

Evidence of Induction of New Nephrons in Immature Kidneys Undergoing Hypertrophy

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Unilateral nephrectomy performed during the first days or weeks of life may or may not induce the development of new nephrons in the remaining kidney. Such an increase has been reported to occur, as discussed in this review, in newborn rats and mice, but not in guinea pigs. These observations are consistent with other data suggesting different patterns of compensatory adaptation in young and in old animals.

In the present article, we review the evidence which supports our belief that unilateral nephrectomy, under certain conditions, induces the development of additional nephrons in the remaining hypertrophied kidney, so that the number of nephrons becomes greater in these kidneys than in control kidneys from intact animals of the same age.

All investigators agree in the conclusion that, in adult animals, the number of nephrons does not increase after contralateral nephrectomy. There are, however, discrepancies concerning the possibility of the appearance of new nephrons after contralateral nephrectomy in young and growing animals. Some investigators, including ourselves, obtained experimental results which favor this possibility whereas others did not find any evidence of such a phenomenon.

When looking at the literature data published during a century on this issue, we are impressed by the constancy with which discrepant results have been reported. Since contradictory results have often been reported by investigators using the same method, it appears unlikely that methodological bias could be responsible for each single negative or positive result. We rather believe that discrepancies are due to still unidentified factors, which deserve further investigation.

In 1926, Hinman [1] published a review entitled "renal counterbalance," in which he supported the statement of Galeotti and Villa Santa [2] that "the hypertrophy which follows opposite nephrectomy varies markedly according to whether the animal is young and growing or is fully developed at the time of operation. In the former case, there is a marked increase in the number of glomeruli. In the latter case, the number of glomeruli and of convoluted tubules is not changed, but there is a marked increase in the size of each."

The experimental results obtained up to this time were summarized by Jackson and Shiels in 1927 [3] and were, in fact, highly contradictory (Table 1), though all results had been obtained by histological methods (glomerular counts on serial slices).

In the same year in which Hinman's review was published, Arataki [4] found, by similar histological methods, that the number of glomeruli (NG) did not vary in

TABLE 1
Number of Glomeruli in Hypertrophied Kidneys

Authors	Species	Unilateral Nephrectomy in	
		Young Animals	Adult Animals
1882, Ribbert	Rabbit-Dog	no increase	
1883, Tizzoni and Pisenti	Rabbit	increase	
1886, Lorenz	Rabbit	increase	
1894, Manchle	Rabbit		no increase
1901, Fiori	Rabbit, Dog, Guinea pig		no increase
1902, Galeotti and Villa Santa	Rabbit-Dog	increase	no increase
1911, De Benedetti	Rat	no increase	no increase
1911, Zanetti	Rabbit	increase	
1922, Hinman	Dog-Rat		no increase
1924, Oliver	Rabbit		no increase
1926, Arataki	Rat	no increase	no increase
1926, Bayle	Rabbit	no increase	no increase

From Jackson CM, Shiels M: *Anat Rec* 36:221-237, 1927.

hypertrophied kidneys, either in the young or in the adult rat. Following this work, Arataki's view prevailed up to the early 1970s [5].

Investigations on this problem were resumed following our 1972 observations in the rat [6]. The methods used, now, were either glomerular counts derived from Damadian's procedure [7] or physiological methods [8] based on the comparison of total inulin clearance and the mean value of single nephron glomerular filtration rate. Again, there were discrepancies concerning the induction of supplementary nephrons in the remaining kidney after unilateral nephrectomy in young animals, as shown in Table 2.

The experimental evidence obtained in our laboratory in favor of the induction of new nephrons after unilateral nephrectomy in young animals may be summarized as follows:

RAT STUDIES

In the Wistar rat, a significant increase in NG was found in the remaining kidney after unilateral nephrectomy in young, but not in adult animals, by either Damadian's method [6] or by physiological methods based on the comparison of total GFR and mean SNGFR values [8]. The results are depicted in Fig. 1. The latter study [8] also confirmed that ponderal hypertrophy is more important in young animals, an already well-known phenomenon [8,9,10,11,12,13], and showed that kidney weight is

TABLE 2
Number of Glomeruli in Hypertrophied Kidneys of Rats
(Recent Data)

Authors	Species	Unilateral Nephrectomy in	
		Young Animals	Adult Animals
1972, Bonvalet et al.	Rat	increase	no increase
1974, Imbert et al. (physiological study)	Rat	increase	no increase
1975, Kaufman et al.	Rat	no increase	no increase
1975, Canter and Goss	Rat	increase	no increase
1976, Kunes et al.	Rat	increase	no increase

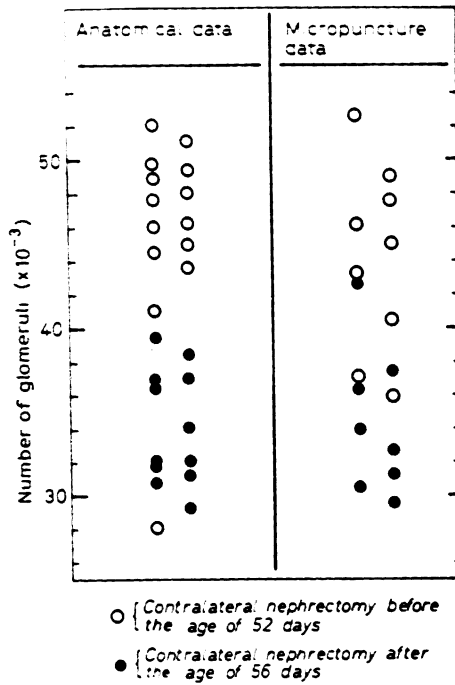


FIG. 1.

correlated to NG in hypertrophied kidneys (Fig. 2). An increase in NG was also observed in hypertrophied kidneys following contralateral renal artery constriction (Goldblatt technique) in young but not in adult rats (unpublished data). Finally, using a modified Damadian technique [13], we confirmed our initial 1972 results [6] (unpublished data).

These conclusions have been confirmed and extended by Canter and Goss [12] and Kunes et al. [14]. In contrast, they were challenged by Kaufman et al. [13]. We have, at the present time, no explanation for this discrepancy. However, agreement of results obtained in several laboratories in normal kidneys, as well as the agreement of

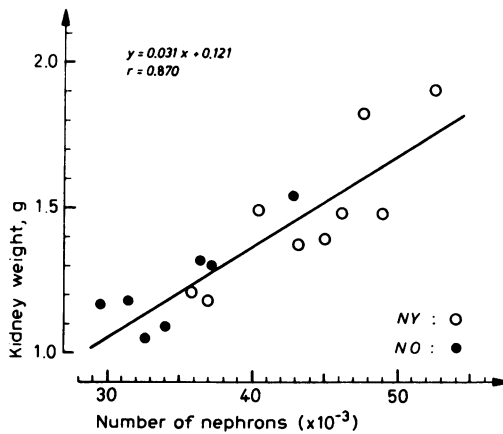


FIG. 2.

our own results obtained in hypertrophied kidneys by different methods, comprising that used by Kaufman [13], induce us to believe that the discrepancy cannot be ascribed to particular problems of the counting methods. Strain differences also are an unlikely explanation, since similar conclusions were reached by Canter and Goss [12] in Sprague-Dawley, and by ourselves [6] in Wistar rats. Unidentified differences of experimental conditions, therefore, appear to be responsible for the contradictory results reported.

OTHER SPECIES STUDIED: MOUSE AND GUINEA PIG

Experiments were undertaken in mice and guinea pigs in order to investigate possible relations between the ability of the remaining kidney to develop additional nephrons after contralateral nephrectomy and the pattern of kidney maturation in growing animals [15]. The guinea pig is known to be almost mature at birth [16,17], whereas the kidney of the newborn rat [17,18,19,20,21,22] and mouse [23] is immature.

We found that, in guinea pigs, at birth, the NG was almost the same as in adult animals, a fact also observed by Merlet-Benichou and Rouffignac [24]. In contrast, in mice, there was a sharp increase in NG after birth, since it doubled between the fifth and the tenth day of age and then continued to increase more slowly.

In both these species, unilateral nephrectomies were done at ages ranging from 2 to 65 days. In guinea pigs, no increase in NG was detected in hypertrophied kidneys whatever the age at the time of nephrectomy. In mice, contralateral nephrectomy, when performed up to 10 days of age, induced a significant increase in NG in the hypertrophied kidneys. After ten days and up to 65 days of age, the observed increase of NG was only 9 percent as compared to controls. As already described [8,9,10,11,12,13], the increase of renal weight after contralateral nephrectomy was greater in young than in adult animals.

CONCLUSION

In two species, thus, the rat and the mouse, the number of glomeruli normally increases after birth for a more or less extended period, and contralateral nephrectomy performed during this period induces the formation of additional nephrons in the remaining enlarged kidneys. In contrast, in one species, the guinea pig, the number of glomeruli is almost completed at birth and contralateral nephrectomy does not influence the number of glomeruli in the remaining kidney at any age.

In rats and mice, a number of observations indicate that the pattern of compensatory renal hypertrophy differs in young and in adult animals. Ponderal hypertrophy is more important in young animals [8,10,12,13,20]. Following unilateral nephrectomy, the RNA/DNA ratio in the remaining kidney is lower in young than adult animals [11,25]. DNA polymerase, an index of hyperplasia, increases more in hypertrophic kidneys of young than of adult nephrectomized animals [25]. ³H-Thymidine incorporation in the remaining kidney after unilateral nephrectomy in young rats has been found to occur mainly within nephrogenic areas [26]. Another interesting point is the presence of nephrogenic zones in the kidney of newborn animals of these species, which can be seen up to 3 or 4 weeks of age in the rat [27,28,29,30] and at least up to ten days in the mouse [23].

In guinea pigs, on the other hand, the pattern of compensatory renal hypertrophy in young and in adult animals does not appear to differ to any extent [20].

In conclusion, we think that the production of additional nephrons after contralateral nephrectomy can occur in certain conditions and that, after birth, the presence

or absence of the ability to produce new nephrons depends on the maturational state of the kidney at birth.

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