The Physiological Basis of Urinary Bladder Hypertrophy[1] (37235)

RICHARD J. GOSS, MARC D. LIANG, STEVEN J. WEISHOLTZ, AND THOMAS J. PELTZER
Division of Biological and Medical Sciences, Brown University, Providence, R. I. 02912

If both kidneys are removed from one partner of a parabiotic pair of rats, the urinary bladder of the operated animal atrophies while that of the intact partner hypertrophies (1). The present investigation has been undertaken to find out if this hypertrophy results from voidings of increased frequency or increased volume. It would appear to be a little of both.

Materials and Methods. Sprague–Dawley rats (Charles River CD®) were parabiosed as littermates weighing less than 100 g. They were joined together from shoulder to hip with confluent peritoneal cavities. The animals were allowed to reach maturity, and during the course of their first year both kidneys were removed from the right partner via dorsolateral incisions. At this time, both animals were approximately the same size, but the nephrectomized partner tended to lose weight thereafter.

The pattern of micturition was monitored in these animals before and after nephrectomy to determine how the frequency and volume of urination were affected by the operation. Animals were placed in metabolism cages, and their urine was carried through plastic tubes to a fraction collector equipped with 60 centrifuge tubes per revolution. At 15-min intervals, the fraction collector shifted a new collecting tube into position. In this way, the apparatus could be allowed to run for up to 15 hr without attention. Urine was collected in the above manner from parabiotic rats for periods of 1 wk at a time. The urine tubes were replaced twice a day, and the amounts of urine weighed and recorded for each voiding. Urine was collected for 1 wk from each parabiotic pair prior to nephrectomy and, thereafter, for the 1st, 5th, 10th, and 15th weeks. A total of 27 pairs of rats were analyzed in this way, but owing to the premature demise of some animals the data reflect diminishing returns to 17 pairs by the 5th week, 9 by the 10th week, and 7 by the 15th week.

Results have been expressed in terms of frequency of urinations, amount of urine per voiding, and total urine produced. The latter two items were corrected for changes in body weights during the course of the experiment, and all data have been calculated on a percentage basis of the original preoperative figures. Prior to nephrectomy, when both partners of a parabiotic pair were urinating into the same tube, it has been necessary to correct the results to take into account occasional simultaneous urinations in a given 15-min interval. Thus, the number of tubes with urine in them per 24-hr period was recalculated according to the formula $N = n + (n^2/96)$, where N is the actual number of urinations, n is the observed number, and 96 is the number of 15-min intervals in a 24-hr period. It was not necessary to make this correction postoperatively, since only the intact partner would be urinating at that time.

Animals were sacrificed at the end of the 15th postoperative week. Those that died prematurely were autopsied whenever possible. Rats were cut apart, and their body weights measured separately. The wet weights of both kidneys of the intact partner and of the bladders of both partners were determined.

Results. The total amount of urine produced per week by each parabiotic pair is plotted in Fig. 1. These data are expressed as percentages of one-half the combined preoperative output, that is, in relation to the amount of urine assumed to have been pro-

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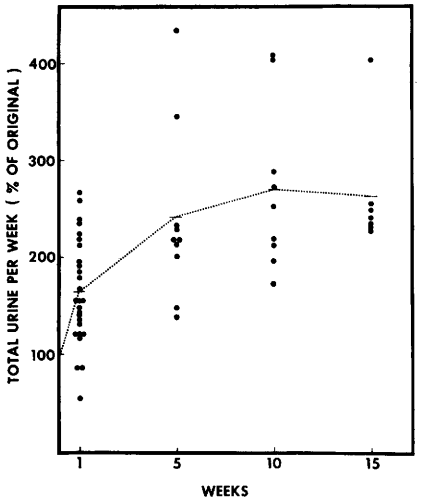

FIG. 1. Urine output by parabiotic rats at successive intervals after nephrectomy of one partner. Calculations based on percentages of one-half preoperative quantities of urine produced. Broken line connects mean values.

duced by the intact rat even before the kidneys were removed from his partner. Although the intact rat did not immediately double his output of urine, he did produce 80% more urine during the first week than he excreted preoperatively. Ultimately, more than twice the amount of urine originally produced was excreted by these rats. This was made possible by a combination of increased frequencies of voiding and greater quantities of urine per urination.

The frequency of voidings, graphically presented in Fig. 2, increased immediately in the intact rat after bilateral nephrectomy of its partner. The mean number of urinations per day rose an average of 30% during the first postoperative week ($p < 0.01$) and did not change significantly thereafter. Thus, although the intact animal voided more frequently after his partner had been nephrectomized, he did not double the frequency of voidings and, therefore, did not entirely compensate for his partner's deficiency in this way.

Figure 3 shows the amount of urine produced each time the bladder was emptied. These data indicate that this also increased an average of 30% during the first week after operation, but this difference was not statistically significant ($p > 0.05$). Unlike the frequency of voidings, however, the quantity of urine per voiding continued to rise to about twice the original volume by the 5th week ($p < 0.01$), where it remained for the rest of the experiment. This reflects an increased capacity of the bladders in the intact rats as hypertrophy took place.

It is worth noting the reactions of the kidneys in intact rats to bilateral nephrectomy of their parabiotic partners. As expected, compensatory hypertrophy was found to have occurred when the animals were autopsied 16 wk after operation. The kidneys originally removed from the one partner had a mean relative weight of 0.319%. At the end of the experiment, the relative weights of the kidneys of the intact partners averaged 0.364%, an increase of 14.11% over a period of 15 wk. This value, however, was 56% less than that of single rats deprived of one kidney, in which the remaining organ hypertrophied 32.18% above normal.

Discussion. When faced with the task of excreting for two, a rat parabiosed to a nephrectomized partner first increases the frequency of micturition. This reaction is an immediate one and persists without significant change thereafter. The quantity of urine pro-

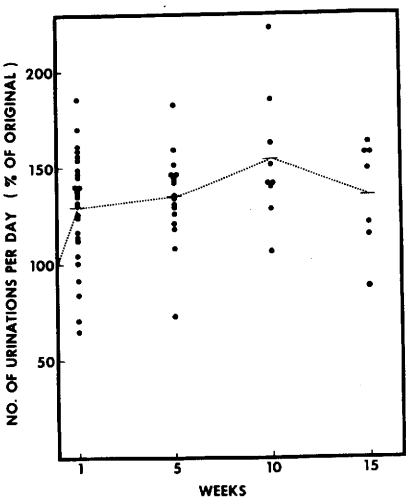

FIG. 2. Frequency of urinations following nephrectomy of one partner of a parabiotic pair, based on percentages of one-half preoperative rates. Mean values at postoperative intervals are connected by broken line.

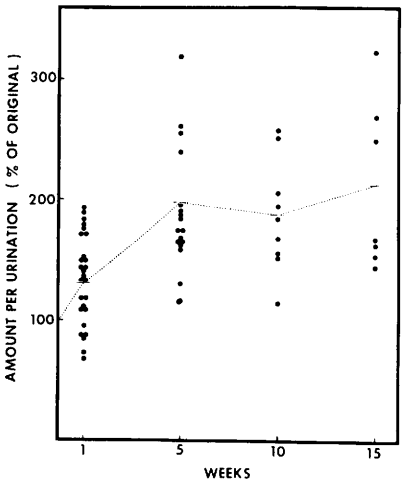

FIG. 3. Increasing capacity of urinary bladders is represented by amounts of urine excreted at each voiding, shown here in relation to original levels before operation.

duced per voiding also increases, but at a more gradual rate. Slightly elevated during the first postoperative week, the capacity of the bladder plateaus at twice its original level from the 5th week onward. These two parameters, the increases in frequency and quantity of urination, combine to yield an eventual output of urine that is more than double that which would otherwise be excreted by intact parabiotic rats. This overcompensation may be attributed to the fact that the frequency of micturition increases, as it must, prior to a rise in the amount of urine produced per urination. Eventually, the capacity of the bladder becomes great enough to handle the excretory needs of both rats, but once this has been achieved the frequency of urinations fails to decline to preoperative levels.

The original purpose of this investigation was to find out if the hypertrophy that occurs in the bladder of an intact rat parabiosed to a nephrectomized partner is caused by more frequent voidings or by increased quantities of urine produced per urination. Both of these processes seem to be involved. The increased frequency of micturition, being a physiological adaptation, is the more prompt form of compensation. The growth response takes longer, yet there is reason to believe that it may begin just as soon, even though more time is required for its effects to become statistically valid.

These results do not reveal whether it is the heightened hydrostatic pressure stretching the bladder, or the more frequent contractions emptying it, which accounts for the observed hypertrophy. Since contractions are triggered by stretching, it is difficult to distinguish between these two effects. However, experiments have shown that artificial distension will stimulate growth of the bladder (2, 3) and ureter (4, 5). Moreover, parasympathectomized bladders which become excessively distended because they cannot empty themselves by active contraction tend to undergo muscular hypertrophy (6–11). This evidence would suggest that stretching alone can indeed promote hypertrophy, but it does not prove that contraction of the bladder musculature could not also cause the same effect.

Finally, one wonders why the degree of compensatory renal hypertrophy observed in intact rats parabiosed to bilaterally nephrectomized partners should be so much less than in single animals following unilateral nephrectomy. In the present experiments, the kidneys enlarged only 44% as much as if one kidney had been removed from each partner instead of both from one animal. Clearly, two parabiosed rats subsisting on the kidneys of one of them are not physiologically equivalent to a single rat with a solitary kidney, even though the ratios of kidney mass to body weight may be the same.

It has long been known (12) that the coeloms of parabiosed rats must be joined if they are to survive resection of both kidneys from one partner. Under these conditions, the kidneys in the intact rat become enlarged (13–15). On the other hand, if one kidney is excised from one parabiotic partner, compensatory renal hypertrophy is more marked in the operated rat that in the unoperated one (15-17), and if the animals are not joined coelomically no hypertrophy occurs at all in the intact partner (16).

It can only be concluded that the inequities between the three kidneys remaining in a parabiotic pair may be more profound than hitherto suspected. The two kidneys of the intact partner may assume the lesser

burden of hypertrophy not simply because the remaining kidney of the unilaterally nephrectomized rat compensates first and most, but because the parabiotic union itself may not communicate efficiently whatever message it is that promotes compensatory renal hypertrophy.

Summary. When both kidneys are removed from one partner of parabiosed rats, the unused bladder atrophies while that of the intact partner hypertrophies. This hypertrophy is brought about by a prompt and sustained increase of 30% in the frequency of micturition, together with a more gradual rise in the quantity of urine excreted at each voiding. The capacity of such bladders levels off at approximately double preoperative values by the fifth week, while the heightened frequency of urinations remains elevated. The two remaining kidneys of the intact rat undergo hypertrophy in compensation for the renal losses of its partner, but the degree of enlargement is less than half that observed in single rats deprived of one kidney.

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1. Goss, R. J., and Singleton, S. D., Proc. Soc. Exp. Biol. Med. **138**, 861 (1971).

2. Carey, E. J., Amer. J. Anat. **29**, 341 (1921).

3. Liang, D. S., J. Urol. **96**, 304 (1966).

4. Cass, A. S., Dewey, A. W., and Hinman, F., Jr., Invest. Urol. **6**, 393 (1969).

5. Swartzberg, J. E., Heilbron, D., and Hinman, F., Jr., Urol. Int. **26**, 51 (1971).

6. Elliott, T. R., J. Physiol. **35**, 367 (1907).

7. Langworthy, O. R., and Kolb, L. C., Anat. Rec. **71**, 249 (1938).

8. Jacobson, C. E., Jr., J. Urol. **53**, 670 (1945).

9. Carpenter, F. G., Amer. J. Physiol. **166**, 692 (1951).

10. Carpenter, F. G., and Root, W. S., Amer. J. Physiol. **166**, 686 (1951).

11. Veenema, R. J., Carpenter, F. G., and Root, W. S., J. Urol. **68**, 237 (1952).

12. Sibley, J. A., and Huggins, C., Proc. Soc. Exp. Biol. Med. **63**, 85 (1946).

13. Braun-Menéndez, E., Acta Physiol. Lat. Amer. **2**, 2 (1952).

14. Braun-Menéndez, E., Circulation **17**, 696 (1958).

15. Kurnick, N. B., and Lindsay, P. A., Lab. Invest. **19**, 45 (1968).

16. Thompson, J. W., and Lytton, B., J. Urol. **98**, 548 (1967).

17. Lytton, B., Schiff, M., Jr., and Bloom, N., J. Urol. **101**, 648 (1969).

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