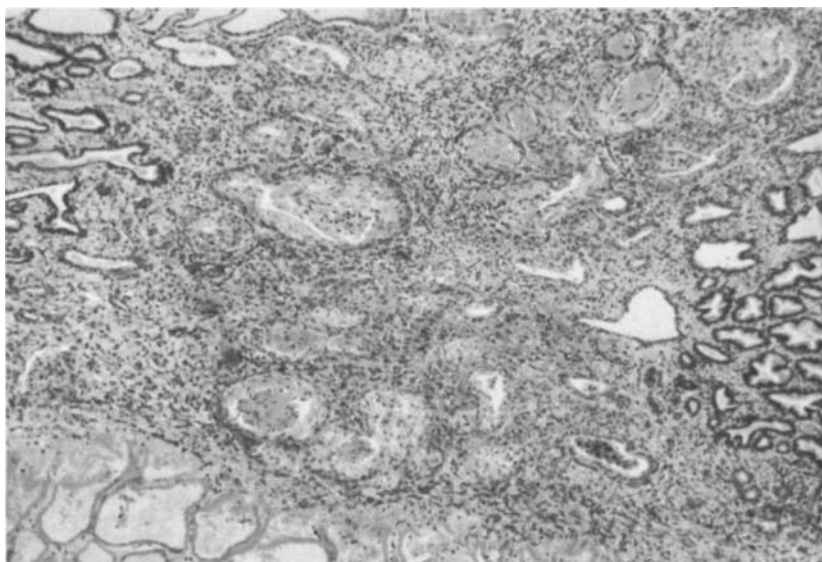
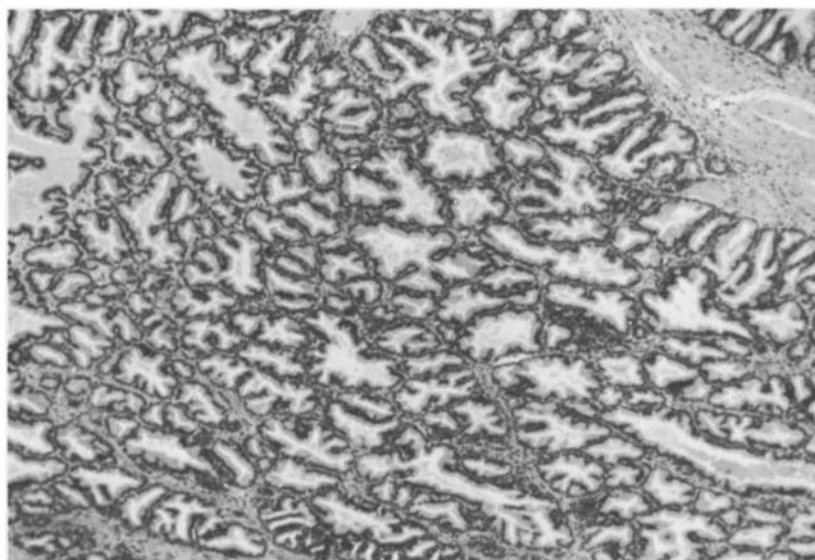


Fig. 7. Proresid: HE-LG x 90

Fig. 8. Normal saline:
HE-LG x 90

- | | |
|------------------------------|--|
| 7. Mitopodozide:
(n = 2) | Podophyllinic acid
2-ethylhydrazide.
(Proresid, Sandoz)
200 mg (1 ml) |
| 8. Normal saline:
(n = 2) | Controls. (2 ml) |

RESULTS

Most of the prostates appeared normal on external examination, except for a few which showed changes at the biopsy sites. On transverse section the biopsy site was clearly seen as an haemorrhagic spot, but the injection site could not be located macroscopically.

Histological examination of the intra-operative biopsy of the left lobe revealed a normal gland in some animals but hyperplastic changes varying from mild to severe were seen in others, usually accompanied by local areas of chronic prostatitis.

The histological patterns in the injected lobes related to the individual compounds are illustrated in Figures 1-7 and may be summarised as follows:

"Focal necrosis surrounded by an inflammatory reaction and with atrophy of the neighbouring acini. Some of the acini appeared dilated with desquamated glandular epithelium."

The apparent differences in the histological details of the prostates injected with related

compounds do not alter the major aspects of the changes described. These differences may be the result of a varying intensity of action or of the concentrations of the solutions injected.

DISCUSSION

The drugs injected into the prostate gland of adult dogs in this study had a strictly local effect with no damage to the areas surrounding the affected tissue. These compounds do not appear to diffuse through the entire gland as might be expected (7) .

In spite of the high local concentrations no pathological changes were observed in the other organs or tissues examined. All the dogs made rapid post-operative recovery and no clinical signs of drug side effects were observed. This suggests that the use of relatively high quantities of cytotoxic drugs by local injection may be possible without the danger of damaging other organs.

Histologically, pronounced necrosis at the site of the injection and atrophy of the peripheral glandular epithelium were seen in all specimens. It appears that the necrosis is the result of a local effect of the high concentration of the cytotoxic compounds while the atrophy is a mild response to a more dilute concentration of the drugs. The histological variations may be the result of variations in the local action of the drugs investigated, but an essentially similar histological pattern was observed in all of them.

These observations demonstrate the ability of the prostate gland of dogs to be locally modified in its structure by the action of antitumour compounds and supports the results obtained by injecting these substances into rat prostates (8).

The relative harmlessness of the drugs tested indicates the need for similar experi-

ments with other compounds in the search for a drug with a specific action on the prostate gland.

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