Testicular Atrophy in the Spontaneously Diabetic BB Wistar Rat

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Complete gross and microscopic postmortem examinations were performed on 100 BB Wistar diabetic rats, 27 BB Wistar nondiabetic siblings, and 41 Wistar rats, and the incidence of testicular lesions was tabulated. Testicular atrophy was the predominant finding in all three groups of rats, but atrophy occurred at a much younger age in the diabetic rats. There was a strong relationship between the duration of diabetes and the presence of atrophy, which was stronger than the relationship between age and atrophy. The testicular atrophy observed in the diabetic rats was morphologically similar to the senile testicular atrophy in the nondiabetic rats. Histologic findings that were associated with increasing severity of atrophy were multinucleated giant cells in the lumens of seminiferous tubules, increased interstitial connective tissue, Leydig cell hyperplasia, and thickening of the tunica albuginea. Testicular atrophy has also been reported in human diabetics. Therefore, the BB Wistar rat may be a useful model for investigating this aspect of diabetes mellitus. (Am J Pathol 1982, 108:72-79)

THE BB WISTAR (BBW) rat is an outbred strain of spontaneously diabetic rats that originated in the Bio Breeding Laboratories Ltd. of Ottawa, Canada. The BBW rat is a promising model for insulin-dependent diabetes because it spontaneously develops beta cell destruction with subsequent insulinopenia, hyperglycemia, hyperglucagonemia, glycosuria, ketoacidosis, and hyperlipemia.[1,2] However, except for the pancreatic lesions, very little is known about other spontaneous diseases that occur. Therefore, we conducted a necropsy study to determine the types and frequencies of pathologic abnormalities in our breeding colony of BB rats.[3] The most frequent abnormality in the male rats was testicular atrophy. Although testicular atrophy has been reported in both human diabetics[4-6] and in a wide variety of diabetic animals,[7] there are few reports of systematic detailed studies of this abnormality.

Materials and Methods

A total of 100 BB Wistar diabetic rats (BBWd), 27 BB Wistar nondiabetic siblings (BBWnd), and 41 standard Wistar (w) rats with mean ages of 254 ± 100 days, 241 ± 122 days, and 281 ± 162 days, respectively, were examined. Because of the extreme susceptibility of BB Wistar rats to infection,[3] all rats were maintained in a semibarrier housing facility. The details of animal maintenance and care have been reported previously.[8] Every day all animals were weighed, and the urine of diabetic rats was examined for ketones and glucose with the use of Ketostix (Ames Co., Elkhart, Ind) and Testape (Eli Lilly, Indianapolis, Ind), respectively. We administered protamine zinc (U-40) insulin (Eli Lilly) subcutaneously on a daily basis to maintain 4+ glycosuria without ketonuria.

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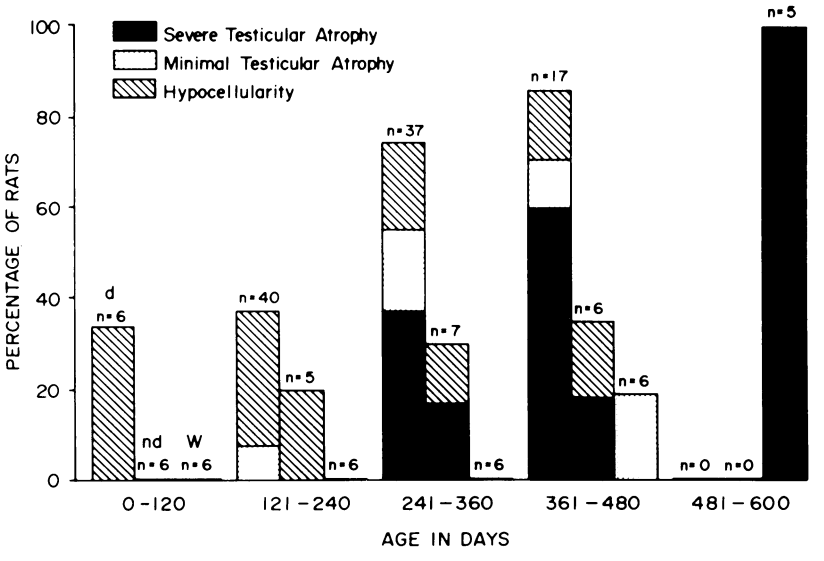

Figure 1—Bar graph showing percentage of rats with testicular lesions by age in days. Rats appear in the following order for all age groups: BBWd, BBWnd, and Wistar. The number of rats in each group is noted above each bar.

Necropsy was performed on all rats that died spontaneously or were sacrificed for experimentation either immediately or following storage at 4 C, usually for no longer than 12 hours after death. Thoracic and abdominal organs were removed *en block*; and, following dissection, individual organs were weighed, fixed in neutral phosphate-buffered formalin, and processed for light microscopy. Tissue sections were routinely stained with hematoxylin and eosin. Tissue and fluid specimens suspected of antemortem bacterial infection were placed in disposable collection tubes and cultured for aerobic and anaerobic microorganisms. Paraffin sections of such tissues were stained with Gram's stain, acid fast blue, and Gomori's methenamine silver for bacteria and fungi.

In addition to determining testicular mass and body mass, we determined the presence and distribution of testicular atrophy (unilateral and bilateral) histologically. Testes from all three groups of rats were rated as normal, hypocellular, or atrophic. Hypocellular testes had seminiferous tubules with decreased cellularity, but all retained some germ cells. Atrophic testes were those that had seminiferous tubules without any germ cells. We classified these as Grades 1 or 2 on the basis of the extent of atrophy. Testes were considered to have Grade 1 (minimal) atrophy if there were fewer than 5 atrophic tubules per cross-section; testes with Grade 2 (severe) atrophy were those with more than 5 atrophic tubules per cross-section. We used chi-square analysis to compare these categories with a variety of specific histologic abnormalities, including the presence of multinucleated giant cells in the lumens of tubules, increased amounts of interstitial tissue, increased density of Leydig cells, and increased thickness of tunica albuginea. All of these were rated subjectively as normal or as having one of three grades of severity and related to the ages of the animals by the chi-square test. Since pneumonia is known to affect spermatogenesis severely,[9,10] the presence or absence of pneumonia was also noted. The duration of diabetes in days for each BBWd rat was taken from its treatment records.

Results

Figure 1 shows the distribution and severity of testicular lesions according to the ages of the rats. All three types of rats (BBWd, BBWnd, and W) developed minimal and severe testicular atrophy. One-third of BBWd rats in the youngest age group had hypocellular testes. Both minimal testicular atrophy and hypocellularity occurred in the 121–240-day-old age group of BBWd, and the frequency and severity of the lesions progressively increased with age in these rats. Similar changes occurred in the BBWnd rats, but at an older age and with less severity. Testes from Wistar rats showed no degenerative testicular changes until the second oldest age group, but all rats had severely atrophic testes in the 481–600-day-old age group. The relationship between the age of the rats and the degree of atrophy was examined by a one-way analysis of variance (unweighted means solution). Table 1 shows that the severity of atrophy increased significantly ($P < 0.001$) with age in both BBWd and W rats. The same trend is seen in the BBWnd rats but is not statistically significant, because only 3 of these rats developed atrophy. The presence of atrophy related more strongly to dura-

Table 1—Distribution of Age and Duration of Diabetes by Degree of Testicular Atrophy*

Rat type	Days 0-120	121-240	241-360	361-480	481-600	Mean ± SEM†	Statistical relationship to degree of atrophy‡
BBWd							
Age	6	40	37	17	0	254 ± 10.0 *n* = 100	*P* < .001 F(2, 97) = 21.25
Duration	49	30	21	0	0	147 ± 10.0 *n* = 100	*P* < .001 F(2, 97) = 38.29
BBWnd							
Age	6	7	7	6	0	240 ± 23.8 *n* = 26	NS F(2, 23) = 2.28
Wistar							
Age	6	6	6	6	5	280 ± 30.1 *n* = 29	*P* < .001 F(2, 26) = 17.56

* Values are numbers of rats for which precise ages and duration of diabetes are known.
† SEM = standard error of the mean.
‡ Statistical analysis by one-way analysis of variance using the unweighted means solution. NS = not statistically significant.

tion of diabetes than to age alone (Table 1), as indicated by the higher F-value for the former (38.29, compared with 21.25) with the same degrees of freedom. This is an important distinction, because many of the old BBWnd rats became diabetic shortly before dying (the range for age at onset of diabetes was 42 to 426 days; the mean was 107 ± 5 days). For instance, the oldest BBW rat in the study (464 days) was nondiabetic until 38 days before it died. This may explain why some of the older diabetic rats did not develop testicular atrophy and why the percentage of BBWd with atrophy does not reach 100%.

Using an analysis of covariance with body weight as the covariate (Table 2), we found that testicular mass decreased significantly with increasing severity of histologic atrophy for all three groups of rats. Grossly, atrophic testes were small, soft, wrinkled, and frequently light yellow (Figure 2).

Table 3 shows the frequencies of a variety of morphologic features rated semiquantitatively on a scale of severity ranging from 0 (normal) through 3 (severe). Multinucleated giant cells (Figure 3) were not seen in the lumens of normal seminiferous tubules, and the number present was strongly associated with the degree of atrophy, but less so with age. An increase in testicular interstitial connective tissue (Figure 4) was associated with the degree of atrophy at a low level of significance ($P < 0.05$) but was not associated with age. There was a strong direct relationship between Leydig cell hyperplasia (Figure 4) and an increasing degree of atrophy in all three types of rats ($P < 0.01$), but there was no statistically significant relationship between age and Leydig cell hyperplasia. There was also a strong positive relationship between the thickness of the tunica albuginea (Figure 5) and the degree of atrophy ($P < 0.001$), but only in diabetic rats. No relationship between the presence of pneumonia and testicular degenerative changes was present in BBWd or BBWnd rats, and none of the Wistar rats had pneumonia. Orchitis was present in 2 BBWd rats, and bilateral testicular granulomas were observed in 1 BBWd rat, but no organisms were found. Adrenal and pituitary were histologically normal in all three groups of rats.

Table 2—Body and Testicular Weights

	Body mass (grams)†‡	Testicular weights ± SEM (grams)* Normal	Minimal atrophy	Severe atrophy
BBWd	329.8 ± 8.5 *n* = 87 F (1, 83) = 42.81, *P* < 0.001	2.88 ± 0.08 *n* = 56	2.38 ± 0.31 *n* = 8 F (2, 83) = 88.79, *P* < 0.001	1.27 ± 0.10 *n* = 23
BBWnd	381.9 ± 26.3 *n* = 19 F (1, 15) = 43.05, *P* < 0.001	3.13 ± 0.15 *n* = 17	1.76 ± 0 *n* = 1 F (2, 15) = 4.96, *P* < 0.05	0.78 ± 0 *n* = 1
Wistar	449.7 ± 27.8 *n* = 33 F (1, 29) = 40.64, *P* < 0.001	3.56 ± 0.10 *n* = 26	2.80 ± 1.24 *n* = 2 F (2, 29) = 36.36, *P* < 0.001	1.61 ± 0.36 *n* = 5

* Each measure is the combined mass of both testes from each rat. SEM = standard error of the mean.
† Statistical analysis examining testicular weight with respect to histologic severity of atrophy was by analysis of covariance with body weight as covariate. Includes only rats for which both body mass and testicular mass were known.
‡ Correlations between testicular weight and body weight were 0.376, 0.796, and 0.534 for BBWd, BBWnd, and Wistar rats, respectively.

Discussion

Structural changes in the testes of human diabetics were first observed in 1878 by Paschutin[4] and later substantiated by others.[5,6,11-13] Several of these investigators[11,12] attempted to relate these histologic abnormalities to sexual impotence, a disorder present in approximately 50% of diabetic men of reproductive age.[14] A study by Singhal et al[13] suggests that testicular abnormalities are present in both impotent and sexually potent diabetics with similar frequency. Impotence is presently believed to be due to diabetic peripheral neuropathy and unrelated to these testicular changes.[14]

Although the histologic changes in the testes have been studied extensively in chemically induced diabetes,[20,21,23,25-27,32] they have been examined in only two other strains of spontaneously diabetic animals, the obese-hyperglycemia AO mouse[10] and the Chinese hamster.[21] Both studies described hypocellularity or maturation arrest as the predominant finding, rather than a total absence of germ cells within seminiferous tubules. In addition to these milder changes, histologic changes observed in the BB Wistar rat include both mild and severe atrophy. Furthermore, we have examined these changes with respect to both age and duration of diabetes and have simultaneously compared them with the senile testicular atrophy that occurs in nondiabetic rats.

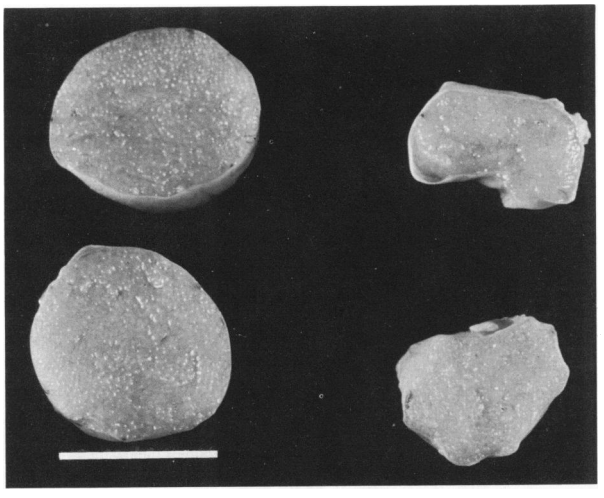

Figure 2—Transected rat testes. Normal Wistar rat on the *left* and BB Wistar diabetic rat with bilateral atrophy on the *right*. Line is 1 cm.

Since testicular atrophy is prevalent in most strains of aged rats,[15-17] age was considered a likely contributing factor to the high incidence of testicular lesions in the BBW Wistar rats. Burek[15] reported that

Table 3—Numbers of Rats With Different Degrees of Severity of Testicular Histologic Abnormalities and Their Relationship to Degree of Atrophy and Age

		Degree of severity				Relationship to*	
	Rat type	Normal	1	2	3	Degree of atrophy	Age group
Giant cells	BBWd	65	22	9	4	$P < 0.001$ $\chi^2 = 28.24$, $df = 6$	$P < 0.01$ $\chi^2 = 21.83$, $df = 9$
	BBWnd	23	4	0	0	NS $\chi^2 = 2.23$, $df = 2$	NS $\chi^2 = 6.81$, $df = 3$
	Wistar	36	2	0	0	$P < 0.01$ $\chi^2 = 11.26$, $df = 2$	NS $\chi^2 = 3.24$, $df = 4$
Increased interstitial connective tissue	BBWd	50	39	7	4	$P < 0.05$ $\chi^2 = 13.90$, $df = 6$	NS $\chi^2 = 14.00$, $df = 9$
	BBWnd	25	1	1	0	$P < 0.05$ $\chi^2 = 13.05$, $df = 4$	NS $\chi^2 = 5.86$, $df = 6$
	Wistar	24	12	1	1	$P < 0.05$ $\chi^2 = 14.67$, $df = 6$	$P < 0.05$ $\chi^2 = 27.01$, $df = 12$
Leydig cells hyperplasia	BBWd	92	6	1	1	$P < 0.001$ $\chi^2 = 24.19$, $df = 6$	NS $\chi^2 = 6.12$, $df = 9$
	BBWnd	25	2	0	0	$P < 0.001$ $\chi^2 = 19.71$, $df = 2$	NS $\chi^2 = 6.17$, $df = 3$
	Wistar	35	1	0	2	$P < 0.01$ $\chi^2 = 17.37$, $df = 6$	NS $\chi^2 = 21.50$, $df = 12$
Tunica albuginea thickening	BBWd	45	27	14	10	$P < 0.001$ $\chi^2 = 55.39$, $df = 6$	$P < 0.001$ $\chi^2 = 39.77$, $df = 9$
	BBWnd	16	8	3	0	NS $\chi^2 = 5.09$, $df = 4$	NS $\chi^2 = 39.77$, $df = 9$
	Wistar	20	10	1	0	NS $\chi^2 = 0.90$, $df = 4$	NS $\chi^2 = 6.13$, $df = 8$

* All statistical analyses by chi-square test. Chi-square values and degrees of freedom printed below P values.

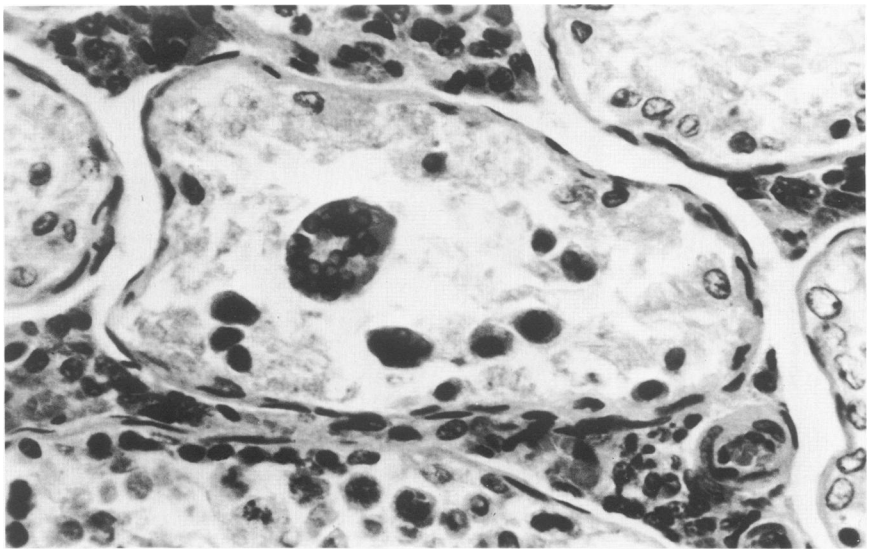

Figure 3—BB Wistar diabetic rat with atrophy. Atrophic seminiferous tubule with several multinucleated giant cells in the lumen. Interstitial tissue shows Leydig cell hyperplasia. Tubules located peripherally to the *right*, *left*, and *above* the central tubule contain only Sertoli cells. (×400)

at least limited atrophy was present in all rats over 18 months of age and was usually severe in rats older than 24 months. He found that atrophic testes of old rats frequently had Leydig cell hyperplasia, interstitial edema, and tubules with multinucleated giant cells or only Sertoli cells. The changes described by Burek were consistent with the histologic changes observed in all three types of rats in our study. Several investigators have frequently reported benign or malignant tumors associated with testicular atrophy in senile rats,[15-17] but these were not seen in any rats in our study. This is probably due to the greater age of their animals. In our study, testicular atrophy was first observed in BBWnd and W rats at 355 and 361 days of age, respectively; the earliest age of onset in the BBW diabetic rats was 148 days. Figure 1 shows clearly that the incidence of atrophy increased with age in all rats but occurred at a much younger age in BBWd rats. Saksena et al[18] reported that sperm production in Sprague–Dawley rats remained maximal from 72 days of age to beyond 450 days of age. This appears consistent with our histologic findings in standard Wistar rats but not in the BBWd rats. Age is undoubtedly a very important factor in determining the presence of atrophy in all groups of rats, but the duration of diabetes is a much better predictor of atrophy in BBWd than is age (Table 1).

The severity of testicular lesions in diabetic men and animals varies widely from study to study. Several have reported only a hypocellularity of germinal cells,[19,20] others more severe atrophy,[21] and some only Sertoli cells present.[22-23] This discrepancy may possibly be explained by the severity of the diabetic state in these different studies. Several investigators have suggested that testicular atrophy is more frequent in poorly controlled diabetics.[21,24]

Several studies on diabetic men[5,7,12] and rats[25] have reported increased interstitial tissue in atrophic testes. Only Schoffling et al[21] reported no increase in interstitial tissue. We observed a slightly significant ($P < 0.05$) increase in interstitial tissue in rats with testicular atrophy, regardless of the presence or absence of diabetes. We therefore feel that increased interstitial tissue is probably a general feature of testicular atrophy and is not specifically related to diabetes.

In all three groups of rats, multinucleated giant cells (Figure 3) were frequently seen in the lumens of degenerating seminiferous tubules. Other studies have reported similar findings in both senile[15] and diabetic[21] rats. These giant cells are believed to be fused spermatids.[15] To our knowledge, multinucleated giant cells have not been reported in the seminiferous tubules of man.

Several studies utilizing either rats with chemically induced diabetic or genetically obese (insulin-resistant) mice have reported a decrease in the number of Leydig cells.[19,21,25] It is possible that the diabetogenic chemicals used by some have a toxic effect on the Leydig cells, because alloxan is known to have severe toxic effects on many organ systems, including the testes.[26,27] Leydig cell hyperplasia was observed in this study and in a study by Rosenmann et al[22] Both his

study and ours utilized rats that were not obese and did not have chemically induced diabetes. Interestingly, Ayad[28] has reported Leydig cell hyperplasia in a series of 30 diabetic men. We also observed Leydig cell hyperplasia in nondiabetic rats with senile testicular atrophy. This is consistent with senile atrophy in nondiabetic rat strains.[15,17]

Maturation arrest within seminiferous tubules has been reported in a variety of studies of human[7,12-13] and animal[20,25] diabetics. Most of these investigators have attributed this to hyposecretion of gonadotropic hormones. This explanation seems unlikely, because several recent studies have shown that testosterone levels and gonadotropin levels are normal in diabetic men,[29,30] but an endocrinologic mechanism is suggested by the observation that pancreatectomy or alloxan diabetes not only affects the germinal epithelium but also suppresses the development of secondary sexual characteristics in animals.[31,32]

Some investigators have attributed testicular lesions in diabetics to diffusion or perfusion problems caused by basement membrane thickening of tunica propria, microangiopathy, or atherosclerosis. Since seminiferous tubules are avascular, diffusion from the interstitial vessels through the tunica propria is necessary to nourish the germ cells and Sertoli cells in each tubule. Only a few studies have reported basement membrane thickening,[12] and others have reported its absence.[33] In the present study, microangiopathy and atherosclerosis were not observed by light microscopy and so could not be involved in the pathogenesis of the lesions. Only a few rats had tubules with marked basement membrane thickening, and this thickening may have been secondary to the atrophy rather than causative.

Spermatogenesis in man and the rat is generally similar, except that it proceeds in waves in the rat.[34] In both, proliferation of the germinal epithelium is controlled by a complex milieu of hormones and other factors. The number of spermatozoa produced depends on temperature, available lighting, nutritional factors, age, pituitary gonadotropin levels, testosterone levels, and other variables.[35] It is unlikely that temperature or lighting played a significant role in the incidence of testicular atrophy, because the housing facility was consistently maintained at 72 F with alternating 12-hour periods of artificial light and darkness.

In summary, a high incidence of testicular abnormalities characterized by a partial or total loss of germinal epithelium, frequently with a relative sparing of Sertoli cells, was observed in BB Wistar diabetic rats, their nondiabetic siblings, and standard Wistar rats. These lesions occurred at a much younger age in the diabetic rats than in either the BBWnd or W rats. Similar findings have been reported in human diabetics as well as other animal models for diabetes. Al-

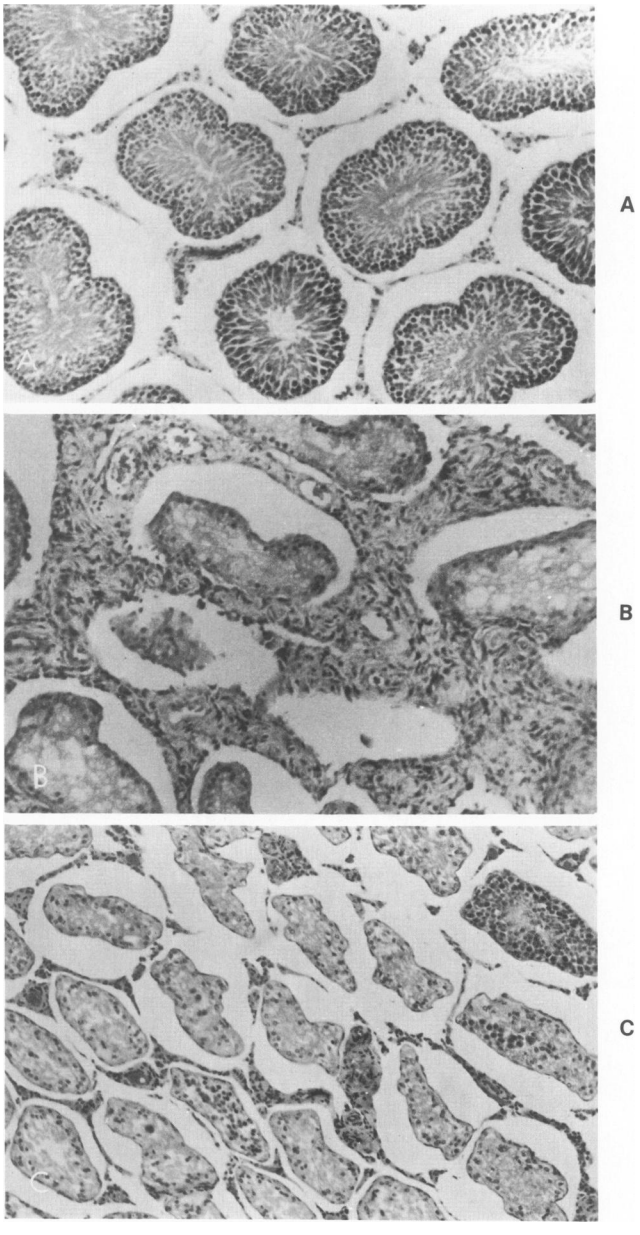

Figure 4—Testes from 3 rats showing different degrees of atrophy and other variables. **A**—Normal seminiferous tubules from a 361-day-old Wistar rat. Full complement of germ cells present. **B**—Testis of a Wistar rat 551 days old with severe atrophy, thickening of interstitial connective tissue (3+), and Leydig cell hyperplasia (3+). **C**—Severely atrophic testis in a 387-day-old BBW diabetic rat. Most tubules have only Sertoli cells. Tubules retaining some germ cells show sloughed epithelium. There is one relatively normal tubule in the field. (H&E, ×100) (With a photographic reduction of 30%)

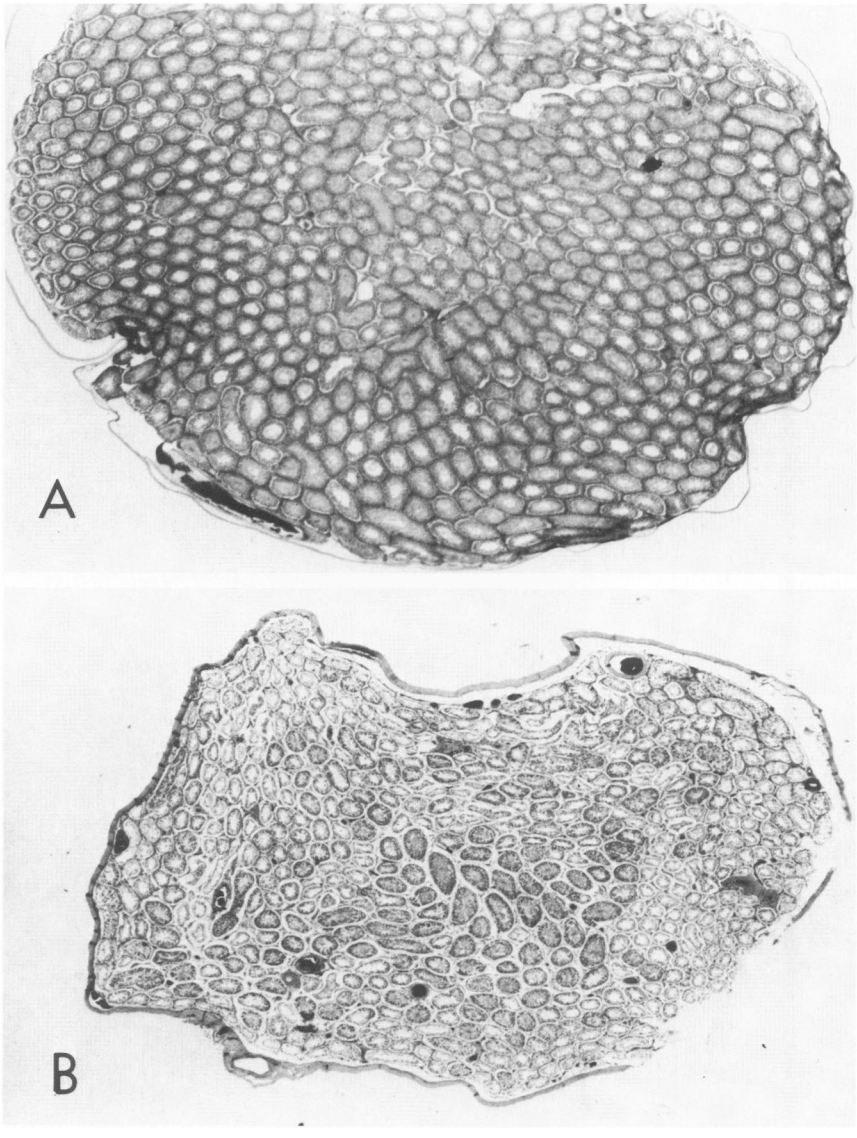

Figure 5A—Normal Wistar rat testis demonstrating normal cellularity of seminiferous tubules and normal thickness of tunica albuginea. (H&E, ×10) **B**—BB Wistar diabetic rat testis with diffuse, severe atrophy of seminiferous tubules, and a thickened tunica albuginea. (H&E, ×10)

though atrophic testes of diabetic animals are histologically similar to those with senile atrophy, the exact etiology and pathogenesis of these lesions remain to be elucidated. The BB Wistar rat appears to be an excellent model for study of the pathogenetic mechanisms involved. Furthermore, the significance of these findings to investigators attempting to breed BB Wistar rats for other types of studies is reflected in the lower rate of breeding success in BBWd rats.

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