Disuse Atrophy of the Urinary Bladder After Bilateral Nephrectomy[1] (36006)

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There is reason to believe that the size to which a urinary bladder grows depends at least in part upon how much it is stretched. Fifty years ago, Carey (1) induced excessive growth of the dog bladder by artificially overloading it with fluid injections. Parasympathetic denervation in the cat, which interferes with normal voiding mechanisms, likewise stimulates bladder hypertrophy (2). Further, regeneration of the rat bladder after cystectomy (3–6) depends on the distention normally exerted by the inflow of urine, and fails to take place if the ureters are diverted to an external drain (7).

The present investigation has been designed to find out what happens to the bladders of growing rats deprived of both kidneys for prolonged periods of time. Nephrectomized animals were kept alive by parabiosis to intact partners and the sizes of their bladders were determined at intervals up to 1 year after operation. The atrophy which occurs in such bladders has been analyzed to learn if it is absolute (outright loss of weight) or relative (continued growth, but at a retarded rate) and to determine if there is a minimal size below which the bladder will not atrophy.

Materials and Methods. Experiments were carried out on Sprague–Dawley rats of both sexes. A total of 119 pairs of littermates weighing between 55 and 105 g were parabiosed under Nembutal anesthesia by uniting their abdominal cavities, tying their adjacent humeri and scapulae together, and joining their skin from neck to hip with wound clips. Deaths due to immunological incompatibilities occurred in 41% of the parabiotic pairs between days 9 and 24 (av = 18.3 days). Bilateral nephrectomies were performed on etherized rats via dorsolateral incisions on one member of each of the 70 surviving pairs. Of these, 16 pairs (23%) died after intervals ranging from 4 to 40 days (av = 18.9 days), presumably owing to renal insufficiency. Fifteen other pairs were lost or discarded for various technical reasons. The experimental results are based on 39 pairs killed in groups of five after 1, 2, 4, 8, 12, 16, and 24 weeks, plus four others that lived to be killed at the end of 1 year. An additional group of 35 normal rats of both sexes, weighing between 130 and 793 g, served as controls.

Rats were killed under Nembutal anesthesia. Parabiotic pairs were first cut apart and their respective body weights measured. The weights of the nephrectomized rats averaged 20.6% less than their intact partners. Each bladder was freed of adhering tissues, separated at the neck, emptied, blotted, weighed, and fixed (usually inflated) in Bouin's solution. Wet weights were also recorded for the kidneys of single control rats and unoperated parabiotic partners. Bladders were sectioned and stained either with Mallory's triple connective tissue stain or with hematoxylin and eosin.

Results. Figure 1 shows the appearance of the bladders at the time of killing 8 weeks postoperatively. That of the nephrectomized rat has atrophied extensively, while the bladder in the intact partner has enlarged. In Fig. 2 the relative weights of the bladders of nephrectomized and intact parabiosed rats are compared with those of unoperated controls. During the first 2 weeks there was little deviation from the normal range, although the mean relative weights of the bladders of nephrectomized rats were consistently ($p < .05$) lower than those of their intact partners. By 4 weeks, however, the differences had increased to the point where the relative bladder weights in the two groups no longer

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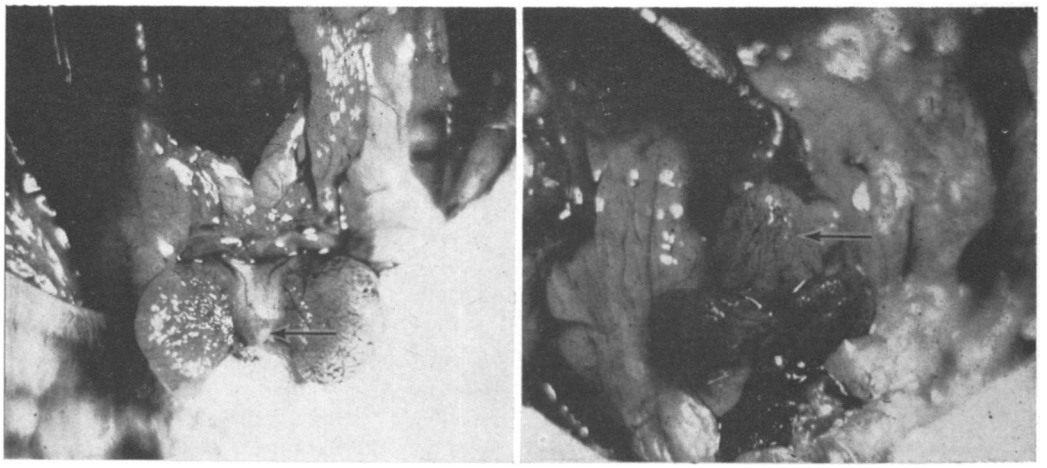

FIG. 1. Atrophic (left) and hypertrophic (right) bladders (arrows) of parabiotic rats at time of killing 8 weeks after nephrectomy of one partner.

overlapped. After 8 and 12 weeks the bladders of the nephrectomized rats were less than half the size of their partners', and after 16 and 24 weeks the discrepancy was over 3-fold. At the end of a year there was a 6-fold difference between the relative weights of the bladders of the two partners.

These figures do not tell the whole story, however. Not only did the unused bladders atrophy, but those of their intact partners increased in weight. In point of fact, the latter hypertrophied to approximately the same extent that the former atrophied. Hence, the total amount of bladder tissue shared by the parabiotic pairs remained very close to twice that present in single control rats of comparable sizes. In other words, what one lost the other gained.

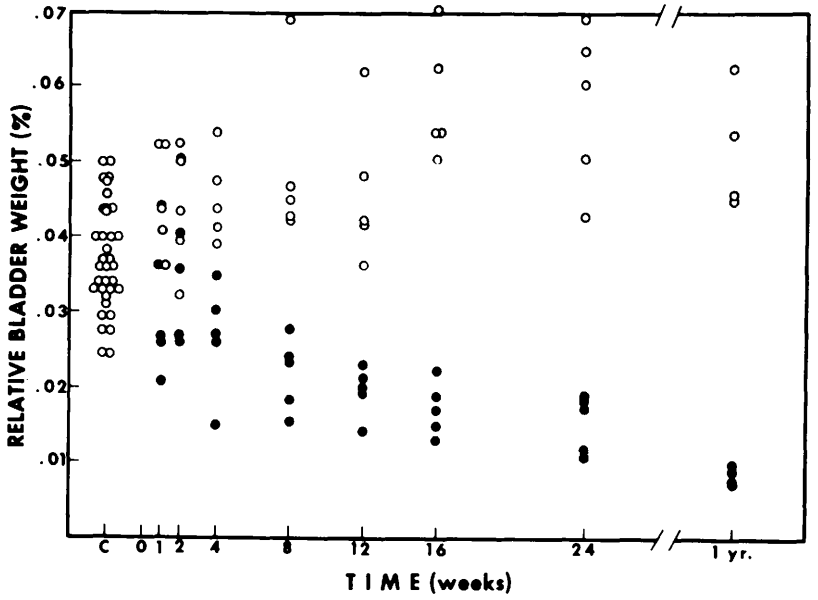

FIG. 2. Relative bladder weights $\left(\frac{\text{bladder wt.}}{\text{body wt.}} \times 100\right)$ as a function of time after bilateral nephrectomy of one parabiotic partner. Compared with normal controls (open circles in left column, C), the unused bladders (●) atrophied while contralateral ones (○) hypertrophied.

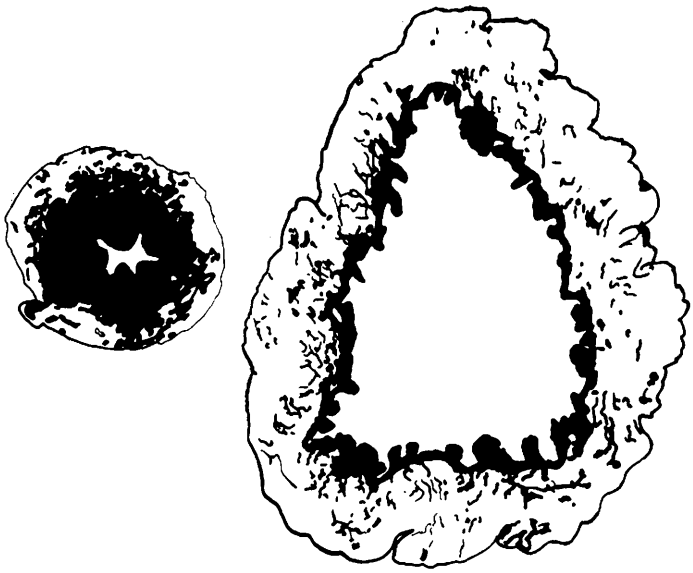

FIG. 3. Comparison between cross sections of atrophic and hypertrophic urinary bladders from a pair of parabiotic rats 1 year after bilateral nephrectomy of one partner. Although both rats weighed the same at sacrifice, their bladder weights were 21.4 and 174.3% of normal, respectively. Collagenous connective tissue is black, smooth muscle white.

The differences between the relative bladder weights of nephrectomized and intact parabiotic rats were statistically significant from the first postoperative week onward. The bladders of the nephrectomized partners, however, were not significantly smaller than those of intact single control rats until the fourth week ($p<.01$). In contrast, the bladders of the intact parabiotic rats showed a significant ($p<.05$) increase in relative weight over the intact single controls as early as 1 week after nephrectomy of their partners. Bladders are apparently quicker to hypertrophy than they are to atrophy.

It must be remembered that the parabiosed rats continued to grow during the course of the experiment. Conceivably, therefore, the atrophy of the unused bladders could be attributed merely to cessation of growth rather than to an actual loss of weight. Either way there would have been a decline in the relative weight, as already observed. In order to distinguish between these alternatives, the weights of experimental bladders were compared with those calculated on the basis of (a) the body weights of the parabiotic rats at the time of nephrectomy, and (b) the weights of bladders from single control rats of equivalent size. The comparison shows conclusively that the bladders lost up to one-half of their original absolute weights during the year of disuse despite the continued growth of the rats. Bladder atrophy, therefore, is not just a cessation of growth, but a gradual and extensive attenuation of the organ. Moreover, most of the depreciation takes place during the first 2 months after nephrectomy. Thereafter bladder weight decreases very slowly, so gradually that it is difficult to decide whether the atrophic process ever really levels off. In contrast, the bladders of the intact partners, when compared with those of single controls of the same weight at the time of sacrifice, had hypertrophied from one-quarter to two-thirds over the weight they would otherwise have achieved.

The mechanism by which the size of the bladder changes does not involve shifts in water content. The ratios of dry to wet weights of both atrophic and hypertrophic bladders, measured 12 weeks after nephrectomy, were not significantly different from each other, nor from normal control bladders.

Histologically, bladder atrophy appears to involve a decline in the amount of smooth muscle, a decline accounted for by substantial narrowing of the muscle fibers. Concomitantly, the relative thickness of the submucosal connective tissue increased considerably, as illustrated in Fig. 3. The transitional epithelium maintained its normal width throughout.

An interesting sidelight on these experiments was the hypertrophic response of the kidneys in the unoperated parabionts. After bilateral nephrectomy of one partner, the two remaining kidneys of the other rat underwent compensatory growth. Statistically, this enlargement did not become significant until after the second postoperative week. From the fourth week onward, such kidneys averaged 19% above the controls in relative weight. Their growth, however, was well below the degree of hypertrophy normally exhibited by unilaterally nephrectomized rats (8, 9). Hence, for unexplained reasons the two kidneys servicing parabiotically paired rats undergo considerably less hypertrophy than do the remaining single kidneys in unpaired animals.

These experiments show that unused bladders atrophy but do not disappear altogether. This is consistent with what happens to other nonfunctional tissues and organs: they dwindle to fractions of their former selves, but persist indefinitely in the atrophic condition. The unexpected discovery, however, that bladders hypertrophy when their kidneys enlarge raises interesting implications concerning the relations between renal function and bladder size.

Summary. If both kidneys are removed from a rat which is kept alive by parabiosis to an intact partner, its unused bladder loses up to one-half the original weight. Such atrophic bladders persist indefinitely as organs composed mostly of dense fibrous connective tissue with attenuation of smooth muscle. In the intact partners, compensatory hypertrophy of both kidneys occurs, and the bladders become 50% larger than normal.

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