Cadmium Carcinogenesis in Male Wistar [Crl:(WI)BR] Rats: Dose-Response Analysis of Tumor Induction in the Prostate and Testes and at the Injection Site

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ABSTRACT

Carcinogenic dose-response effects of CdCl₂ in male Wistar [Crl:(WI)BR] rats were studied over a 2-year period. Groups of rats received a single s.c. injection of CdCl₂ at doses of 0, 1.0, 2.5, 5.0, 10.0, 20.0, or 40.0 μmol/kg in the dorsal thoracic midline. Other groups received either four separate s.c. doses of 5 μmol Cd/kg each (at 0, 48, 96, and 168 h), or low dose cadmium (5.0 μmol/kg, s.c., at 0 h) followed by a higher dose (10.0 or 20.0 μmol/kg, s.c., at 48 h). The cadmium treatments resulted in appearance of tumors at the injection site, in the testes, and in the ventral prostate. Injection site tumors (mostly sarcomas) appeared to be strictly related to accumulated dose of cadmium and approached a 45% incidence at the highest cadmium dose (40 μmol/kg). Testicular tumors (mostly Leydig cell adenomas) were found to be highly dependent on testicular degeneration caused by cadmium. The highest incidence and multiplicity of Leydig cell tumor incidence occurred in the 40 μmol/kg (83%) and 20 μmol/kg (72%) dosage groups. Low dose pretreatment (5.0 μmol/kg) reduced or prevented the testicular degeneration and tumor formation that would otherwise result from a subsequent higher dose of CdCl₂ (20 μmol/kg). Prostatic tumors (mostly adenomas of the ventral lobe) were also found to be associated with cadmium treatment, but in a non-dose related fashion. Prostatic tumor incidence was significantly elevated at the 2.5 μmol/kg dose of CdCl₂ (eight tumors/26 rats; 31%) and showed a strong positive correlation between 0.0 and 2.5 μmol/kg in both tumor incidence and multiplicity. At higher doses, including those that caused marked testicular degeneration and induced prostatic atrophy, an elevated incidence of tumors did not occur. The occurrence of hyperplastic foci of the prostate, however, showed a strong positive correlation with increasing dose after single injections of cadmium up to and including 20.0 μmol/kg. Results indicate that CdCl₂ can induce preneoplastic lesions of the prostate that appear to develop into tumors only at doses well below those causing marked degeneration of the testes and atrophy of the prostate.

INTRODUCTION

Several studies have indicated a carcinogenic potential for the heavy metal cadmium in both humans (1–6) and experimental animals (7–14). In rodent models, specific target sites for cadmium carcinogenesis have been defined and include s.c. or intramuscular injection sites (7–13), the testes (10–14) and, recently, the lung (15, 16). As is the case with several other metallic carcinogens, cadmium injection typically results in the formation of sarcomata at the site of s.c. or intramuscular injection (7–14). After parenteral cadmium exposure, testicular Leydig cell tumors develop in high incidence in both rats and mice (10–14). These Leydig cell tumors are thought to develop in the course of the regenerative hyperplasia that follows the severe acute ischemic tubular necrosis and consequential degeneration induced in mammalian testes by cadmium (17–19). Lung carcinoma have also been recently observed in rats following chronic inhalation of cadmium chloride aerosols (15, 16).

In humans, several investigations have linked cadmium exposure to tumors of the prostate (2–5) and/or the lung (5, 6). The recent reports of lung carcinogenesis in rats following chronic inhalation of cadmium (15, 16) is, therefore, consistent with these epidemiological data concerning lung tumor incidence in humans occupationally exposed to this metal (5, 6). The evidence in experimental animals in support of a role for cadmium in human prostatic carcinogenesis is much less definitive. Local tumors (both adenomas and carcinomas) result from direct injection of cadmium into the rat prostate (20, 21). However, the unrealistic nature of this exposure route must be considered a flaw in these experiments as support for human epidemiological findings of a role of cadmium in prostatic carcinogenesis. In the absence of evidence for prostatic tumors resulting from systemic cadmium exposure in animals, experimental data must be considered doubtful support of the human epidemiology.

Although there are several studies pointing out the carcinogenic potential of cadmium in animals (7–16) very few have used more than a single dosage level, and no complete dose-effect analysis for cadmium exists in the literature. Furthermore, careful histological examination of certain potential target site tissues, specifically the prostate, was in many studies of cadmium carcinogenesis, apparently not carried out (7–11). Therefore, in the present study, a dose-effect analysis of cadmium carcinogenesis was performed, following systemic exposure to a wide range of doses and a variety of dosing regimens. Particular attention was also paid to the prostate as a potential target tissue of cadmium carcinogenesis.

MATERIALS AND METHODS

Animals. A total of 315 male Wistar [Crl:(WI)BR] rats were obtained from the Charles River Breeding Laboratories (Kingston, NY) and were allowed at least 2 weeks of acclimatization prior to treatment. Animals were housed three per polycarbonate cage in a standard barrier facility and provided food and water ad libitum.

Chemicals and Treatments. Cadmium(II) chloride (CdCl₂), anhydrous powder (Baker analyzed reagent) was purchased from VWR Scientific, Inc. (Baltimore, MD). Injection solutions were prepared in sterile normal saline (0.9% NaCl). Rats were randomly placed in groups and treated as described in Table 1. All injections were given at 4 ml/kg, s.c. in the dorsal thoracic midline. Animals were injected when 6 weeks old and weighed approximately 225 g. Rats were then observed for the next 104 weeks.

Pathology. During the course of the experiment, body weights, survival, clinical symptoms, and necropsy findings were recorded. A complete necropsy was performed on each rat whether found dead, killed
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Table 1  Experimental design

<table>
<thead>
<tr>
<th>Group no.</th>
<th>Initial no. of rats</th>
<th>CdCl₂ dose per injectiona</th>
<th>Regimenb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>15</td>
<td>0.0</td>
<td>1 injection (time 0)</td>
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<td>1 injection (time 0)</td>
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<td>1 injection (time 0)</td>
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<td>1 injection (time 0)</td>
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<td>40.0</td>
<td>1 injection (time 0)</td>
</tr>
<tr>
<td>8°</td>
<td>15</td>
<td>0.0</td>
<td>4 injections (time 0, 48, 96, and 168 h)</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>5.0</td>
<td>4 injections (time 0, 48, 96, and 168 h)</td>
</tr>
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<td>10°</td>
<td>15</td>
<td>0.0</td>
<td>2 injections (time 0 and 48 h)</td>
</tr>
<tr>
<td>11</td>
<td>30</td>
<td>5.0/10.0</td>
<td>2 injections [time 0 (low dose) and 48 h (high dose)]</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>5.0/20.0</td>
<td>2 injections [time 0 (low dose) and 48 h (high dose)]</td>
</tr>
</tbody>
</table>

a  Doses are given in µmol/kg.
b  All injections were s.c. in the dorsal thoracic midline.
c  Groups 1, 8, and 10 were statistically invariant from each other in all cases and were thus pooled and are henceforth referred to as pooled controls (PC).

Survival Times and Body Weights. Cadmium treatment had no effect on survival (data not shown). Mean survival times ranged from 99.2 weeks to 88.6 weeks. Likewise, body weights showed little difference with cadmium treatment, although rats given the highest dose of cadmium as a single injection (Group 7; 40 µmol/kg) were consistently the lowest in weight of any group. The differences between this group and pooled control occasionally were statistically significant (Fig. 1).

Tumors at the Site of Cadmium Injection. The cumulative incidence of injection site tumors is shown in Table 2. Tumors were mostly of mesenchymal origin and classifiable as fibrosarcomas. These pleomorphic tumors frequently contained heterogenous cell populations (Fig. 2) including highly elongated cells that formed whorls and interlacing bundles, round cells usually with abundant cytoplasm, and occasionally multinucleated giant cells. The incidence of these injection site tumors appeared to depend strictly on the accumulated dose of cadmium and was highest in Group 7 (40 µmol Cd/kg) followed by Group 12 (25 µmol Cd/kg, cumulative).

Testicular Tumors. The incidence of testicular tumors and of chronic testicular degeneration subsequent to an initial acute ischemic necrosis is shown in Table 3. Depending on the dose, the testes showed bilaterally varying degrees of peritubular fibrosis and intratubular mineralizations (Fig. 3). The size of nontumorous testes from rats treated with higher doses of CdCl₂ was often reduced to 25% or less of those of saline-treated control rats. Tumors were almost exclusively Leydig cell adenomas (Fig. 3) apart from a single seminoma and a rete testis adenocarcinoma. Because of the rarity of the latter two testicular tumors in rats, their histopathology has been described in detail elsewhere (26, 27). The incidence of testicular tumors overall showed a strong dose dependence and a positive correlation with chronic testicular degeneration in those animals given a single dose of cadmium. In animals given multiple doses of cadmium, tumors did not appear to depend strictly on accumulated dose. In Groups 9, 11, and 12 (see Table 1) given multiple cadmium doses, significant increases in tumors or degeneration did not occur, although in at least two cases the accumulated dose in these groups equaled or exceeded 20 µmol/kg, a level which, when given alone as a single dose, resulted in a 72.4% incidence of testicular tumors.

Neoplastic and Prenecrotic Lesions of the Prostate. For every rat, one representative section through both lobes of the ventral and dorsolateral prostates was evaluated. All proliferative epithelial lesions of the prostate (which occurred only in the ventral lobe) were classified according to previous descriptions (28-32) and are shown in Fig. 4, A-C. Hyperplasias (Fig. 4A) were all cribriform proliferations following the alveolar lining without remarkable nodular protrusions into the glandular lumen. If obstructive nodular intraluminal growth was present, the lesion was termed an adenoma (Fig. 4B). Occasionally two to three adjacent alveoli were confluenty affected by hyperplasia and/or adenomas (Fig. 4C). Such cases were counted as a single lesion. Although prostatic adenoma often showed a high mitotic rate and the presence of hemoglobin crystals indicated vascular damage, actual invasion and penetration of basement membranes as major features for malignancy were rarely seen.

The incidence of prostatic tumors in rats treated with cadmium is shown in Table 4. In Group 3 there was a significant increase of approximately threefold in the incidence of prostatic tumors as compared to pooled controls. A strong positive trend also occurred between dosage levels of cadmium given as a single injection of 0 (pooled control), 1.0 (Group 2), and 2.5 µmol Cd/kg (Group 3) and both tumor incidence and number of tumorous foci/prostate (Fig. 5). This correlation between
Table 2 Incidence of injection site tumors in rats given CdCl₂

<table>
<thead>
<tr>
<th>Group</th>
<th>Effective no. of rats</th>
<th>CdCl₂ dose per injection; frequency</th>
<th>Mesenchymal</th>
<th>Epithelial</th>
<th>Papilloma</th>
<th>Keratoacanthoma</th>
<th>Basal cell carcinoma</th>
<th>Total</th>
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<td>0; variable</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>0</td>
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<td>1.0; 1×</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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<td>3</td>
<td>29</td>
<td>2.5; 1×</td>
<td>0</td>
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<td>10.0; 1×</td>
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<tr>
<td>6</td>
<td>30</td>
<td>40.0; 1×</td>
<td>13⁺</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>5.0/10 each; 1× each</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>5.0/20 each; 1× each</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

See Table 1 for details.

Fibrosarcomas with focal histiocytic, osteocytic, or schwannoma-like differentiation.

One animal in Group 7 had both a sarcoma and the basal cell carcinoma at the injection site.

Fig. 2. Pleomorphic fibrosarcoma arising at the s.c. injection site of CdCl₂ in a Wistar rat. A, interlacing bundles of spindle-shaped cells (H & E, × 250); B, round cells with abundant cytoplasm and frequently eccentrically located nuclei (H & E, × 250).

Table 3 Incidence of testicular tumors and degeneration in rats treated with CdCl₂

<table>
<thead>
<tr>
<th>Group</th>
<th>Effective no. of rats</th>
<th>CdCl₂ dose per injection; frequency</th>
<th>Testicular tumors (%)⁺</th>
<th>Testicular degeneration*</th>
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<td>PC</td>
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<td>0; variable</td>
<td>8 (17.8)</td>
<td>0</td>
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<tr>
<td>2</td>
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<td>1.0; 1×</td>
<td>1 (3.3)</td>
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<td>2.5; 1×</td>
<td>3 (10.3)</td>
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<td>30</td>
<td>5.0; 1×</td>
<td>3 (10.0)</td>
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<td>4 (13.3)</td>
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<tr>
<td>6</td>
<td>30</td>
<td>20.0; 1×</td>
<td>21 (72.4)</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>40.0; 1×</td>
<td>24 (82.8)</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>5.0/10 each; 1× each</td>
<td>2 (6.7)</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>5.0/20 each; 1× each</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>5.0/10 each; 1× each</td>
<td>2 (6.7)</td>
<td>30</td>
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<tr>
<td>11</td>
<td>30</td>
<td>5.0/20 each; 1× each</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>5.0/20 each; 1× each</td>
<td>0</td>
<td>30</td>
</tr>
</tbody>
</table>

See Table 1 for details.

Primarily Leydig cell adenomas, except for one seminoma and one rete testis adenocarcinoma.

Rated as absent (0), mild (+), moderate (++), and severe (+++).

Significant difference (P ≤ 0.05) from pooled control (PC).

dose and tumorous foci per prostate or number of animals with tumors disappeared at higher doses.

A positive trend also was observed between preneoplastic (hyperplastic) foci/prostate and cadmium dosage when given as a single injection (Fig. 6). Unlike the correlations with cadmium dosage and tumor incidence (Table 4) or tumorous foci/prostate, the positive trend between cadmium dosage and hyperplastic foci/prostate was not lost at higher doses and continued through all doses (0–20 µmol Cd/kg) in which assessment was possible. In Group 7, which received 40 µmol Cd/kg, severe atrophy with folded alveoli made assessment of hyperplastic foci number unreliable.

Pancreatic Tumors. Incidence of pancreatic tumors in cadmium treated animals is shown in Table 5. When given as a single dose, cadmium dose and pancreatic tumor incidence showed a strong negative tendency. This reduction in tumor incidence with increasing dose occurred regardless of histological type of tumor (acinar cell or islet cell).

Other Tumors. Table 6 shows the incidence of tumors at various sites that were found not to be related to cadmium treatment. The most prominent of such tumors were pituitary adenomas and adrenal pheochromocytomas. Besides those tumors listed in Table 6, compound osteosarcomas at the site of metallic identification tags in the ear also occurred. These tumors were independent of cadmium dose and have been detailed elsewhere (33).
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DISCUSSION

During the last 100 years, levels of cadmium in the environment have risen dramatically (34–36). This increased pollution by cadmium has been reflected in a marked increase (4.7-fold) in the body burden of cadmium in human populations over the same period (34). The influence on human health of this enhanced exposure to cadmium has become an increasing concern (36), of which the possible association between cadmium and carcinogenesis is a major component.

The results of the present study indicate cadmium treatment is associated with tumors at the s.c. injection site, with tumors of the testes, and with the formation of preneoplastic and neoplastic lesions of the prostate in rats. Previous studies have indicated a clear association between cadmium treatment in animals and injection site tumors and/or tumors of the testes (7–14) although no complete dose-effect analysis has, until now, been available. This is the first report that indicates an association between systemic cadmium exposure and prostatic neoplasia. The present findings are in accord with several previous epidemiological investigations that indicate a correlation between cadmium and prostatic carcinogenesis in occupationally (3, 5, 6) or environmentally (4) exposed humans, although such an association has not always been detected (37, 38). Furthermore, cadmium concentrations in human prostate show continuous increases from the normal prostate to benign prostatic hyperplasia to prostatic carcinoma (39) and are highest in the nuclear fractions of poorly differentiated carcinomas (40). Cadmium in the drinking water of rats causes dose-related increases in the prostatic weight over a 6-month exposure period (41), while direct injection of cadmium into the rat prostate will cause tumor formation in some (20, 21), but not all, cases (12). The results with direct injection of cadmium into the rat prostate cannot be considered as definitive evidence in support of a risk in humans, as this exposure route is unrealistic. In any event, the results with systemic cadmium exposure and increased hyperplasia and neoplasia of the prostate in the present study clearly support a possible role of cadmium in human prostatic cancer (3–6).

A complex relationship between cadmium dose and eventual tumor formation appears to exist in the prostate, as tumor incidence was only significantly elevated at a relatively low dose (see Table 5). The growth of animal or human prostate is dependent on androgen (2, 42) and the tissue regresses following castration or estrogen treatment (2, 43). Indeed, higher testosterone levels are found in plasma of men with prostatic cancer (2, 44–46) while hyperestrogenism associated with hepatic cirrhosis is linked with a very low prevalence of prostatic cancer at autopsy (2, 45). Orchietomy is also used to induce regression of prostatic carcinoma (43). In rats, the incidence of N-nitroso-N-methylurea induced prostatic tumors can be markedly increased by testosterone implantations (47). In the current study, tumors did not occur at the higher doses of cadmium, doses that can cause marked reduction of androgen secretion (48, 49). Furthermore, the higher doses of cadmium in this study induced numerous Leydig cell tumors which, although composed of what are normally androgen producing cells, are typically poor producers of androgens (14, 50). In the absence of appropriate support from testicular androgens the prostate can either not grow or regress. The latter was seen with the highest doses of cadmium, as indicated by severe atrophy of the prostate in these groups. More subtle effects undoubtedly occurred at lower doses. Thus, studies which have employed rats with a high spontaneous incidence of Leydig cell tumors cannot be considered to demonstrate a lack of effect of cadmium on the prostate, despite claims to the contrary (51, 52). Although
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Fig. 4. Proliferative lesions of the ventral prostate in Wistar rats. A, prostatic hyperplasia, focally in cribriform pattern following the alveolar lining (H & E X 100); B, prostatic adenoma of nodular cribriform growth arising from hyperplasia (H & E X 100); C, prostatic adenoma obstructing the lumens of several adjacent alveoli (H & E X 100).

Table 4 Incidence of prostatic tumors in rats treated with CdCl₂

<table>
<thead>
<tr>
<th>Group*</th>
<th>Rats at risk*</th>
<th>CdCl₂ dose per injection; frequency</th>
<th>Tumors (%)</th>
</tr>
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<tbody>
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<td>44</td>
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<td>6 (22.2)</td>
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<td>26</td>
<td>2.5; 1×</td>
<td>8 (30.8)</td>
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<td>4</td>
<td>28</td>
<td>5.0; 1×</td>
<td>4 (14.3)</td>
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<td>5</td>
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</tr>
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<td>9</td>
<td>26</td>
<td>5.0; 4×</td>
<td>2 (7.7)</td>
</tr>
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<td>28</td>
<td>5.0/10.0; 1× each</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>5.0/20.0; 1× each</td>
<td>6 (21.4)</td>
</tr>
</tbody>
</table>

* For details see Table 1.
* Reflects deletion of rats that died prior to the appearance of the first prostatic tumor (72 weeks).
* Mainly adenoma with the exception of two adenocarcinomas.
* Significant difference (p ≤ 0.05) from pooled control (PC).

Prostatic tumors did not occur at the higher doses of cadmium in the present study, preneoplastic lesions of the prostate were clearly associated with increasing dose up to and including 20 μmol Cd/kg. Severe atrophy of the prostate prevented accurate assessment of hyperplastic foci in many rats of the 40 μmol Cd/kg group. Thus, it appears that initiation of carcinogenic events in the prostate, as reflected by hyperplastic changes, occurs throughout the dose range of cadmium used in the present study. These preneoplastic lesions appear to develop into prostatic tumors only at doses well below those that induce dysfunction of the testes and reduced androgen production, probably because of the testosterone requirement of prostatic neoplasia.

Among other tumors induced by cadmium, testicular tumors were found to be highly dependent on extent of chronic degeneration of the testes. Cadmium induces acute lesions of the

Table 5 Incidence of pancreatic tumors in rats given CdCl₂

<table>
<thead>
<tr>
<th>Group*</th>
<th>Effective no. of rats</th>
<th>CdCl₂ dose per injection; frequency</th>
<th>Acinar cell</th>
<th>Islet cell</th>
<th>Either</th>
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<td>27 (60.0)</td>
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<td>12 (40.0)</td>
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<td>16 (53.3)</td>
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<td>29</td>
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<td>4 (14.3)</td>
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<td>6 (20.0)</td>
</tr>
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<td>5.0; 4×</td>
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<td>16 (53.3)</td>
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<td>5.0/10.0; 1× each</td>
<td>12 (40.0)</td>
<td>7 (23.3)</td>
<td>15 (50.0)</td>
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<td>30</td>
<td>5.0/20.0; 1× each</td>
<td>12 (40.0)</td>
<td>4 (13.3)</td>
<td>12 (40.0)</td>
</tr>
</tbody>
</table>

* PC, pooled control.
testes, including massive hemorrhagic necrosis and loss of tubular elements (14, 19), that precede the chronic degenerative changes (14, 19). Doses of cadmium ≥20 μmol Cd/kg as a single s.c. injection are well above that required to cause acute lesions in rats (19). These doses in all cases were sufficient to induce tumorigenic events in the testes and it thus appears that the acute necrotizing effects of cadmium on the testes are a primary factor responsible for development of tumors in this organ. Further research is, however, required to determine the exact role of the acute lesions in cadmium-induced testicular carcinogenesis.

When given as a single dose or in multiple doses, cadmium induced injection site tumors (mostly sarcomas) in a fashion clearly dependent on the total cumulative dose of cadmium. An

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td><strong>Pooled control</strong>&lt;sup&gt;a&lt;/sup&gt; (n = 45)</td>
</tr>
<tr>
<td>Skin</td>
<td>Papilloma</td>
</tr>
<tr>
<td></td>
<td>Keratoacanthoma</td>
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<tr>
<td></td>
<td>Basal cell carcinoma</td>
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<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Trichoepithelioma</td>
</tr>
<tr>
<td></td>
<td>Sebaceous gland adenoma</td>
</tr>
<tr>
<td></td>
<td>Granular cell tumor</td>
</tr>
<tr>
<td>Lung</td>
<td>Adenoma</td>
</tr>
<tr>
<td>Vascular system</td>
<td>Hemangiomia</td>
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<td>Adenoma</td>
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<td>Cortical adenoma</td>
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<tr>
<td>Zymbal's gland</td>
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<tr>
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<td>Hepatocellular carcinoma</td>
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<tr>
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<td>Mucinous cholangioma</td>
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<td>Thoracic cavity</td>
<td>Mesothelioma</td>
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<tr>
<td>Kidney</td>
<td>Tubular adenocarcinoma</td>
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<td>Mammary gland</td>
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<td>Intestine</td>
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<tr>
<td></td>
<td>Adenoma</td>
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<tr>
<td>Skeletal system</td>
<td>Osteosarcoma</td>
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<td>Submandibular gland</td>
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<td>Subcutis</td>
<td>Fibroma</td>
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<tr>
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<td>Lipoma</td>
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<td>Adipose tissue</td>
<td>Liposarcoma</td>
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<td>C-cell adenoma</td>
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<td>Lymphoma/Leukemia</td>
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<td>Thymus</td>
<td>Thymoma</td>
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<tr>
<td>Brain</td>
<td>Granular cell tumor</td>
</tr>
</tbody>
</table>

<sup>a</sup> Groups 1, 8, and 10 (see Table 1).

<sup>b</sup> Groups 2, 3, 4, 5, 6, 7, 9, 11, and 12 (see Table 1).
increased incidence of sarcomas occurred at 40 µmol Cd/kg (single injection) and at 25 µmol Cd/kg (one injection of 5 µmol Cd/kg followed by one of 20 µmol Cd/kg). In marked contrast, testicular tumors induced by cadmium occurred in groups given single injections of 20 µmol Cd/kg and above but did not occur when the same total doses were divided into multiple injections (i.e., 5 µmol Cd/kg, 4×, or 5 µmol Cd/kg, 1×, followed by 20 µmol Cd/kg). Acquired tolerance to acute cadmium toxicity in the testes through pretreatment with either cadmium itself (19) or with the closely related element, zinc (53, 54), has been well documented. It would appear from the results of this study that such acquired tolerance induced by relatively low dose pretreatment also occurs with the chronic carcinogenic effects of cadmium. Likewise, the studies of Gunn et al. (10, 11) clearly show that zinc pretreatment essentially abolishes the carcinogenicity of cadmium in mouse or rat testes or at injection sites. This tolerance induced by low dose pretreatment with cadmium, however, does not appear to affect tumor development at the s.c. injection site. The underlying cause of the difference between these two target sites of cadmium cannot be discerned from the present results and requires further study. This marked difference in response, however, may indicate that distinct carcinogenic mechanisms are responsible for tumor development at these two sites.

A decreased incidence of tumors of the exocrine and endocrine pancreas occurred with cadmium treatment in the present study. Both islet cell and acinar cell tumors showed a decreased incidence with increasing cadmium dose. These results are in conflict with a previous report indicating that cadmium causes an increase in pancreatic islet cell tumors in rats (13). This previous observation applies only when groups treated concurrently with calcium or magnesium along with cadmium are considered (13). Both calcium and magnesium have been shown in certain instances to antagonize the biological effects of cadmium (13, 55, 56). However, further research will be required to determine the exact role of cadmium in pancreatic carcinogenesis.

In summary, the results of the present study indicate that cadmium, beyond inducing injection site and testicular tumors, can also be associated with prostatic neoplasia in rats. Injection site tumors were found to be strictly dependent on accumulated dose of cadmium while testicular tumors are clearly associated with chronic degeneration of the testes induced by cadmium.

REFERENCES


Cadmium Carcinogenesis in Male Wistar [Crl:(WI)BR] Rats: Dose-Response Analysis of Tumor Induction in the Prostate and Testes and at the Injection Site


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