

Effects of Orchiectomy, Alone or in Combination with Testosterone, and Cyproterone Acetate on Exocrine Pancreatic Carcinogenesis in Rats and Hamsters

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Summary

The results of a previous 4-mo study in azaserine-treated rats and BOP-treated hamsters indicated that orchiectomy inhibited pancreatic growth and development of putative preneoplastic lesions in the exocrine pancreas of rats but not hamsters. This 12-mo study was carried out to investigate the effects of orchiectomy, alone and in combination with testosterone, and of treatment with cyproterone acetate on pancreatic carcinogenesis in azaserine-treated rats and BOP-treated hamsters. Treatment started 4 mo after injection of the carcinogen. In orchiectomized rats, pancreatic wt was lower than in controls, whereas pancreatic wt of orchiectomized rats treated with testosterone was similar to that of controls. Both orchiectomy and cyproterone acetate caused a decrease in body wt gain and had an inhibitory effect on pancreatic carcinogenesis. Testosterone treatment did not influence the inhibitory effects of orchiectomy on body wt gain and on pancreatic carcinogenesis. In hamsters, neither orchiectomy, alone or in combination with testosterone, nor cyproterone acetate (CA) affected pancreatic growth or pancreatic carcinogenesis. This study indicates that testosterone plays a minor role in the development of pancreatic tumors induced in rats by azaserine but not in that of pancreatic tumors induced in hamsters by BOP.

Key Words: Exocrine pancreas; cancer; rat; hamster; orchiectomy; testosterone; cyproterone acetate.

Introduction

In most countries, the age-adjusted incidence of pancreatic cancer is higher in men than in women

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(1,2). Apart from life-style factors, hormonal factors have been suggested to be responsible for this sex difference. A higher number of atypical acinar cell nodules (AACN) and a higher incidence of pancreatic neoplasms have been found in male than in female rats treated with azaserine (3). Using the AT-Pase staining, Bax et al. found that acidophilic foci in male rats were consistently larger (1.75 times) than in females and concluded that the sex-related differ-

ence in the numbers of acidophilic AACN induced in rat pancreas by azaserine may be ascribed to the difficulty in detecting small acidophilic foci in hematoxylin and eosin (H&E)-stained sections (4). In rats, the inhibitory effect of castration on growth of azaserine-induced AACN has been ascribed to decreased serum testosterone levels (5-7). The inhibitory effect of castration, however, was not influenced by treatment with testosterone. In a previous 4-mo study with azaserine-treated rats, we also found an inhibitory effect of orchietomy on the development of AACN, which was accompanied by a significant decrease in absolute but not relative pancreatic wt. From the results of that study, we concluded that, apart from testosterone, nutritional status and pancreatic growth may play a highly significant role in the development of putative pancreatic preneoplastic lesions (8).

No consistent variations have been found in incidence of pancreatic (pre)neoplastic lesions in male and female hamsters induced by sc injections with nitrosamine derivatives. Pour et al. did not find a difference between male and female hamsters in the incidence of pancreatic tumors after injection with *N*-nitrosobis(2-oxopropyl)amine (BOP) (9,10). Kokkinakis, on the contrary, found that tumor incidence, multiplicity, and size were generally larger in female than in male hamsters after administration of *N*-nitroso(2-hydroxypropyl)(2-oxopropyl)amine (HPOP) (11). Pancreatic (H2T) cells transplanted in hamster cheek pouches developed faster into ductal adenocarcinomas in intact females and castrated males than in ovariectomized females and intact males, respectively, pointing to an inhibitory effect of testosterone or an enhancing effect of estrogen (12). Schally and co-workers, however, found that the development of pancreatic tumors induced in male hamsters by BOP was inhibited by medical or surgical castration (13-18). Furthermore, in a previously conducted 4-mo study, we did not find any effect of castration or Luteinizing Hormone Releasing Hormone (LHRH) treatment on the development of early (pre)neoplastic lesions induced in hamster pancreas by BOP (8). This experiment was performed to evaluate the effects of castration, either alone or in combination with testosterone treatment, and of treatment with the antiandrogen cyproterone acetate (CA) on

pancreatic carcinogenesis in hamsters and rats during a long-term treatment period of 8 mo started 4 mo after tumor induction.

Materials and Methods

Animals and Tumor Induction

Two hundred male weanling SPF albino Wistar Bor rats (WISW, Cpb) were obtained from F. Winkelmann (FRG) and injected ip four times with 30 mg azaserine/kg body wt at 19, 26, 33, and 103 d of age. One hundred and forty male Syrian golden hamsters (Charles River Wiga, Sulzfeld, FRG) were each injected sc, once weekly, with 20 mg BOP/kg body wt at 6, 7, and 8 wk of age according to an injection protocol described previously (19). BOP (Ash Stevens, Inc., 5861 John C. Lodge Freeway, Detroit, MI 48202) and azaserine (Calbiochem-Behring Corp., LaJolla, CA) were dissolved freshly in 0.9% NaCl solution. The animals were allocated by a computerized randomization procedure to four different groups, each of which consisted of either 50 rats or 35 hamsters. The rats were housed in stainless-steel cages, fitted with wiremesh floors and fronts, and the hamsters in macrolon cages on softwood bedding. The animals were kept under standard laboratory conditions, five animals per cage, and fed a high fat/high protein diet during the first 4 mo of the study in order to enhance the development of ductular lesions in the exocrine pancreas.

Treatment

In order to mimic the human situation, treatment started when early (pre)neoplastic lesions had already developed in the pancreas, i.e. 4 mo after the last injection with carcinogen. The animals received one of the following treatments: group A, saline (controls); group B, surgical castration; group C, surgical castration plus testosterone; and group D, CA. Testosterone was administered as testosterone propionate by silastic implants as described previously (20). Rats received two, 3-cm implants per animal, and hamsters, in view of lower body wt, received one implant per animal once at start of treatment. Cyproterone acetate was used as Androcur tablets (50 mg) dispersed in tap

water. The animals were given CA by gavage daily at a dose of 50 mg/kg, as described previously (21).

During treatment, the animals were fed the TNO Institute's basal diet, which is low in fat (5%) and compounded from natural feed ingredients. Body wt were recorded weekly during the first 3 mo and once a month during the rest of the experiment. The general condition and behavior of the animals were checked daily.

Autopsy and Histological Analysis

In rats, an interim kill was performed on 20 animals of each group after 4 mo of treatment. Terminal autopsy on rats and hamsters was performed after 8 mo of treatment on days 371 (rats), and 363 and 364 (hamsters) after the last injection with carcinogen. The animals were anesthetized by ether, exsanguinated by cannulating the abdominal aorta, autopsied, and then examined for gross pathological changes. From each animal, the pancreas, liver, testes (if present), adrenals, and pituitary were excised and weighed. These organs were fixed in 10% buffered formalin. The pancreata were completely processed for microscopy by conventional methods, step-sectioned at 5 μm (about 5 per pancreas), stained with H&E, and examined by light microscopy. About 200 mm^2 of pancreatic tissue of each rat were microscopically screened for the number and size of azaserine-induced AACN using a grid inside the ocular as described before (22). Only acidophilic AACN with transection areas greater than 0.5 mm^2 have been counted and classified. AACN, acinar cell adenomas (AACN with a transection area larger than 3 mm^2), and (localized) carcinomas were identified and classified according to the criteria of Longnecker et al. (3,23).

In the hamster pancreas, major attention was paid to tubular ductal complexes showing dysplasia or anaplastic changes, or desmoplasia, inflammation, with or without apoptosis, suggestive of progression to malignancy. Tubular ductal complexes exhibiting one or more of the characteristics were classified as "borderline lesions" (24). The ductular carcinomas induced by BOP were identified and classified according to Pour and Wilson (25).

Body and organ wt data were statistically evaluated with one-way analysis of variance (ANOVA)

using initial body wt as covariable. The number of borderline and other (pre)neoplastic lesions were statistically evaluated with a generalized linear model (26). With such a model, the effects of type of treatment (control, surgical castration, surgical castration plus testosterone, or CA) were assessed. For rats, the influence of time of sacrifice (interim kill, terminal autopsy) and possible interaction between type of treatment and time of sacrifice were assessed as well. A Poisson error distribution was used for evaluation of the lesions.

Evaluation of the prevalence (incidence) of tumors (terminal autopsy animals only) was done with a generalized linear model. The difference with the model used for lesions was the error distribution. With respect to prevalence, the binomial distribution was appropriate.

Endocrine Investigations

Blood sampling for hormone estimations was performed at the start of the treatment period ($n = 19-20$), after 4 mo ($n = 10$) and after 8 mo ($n = 10$) of treatment at the end of the experiment by exsanguination. In groups of five animals, blood sampling was also performed after 2 and 6 mo by orbital punctions. In Table 1, only the data obtained at 0, 4, and 8 mo after treatment have been included. EGF- and IGF-1-like activities were measured in acid-ethanol extracted EDTA-plasmas by radioreceptor assays using human placental membrane preparations as receptor source. All procedures were exactly as described before for determination of EGF- and IGF-1-like activities in human breast tumor cytosols (27). Growth hormone (GH) levels were determined by radioimmunoassay (RIA) (28). Testosterone levels were estimated as described by Verjans et al. (29). The treatment effects on plasma hormone and growth factor levels were determined by ANOVA on the pooled data of all treatment groups and controls at the end of treatment. Small p values from these analyses, performed for each growth factor or hormone in rats and hamsters, are an indication of a difference in effect, either a decrease or increase of plasma concentrations. In addition, to prevent the influence of outflyers, the Wilcoxon test has also been applied where useful.

Table 1
Treatment Effects on Plasma Growth Factor and Hormone Levels

Postinitiation treatment group	GH (ng/mL)			Testosterone (nmol/L)		
	0 Mo	4 Mo	8 Mo	0 Mo	4 Mo	8 Mo
Rats						
Controls	11.7 ± 4.1 ^b	2.4 ± 0.8	16.9 ± 6.2 (12) ^c	11.6 ± 3.2	2.7 ± 0.5	4.6 ± 0.6 (10) ^c
Castration	—	5.7 ± 1.8	3.0 ± 0.7 (10) ^c	—	0.1 ± 0.0	0.1 ± 0.0 (10) ^c
Castration + T ^d	—	11.3 ± 3.2	20.8 ± 9.1 (10) ^c	—	16.9 ± 1.2	10.2 ± 1.2 (10) ^c
CPA	—	24.5 ± 14.4	14.8 ± 6.6 (12) ^c	—	5.3 ± 1.3	11.6 ± 3.1 (12) ^c
<i>p</i> value ^a			<i>p</i> = 0.29			<i>p</i> = 0.0003
Hamsters						
Controls	5.5 ± 1.6	—	2.8 ± 0.7 ((12) ^c	15.3 ± 4.2	6.3 ± 0.8	17.0 ± 5.1 (10) ^c
Castration	—	—	4.3 ± 0.6 (10) ^c	—	0.1 ± 0.0	0.1 ± 0.0 (10) ^c
Castration + T ^d	—	—	2.0 ± 0.5 (9) ^c	—	3.8 ± 1.3	2.2 ± 0.5 (10) ^c
CPA	—	—	3.3 ± 0.5 (12) ^c	—	10.8 ± 1.5	13.0 ± 2.2 (7) ^c
<i>p</i> value ^a			<i>p</i> = 0.09			<i>p</i> = 0.0000
Postinitiation treatment group	EGF (ng/mL)			IGF (ng/mL)		
	0 Mo	4 Mo	8 Mo	0 Mo	4 Mo	8 Mo
Rats						
Controls	29.0 ± 4.5	53.4 ± 6.3	47.6 ± 31.2 (12) ^c	131 ± 9	200 ± 11	101 ± 14 (12) ^c
Castration	—	68.2 ± 8.7	43.4 ± 8.8 (10) ^c	—	191 ± 16	94 ± 11 (10) ^c
Castration + T ^d	—	46.7 ± 10.1	31.0 ± 5.1 (9) ^c	—	161 ± 19	107 ± 14 (10) ^c
CPA	—	15.2 ± 6.5	45.2 ± 28.7 (12) ^c	—	145 ± 11	127 ± 16 (12) ^c
<i>p</i> value ^a			<i>p</i> = 0.97			<i>p</i> = 0.35
Hamsters						
Controls	22.2 ± 1.8	—	62.8 ± 4.5 (12) ^c	255 ± 14	—	144 ± 7 (12) ^c
Castration	—	—	60.8 ± 5.5 (10) ^c	—	—	244 ± 19 (10) ^c
Castration + T ^d	—	—	60.0 ± 5.5 (10) ^c	—	—	194 ± 15 (10) ^c
CPA	—	—	76.5 ± 5.6 (13) ^c	—	—	206 ± 18 (13) ^c
<i>p</i> value ^a			<i>p</i> = 0.09			<i>p</i> = 0.0005

^a*P* value associated with test of difference between the five groups after 8 mo of treatment. ^bAll values are means ± SEM. ^cNumber of animals used at 8 mo between brackets; at start of treatment 19–20 animals, and after 4 mo 10 animals were used for assays. ^dT = testosterone.

Results

Body Weights

In rats but not hamsters, orchietomy inhibited body growth by 19% (*p* < 0.01) (Figs. 1,2; Tables 2,3). Body wt of orchietomized rats treated with testosterone was also significantly lower (15%) than that of controls. Rats treated with CA also showed a lower body wt (*p* < 0.01) than controls, whereas body wt of hamsters treated with CA had increased by 10% (*p* < 0.05) compared to controls.

Organ Weights

In rats, absolute but not relative pancreas wt had decreased (*p* < 0.01) by orchietomy and by treatment with CA (*p* < 0.05), when compared with controls (Table 2). Suppletion with testosterone restored greatly the loss of absolute pancreas wt caused by orchietomy, resulting in the absence of a significant difference with the control group.

In orchietomized rats, absolute and relative pituitary wt increased (*p* < 0.01). Suppletion with testosterone prevented the absolute increase but not the

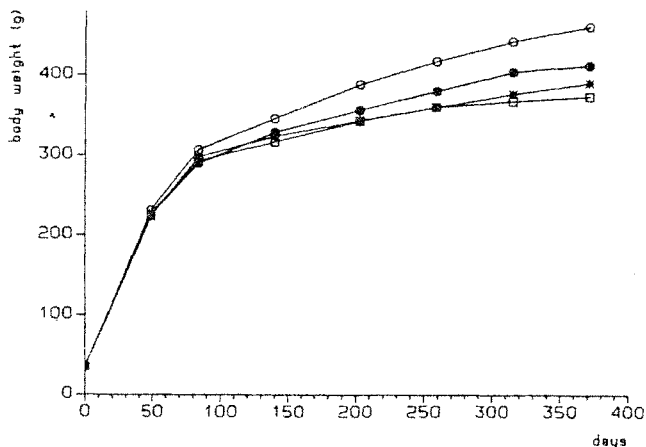


Fig. 1. Mean body wt in rats. ○ = control; □ = castration; * = castration + testosterone; and ● = CA.

relative increase in pituitary wt. Adrenal wt was not significantly affected by any of the treatment modalities.

In rats, absolute liver wt was lower ($p < 0.01$) in all treated groups, whereas relative liver wt was only lower in orchiectomized rats not treated with testosterone ($p < 0.01$). In hamsters, apart from an increase of pituitary wt by castration, none of the treatments significantly influenced absolute or relative organ wt (Table 3).

Plasma Growth Factor and Hormone Levels

In rats, significant differences among groups were observed at the end of the experiment with respect to EGF- and IGF-1-like activity and plasma GH levels (Table 1). Plasma IGF-1 levels increased until 4 mo of treatment and subsequently decreased to adult values when the growth curves were (nearly) flattened. Plasma GH levels tended to decrease after surgical castration and to increase in case of testosterone substitution, but the differences were not significant compared to controls (by ANOVA and Wilcoxon-test analyses). During the treatment period, plasma-testosterone concentrations were lower than before in the control group, maybe as a consequence of late damage of testicular function by carcinogens. As expected, surgical castration caused very low plasma testosterone levels. Substitution with testosterone implants caused significant plasma testosterone concentrations comparable with those present in the con-

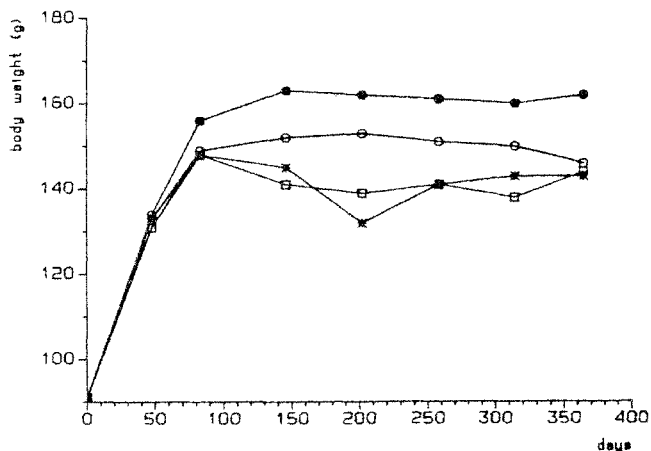


Fig. 2. Mean body wt in hamsters. ○ = Control; □ = castration; * = castration + testosterone; and ● = CA.

rol group before treatment. Cyproterone acetate did not decrease plasma testosterone, as could be expected.

In hamsters, no differences were found among groups with respect to EGF-like activity, whereas IGF-1 levels were higher in the treatment groups compared with those of controls (all $p < 0.01$, Wilcoxon test). Although plasma GH tended to be higher in castrated animals, overall there were no clear differences among groups. As expected, after castration, plasma testosterone levels were very low. Testosterone substitution caused significant plasma testosterone concentrations, but lower than in rats possibly as a consequence of the lower dose used.

Microscopy

In rats, multiplicity of lesions increased significantly in time (Table 4). After 8 mo of treatment, the number of AACN with transection areas larger than 0.5 mm^2 was lower ($p < 0.01$) in each of the treatment groups in comparison with controls. The number of adenomas was similar in all groups, controls included. The total number (multiplicity) but not the incidence (Table 6) of carcinomas was lower ($p < 0.05$) in all treatment groups after 8 mo of treatment (Table 4).

In hamsters, none of the treatments had a significant effect on either the number of borderline lesions, the multiplicity or the incidence of carcinomas (Tables 5,6). Surgical castration decreased the number and the incidence of total carcinomas with about 50%, but this difference did not appear to be statistically significant.

Table 2
Treatment Effects on Body and Organ Weight of Rats^a

Treatment	N	Body wt (g) ^b	Pancreas	Testes	Pituitary	Adrenals	Liver
Absolute organ wt (g)							
Control	27	460.7 ± 10.9	1.40 ± 0.05	3.55 ± 0.06	0.014 ± 0.000	0.054 ± 0.002	13.01 ± 0.37
Castration	24	373.7 ± 6.9 ^d	1.14 ± 0.04 ^d	—	0.018 ± 0.001 ^d	0.047 ± 0.002	9.33 ± 0.25 ^d
Castration + testosterone	19	391.4 ± 8.0 ^d	1.28 ± 0.06	—	0.015 ± 0.001	0.054 ± 0.002	11.69 ± 0.33 ^d
Cyproterone acetate	26	413.1 ± 8.0 ^d	1.22 ± 0.04 ^c	3.37 ± 0.06	0.013 ± 0.000	0.051 ± 0.002	11.52 ± 0.23 ^d
Relative organ wt (g/kg body wt)							
Control	27	460.7 ± 10.9	3.06 ± 0.12	7.77 ± 0.15	0.031 ± 0.001	0.118 ± 0.005	28.3 ± 0.7
Castration	24	373.7 ± 6.9 ^d	3.07 ± 0.11	—	0.048 ± 0.001 ^d	0.128 ± 0.007	25.1 ± 0.7 ^d
Castration + testosterone	19	391.4 ± 8.0 ^d	3.26 ± 0.11	—	0.038 ± 0.001 ^d	0.138 ± 0.004	29.9 ± 0.6
Cyproterone acetate	26	413.1 ± 8.0 ^d	2.96 ± 0.10	8.18 ± 0.13	0.031 ± 0.001	0.125 ± 0.005	27.9 ± 0.3

^aStatistics: One-way ANOVA followed by Student's *t*-test (two-tailed) for comparison with control group. Expressed as mean ± SEM after 8 mo of therapy.

^bAt autopsy. ^c*p* < 0.05. ^d*p* < 0.01.

Table 3
Treatment Effects on Body and Organ Weight of Hamsters^a

Treatment	N	Body wt (g) ^b	Pancreas	Testes	Pituitary	Adrenals	Liver
Absolute organ wt (g)							
Control	24	145.8 ± 4.3	0.531 ± 0.034	2.12 ± 0.19	0.007 ± 0.000	0.024 ± 0.001	12.10 ± 1.06
Castration	19	144.2 ± 4.3	0.578 ± 0.030	—	0.010 ± 0.000 ^d	0.021 ± 0.001	15.58 ± 2.19
Castration + testosterone	16	142.9 ± 2.3	0.541 ± 0.037	—	0.009 ± 0.001 ^c	0.023 ± 0.001	12.79 ± 1.51
Cyproterone acetate	23	162.3 ± 5.8 ^c	0.497 ± 0.040	2.67 ± 0.14	0.007 ± 0.000	0.026 ± 0.002	12.40 ± 1.15
Relative organ wt (g/kg body wt)							
Control	24	145.8 ± 4.3	3.67 ± 0.27	14.33 ± 1.14	0.05 ± 0.00	0.17 ± 0.01	83.42 ± 7.27
Castration	19	144.2 ± 4.3	3.99 ± 0.20	—	0.07 ± 0.00 ^d	0.15 ± 0.01	105.33 ± 12.14
Castration + testosterone	16	142.9 ± 2.3	3.81 ± 0.28	—	0.06 ± 0.00 ^c	0.16 ± 0.01	87.85 ± 8.88
Cyproterone acetate	23	162.3 ± 5.8 ^c	3.05 ± 0.22	16.60 ± 0.92	0.05 ± 0.00	0.17 ± 0.01	78.25 ± 7.9

^aStatistics: one-way ANOVA followed by Student's *t*-test (two-tailed) for comparison with control group. Expressed as mean ± SEM after 8 mo of therapy.

^bAt autopsy. ^c*p* < 0.05. ^d*p* < 0.01.

Table 4
Treatment Effects on Number of Neoplastic Lesions in Exocrine Pancreas of Azaserine-Treated Rats^{a,c}

Nodules and carcinomas observed	Number of Lesions After Treatment Period							
	4 Mo				8 Mo			
	Control	Castr.	Castr. + testost.	Cyproterone acetate	Control	Castr.	Castr. + testost.	Cyproterone acetate
Effective number of rats	14	13	11	13	29	26	24	29
Nodules 0.5 < TA ^b < 1 mm ²	4	1	1	1	89	27 ^e	8 ^{e,f}	23 ^e
Nodules 1.0 < TA < 3 mm ²	1	0	2	0	39	6 ^e	5 ^e	11 ^e
Adenomas	1	0	0	0	3	4	2	2
Carcinoma <i>in situ</i>	0	0	0	0	17	5	4	7
Microcarcinoma	0	0	1	0	5	1	1	1
Carcinoma	0	0	0	1	4	3	3	6
Total carcinoma	0	0	1	1	26	9 ^d	8 ^d	14 ^d

^aValues are totals per group. ^bTA: transection area. ^cStatistics: log linear model with a Poisson distribution; ^d $p < 0.05$ compared to controls; ^e $p < 0.01$ compared to controls. ^fCastration + testosterone vs castration or cyproterone acetate; $p < 0.05$.

Table 5
Treatment Effects on Number of (Pre)neoplastic Lesions
in Exocrine Pancreas of BOP-Treated Hamsters^{a,b}

Advanced Ductular Lesions Observed	Number of lesions			
	Control	Castration	Castration + testosterone	Cyproterone acetate
Effective number of animals	26	26	26	28
Borderline lesion	227	214	204	221
Carcinoma <i>in situ</i>	5	0	0	2
Microcarcinoma	5	1	3	0
Carcinoma	5	6	8	11
Total carcinoma	15	7	11	13

^aValues are totals per group. ^bStatistics: log-linear model with a Poisson error distribution. There were no significant differences between the treatments.

Table 6
Treatment Effects on Incidence of Carcinomas
in Exocrine Pancreas of Azaserine-Treated Rats and BOP-Treated Hamsters

Neoplastic lesion observed	Number of lesions			
	Control	Castration	Castration + testosterone	Cyproterone acetate
Incidence of pancreatic carcinomas in rats ^a				
Effective number of animals	29	26	24	29
Number of animals bearing a lesion	11	6	7	13
Incidence of pancreatic carcinomas in hamsters ^b				
Effective number of animals	26	26	26	28
Number of animals bearing a lesion	14	7	10	10

^aStatistics: generalized linear model with a binomial error distribution. ^bStatistics: generalized linear model with a binomial error distribution. There were no significant differences between the treatments.

Discussion

The results of the present 12-mo study indicate that orchiectomy and treatment with CA cause a decrease in body wt gain and absolute pancreatic wt in rats but not hamsters and inhibition of pancreatic carcinogenesis in azaserine-treated rats but not BOP-treated hamsters. Moreover, treatment of orchiecto-mized rats with testosterone did not affect the inhibitory effect of surgical castration on body wt gain in spite of the presence of normal plasma testosterone levels, whereas pancreas wt of testosterone-treated castrated rats had increased in comparison to orchiectomized rats not treated with testosterone.

The conclusion that testosterone has an enhancing effect on pancreatic carcinogenesis in azaserine-treated rats has been based on the observation that orchiectomy and estradiol treatment inhibited the development of AACN (6,7). In a previously performed 4-mo study with azaserine-treated rats (8), we also found that orchiectomy reduced the yield of AACN significantly, but this effect was accompanied by a significant decrease in growth of absolute pancreatic wt. After correction for pancreas wt, the number of AACN in the orchiectomized rats was almost similar to that in intact controls (8).

Based on these findings, we concluded that a substantial decrease in body growth rate as observed in

surgically castrated rats has to be considered a confounding factor in such experiments, which, if not taken into account, may have led to an overestimation of the direct, enhancing effect of testosterone on pancreatic carcinogenesis.

The results of this study support this conclusion, since it appears that castrated rats treated with testosterone develop even less AACN in comparison with castrated rats not treated with testosterone (Table 4). Treatment of orchiectomized rats with testosterone did not result in a tumor yield similar to that of intact controls, notwithstanding the fact that pancreatic wt in the testosterone-treated group was almost similar to that of controls. This observation indicates that changes in body wt during different treatment modalities are at least as important as changes in plasma-testosterone concentrations. On the other hand, the level of plasma testosterone concentrations might be of importance, i.e., high and castration levels, inhibitory and intermediate levels, stimulatory. In agreement with this hypothesis are the findings of Greenway and colleagues (30), showing low but not castration levels of testosterone in patients with carcinoma of the pancreas. Furthermore, relative loss of body wt might decrease (intratumoral) aromatase activity, resulting in a decreased conversion of androgens to estrogens.

The findings in hamsters are in agreement with those in our previous 4-mo study (8). In BOP-treated hamsters, orchiectomy did not influence body wt gain, and only slightly but not significantly inhibited pancreatic carcinogenesis. The present findings support partly those of Zalatnai and Schally (13-18) who found a significant decrease in tumor wt and tumor volume but no effect on the incidence of ductular adenocarcinomas in chemically (LHRH-treated) castrated (BOP-treated) hamsters.

Based on the aforementioned findings, it might be possible that early putative preneoplastic acinar and ductular lesions, which develop in the pancreas of rats and hamsters after treatment with azaserine and BOP, respectively, do not contain steroid receptors and, hence, cannot be modulated by testosterone. It may be concluded, therefore, that manipulation of pancreatic carcinogenesis by steroid hormones is only relevant for the treatment of existing carcinomas.

Based on the findings described in this article, it may be concluded that the observed inhibitory effects of orchiectomy and cyproterone acetate on pancreatic carcinogenesis in azaserine-treated rats may, at least partly, be ascribed to a significant decrease in body growth. However, the mechanism of action of relative delay in body growth on pancreatic carcinogenesis is still unclear. Importantly, we did not observe a significant decrease in GH and growth factor secretion, or in our previous study in gastrin secretion (8). Therefore, studies on the effect of relative wt loss on other factors potentially involved in pancreatic carcinogenesis are needed.

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