Urological Research 4, 19-22 (1976)

Urological Research

Intraprostatic Injections of Various Antitumour Compounds into Rats
Part II. Chronic Effects

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Received: November 18, 1975

Summary. Histopathological studies were carried out at intervals of one, two and three months after a single injection of one of seven antitumour compounds into the prostates of adult male CR rats. The histological findings indicate mainly a long term effect of the compounds tested on the glandular epithelium of the rat prostate. The effect is strictly local and no side effects were seen.

Key words: Intraprostatic injections, Antitumour drugs.

In a previous paper (1) we presented the acute and subacute histopathological changes found in the prostates of adult male CR rats after single local intraprostatic injections of seven antitumour compounds. The present work deals with the chronic effects of the same antitumour substances on the prostate gland.

MATERIALS AND METHODS

Ten-week-old male CR rats were subjected to laparotomy and the prostate gland was injected once with one of the seven drugs listed below. Each drug was administered to a group of 15 animals, and a control group was injected with saline only.

Five animals from each group were sacrificed at intervals of one, two and three months respectively, following the injection, and histological examinations were performed as described previously (1).

The drugs tested and the doses administered were:

1. Epodyl	0.01	mg
2. Thiotepa	0.06	mg
3. Mitomycin-C	0.01	mg
4. Actinomycin-D	0.005	mg
5. Methotrexate	0.1	mg
6. Proresid	1.0	mg
7. Fluorouracil	0.01	mg

RESULTS

Only the prostate gland showed histological changes following local injections of the antitumour agents. None of the other organs examined revealed any histopathological changes. The specific findings in each experimental group are detailed below; (It must be noted that the drugs which caused severe damage and a high death rate in the acute experiment were administered this time in reduced dose)

The histopathological findings are as follows:

1. Epodyl

After 1 month: Areas with epithelial atrophy together with some regeneration were noted. Other areas showed a chronic inflammatory reaction and some of the acini were packed with cellular debris and inflammatory cells. Macrophage activity was pronounced together with some foreign body giant cell reaction.

After 2 months: A mild chronic interstitial inflammation was observed together with foci which showed atrophy of glandular epithelium.

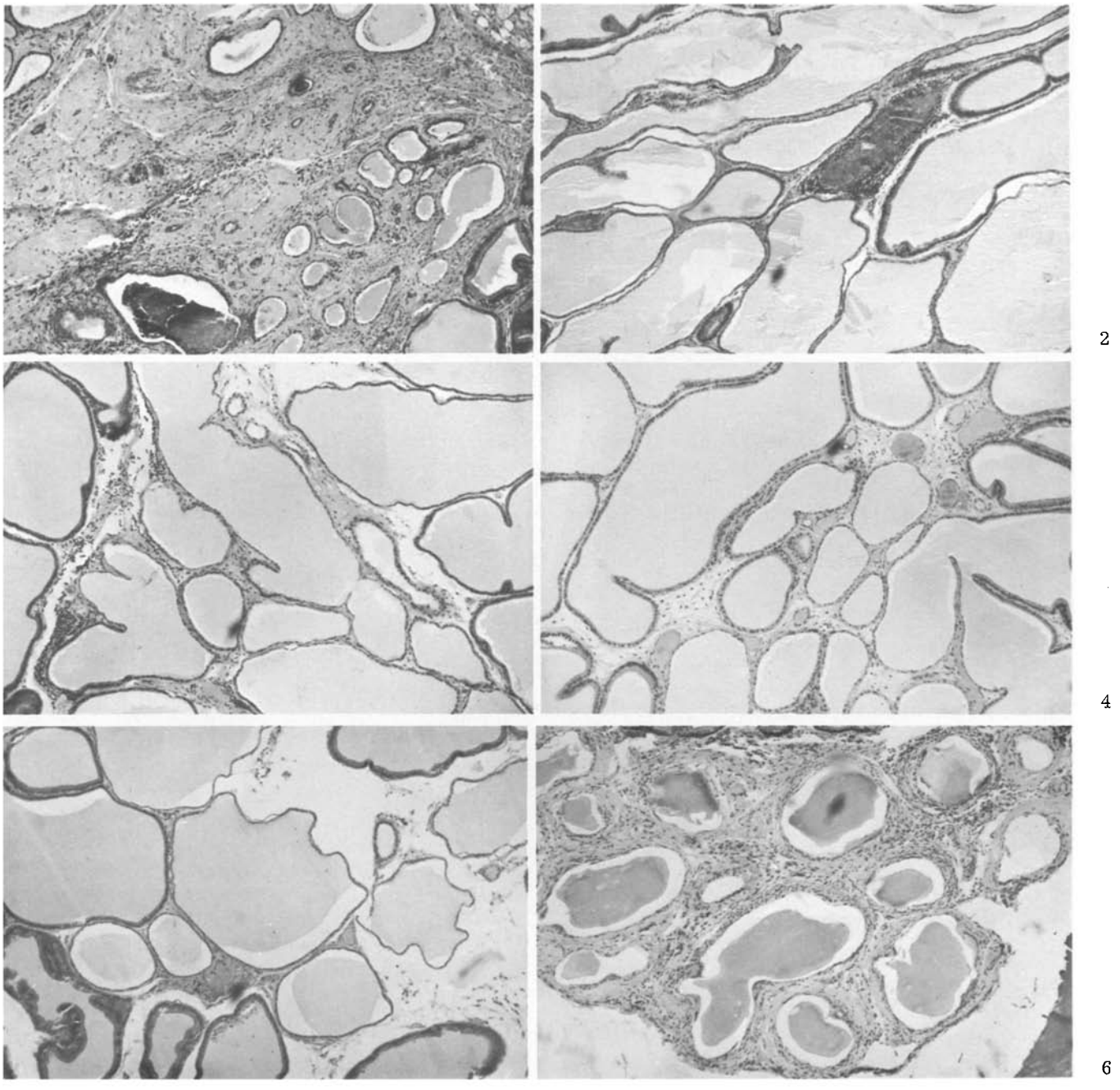
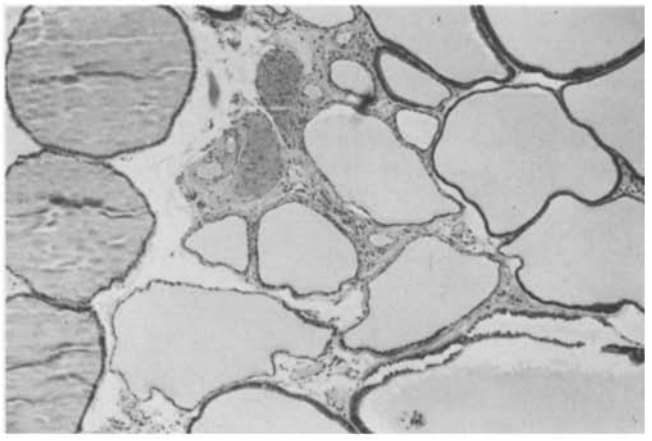


Fig. 1. Epodyl, after 3 months: affected areas show atrophic epithelium and fibrosis. HE-LG x 120
Fig. 2. Thiotepa, after 3 months: mild interstitial inflammation with flattened and slightly atrophied epithelium. HE-LG x 120
Fig. 3. Mitomycin-C, after 3 months: the acinar epithelium is flattened and partially atrophic. The interstitium shows mild inflammation and oedema. HE-LG x 120
Fig. 4. Actinomycin-D, after 3 months: glandular epithelium atrophy; slight fibrosis of the interstitium. HE-LG x 120
Fig. 5. Methotrexate, after 3 months: atrophic changes of the glandular epithelium. HE-LG x 120
Fig. 6. Proresid, after 3 months: foci of desquamated and atrophied epithelium; interstitial inflammation and fibrosis HE-LG x 120



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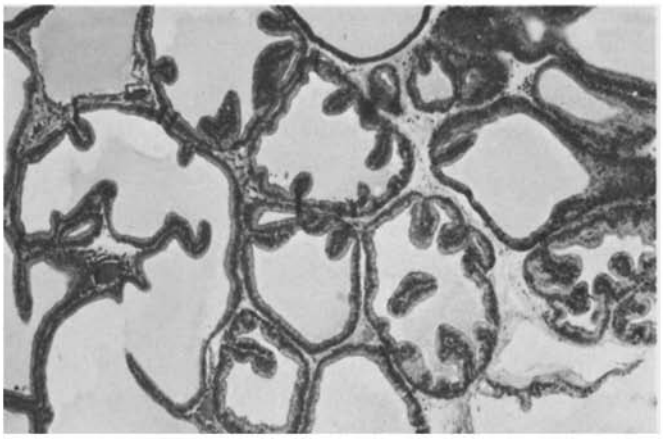

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Fig. 7. Fluorouracil, after 3 months: foci of glandular atrophy and mild chronic interstitial inflammation. HE-LG x 120
Fig. 8. Saline (control group), after 3 months: normal prostate gland. HE-LG x 120

After 3 months: Affected areas showed atrophied foci of glandular epithelium and fibrosis (Fig. 1).

2. Thiotepa

After 1 month: Some focal flattening and slight atrophy of glandular epithelium together with chronic intestitial inflammation were found.

After 2 months: The inflammatory reaction was milder and there was focal atrophy of glandular epithelium.

After 3 months: Focal atrophy was pronounced together with interstitial fibrosis (Fig. 2).

3. Mitomycin-C

After 1 month: Areas of focal glandular desquamation and atrophy were surrounded by chronic interstitial inflammation. Some acini were packed with inflammatory cells and debris.

After 2 months: The glandular epithelium was flattened and partially atrophied.

After 3 months: The atrophy was more advanced and accompanied by a mild fibrosis (Fig. 3).

4. Actinomycin-D

After 1 month: Focal glandular atrophy and some interstitial fibrosis was noted.

After 2 months: Glandular atrophy and mild fibrosis.

After 3 months: The same changes were observed (Fig. 4)

5. Methotrexate

After 1 month: Focal glandular atrophy and some chronic interstitial inflammation could be seen.

After 2 and 3 months: Foci of atrophied glandular epithelium and some interstitial inflammation were still present (Fig. 5).

6. Proresid

After 1 month: Some atrophic and inflammatory foci together with macrophagic activity was observed.

After 2 months: There was pronounced glandular atrophy with an exudative interstitial reaction.

After 3 months: Foci with destruction of glandular tissue; chronic interstitial inflammation and some fibrosis were seen (Fig. 6).

7. Fluorouracil

After 1 month: Areas showing some glandular epithelium atrophy and mild interstitial inflammation.

After 2 and 3 months: The same changes were observed (Fig. 7).

8. Saline

After 1, 2 and 3 months: Normal prostate gland (Fig. 8).

DISCUSSION

The effects of all of the antitumour compounds tested were restricted to the prostatic areas where the materials had been injected. Other parts of the prostate remained unaffected and no systemic effects were noted. The pathologic patterns induced by the different drugs showed marked similarity; however, there were differences in the intensity of the histological changes produced. According to the severity of the histopathological response, the different drugs could be divided into two groups, as in the earlier acute studies.

In group A' Thiotepa, Fluorouracil and Methotrexate showed only mild changes in the acute experiments. The later chronic changes were of the same mild nature, namely focal glandular epithelial atrophy, mild chronic interstitial inflammation and some fibrosis.

In the other group B' Epodyl, Mitomycin-C, Actinomycin D and Proresid showed severe local damage in the acute experiments in the form of sterile abscesses and necrosis. The chronic changes were also more pronounced, with inflammatory processes, macrophage activity, glandular atrophy and fibrosis.

The main histological finding in the chronic studies was related to the glandular prostatic epithelium with lesser and variable changes in the interstitium. Interstitial changes were not pronounced with Mitomycin-C and Epodyl.

REFERENCES

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