Growth of Baby Kidneys Transplanted Into Adults

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• To determine whether the growth of a kidney is affected by the age of the host or is independently programmed, baby rat kidneys were isologously transplanted into adult rats that underwent unilateral or bilateral nephrectomies. The growth of these transplanted baby kidneys was compared to the growth of baby kidneys that were left intact in the growing baby rat. After allowing for compensatory hypertrophy, the kidneys, whether in babies or adults, were found to grow at the same rate and to the same ultimate size. Renal size could be predictably related to renal age, but not to the age of the host.

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Experimental transplantation in rats indicates that there are two kinds of renal growth. Obligatory renal growth is that which normally occurs with growth of the animal. It is not reversible and is not dependent on functional need. Compensatory renal growth is that which is only a function of excess need, and it is reversible.

When an extra adult rat kidney is isologously transplanted into an adult rat, there is no decrease in the size or function of any of the three kidneys.[1,2] In addition, when an extra baby rat kidney is transplanted into a baby rat, all three kidneys grow at the same rate as in normal two-kidney rats.[3] When an adult kidney that has undergone compensatory hypertrophy is transplanted into a similar adult, both hypertrophic kidneys return to their previous size and function.[1,2]

However, when an extra baby kidney was transplanted into adult rats, its growth was moderately suppressed.[3] This could have been due to a dependence of the growth of the baby kidney on factors in the growing rat that might not be present in the adult. Alternatively, it could be due to the "counterbalance" phenomenon, or hypotrophy, recently revived by Klein and Gittes.[4] So as to clarify this matter and determine if normal obligatory renal growth is dependent on the growth of the host, baby rat kidneys were transplanted into adults that underwent unilateral or bilateral nephrectomies.

This study has also attempted to delineate whether the increased compensatory hypertrophy observed in young rats as opposed to old is due to the age of the kidney itself or due to the age of the host.

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MATERIALS AND METHODS

Five groups of DA male rats were established for this study, consisting of five rats in each group. Group 1 consisted of adult rats ("adult" herein considered 12 weeks old), with an average weight of 250 gm. These rats underwent unilateral nephrectomy when they were 12 weeks old, and were followed up until they were 17 weeks old. Group 2 included adult rats that underwent bilateral nephrectomies when 12 weeks old. The group 2 rats received kidney transplants from baby rats ("baby" herein considered to be 4 weeks old, with an average weight of 70 gm [Fig 1]). Group 3 was comprised of baby rats that underwent unilateral nephrectomies and were allowed to grow to 12 weeks of age. Group 4 included baby rats that were allowed to grow with no intervention. Group 5 consisted of adult rats who underwent unilateral nephrectomies at 12 weeks of age. The group 5 rats each received a kidney transplant from a baby rat (Fig 2).

All rats underwent periodic estimation of renal size by direct measurement of longitudinal axis under the operating microscope. The transplantation technique employed has been previously described and modified.[3,5]

Renal volume was assumed to be a function of the cube of renal length. For example, if $V=(4\pi/3)\ (L/2)\ (W/2)\ (D/2)$ and a standard proportion of the kidney is assumed, then $W/2=L/2A$ and $D/2=L/2B$, A and B being constants. Then $V=K\ (L^3)$ and $K=4\pi/24\ AB$.[6]

RESULTS

As can be seen from Table 1, isologous baby kidneys that were transplanted into bilaterally nephrectomized adult rats grew at nearly the same rate as did a single baby kidney in unilaterally nephrectomized baby rats.

Similarly, as demonstrated in Table 2, baby kidneys that were transplanted into unilaterally nephrectomized adults grew at essentially the same rate as baby kidneys in a two-kidney baby rat.

Kidneys of adult rats that underwent unilateral nephrectomies at 12 weeks of age rapidly became hypertrophic to a size equal to that of a solitary kidney that had been transplanted eight weeks earlier from a 4-week-old baby to a bilaterally nephrectomized adult (Table 3). Thus, after allowing for compensatory hypertrophy, renal growth seemed to depend solely on the age of the kidney and not on the age of the rat.

If compensatory hypertrophy were more marked in the 4-week-old baby than in the adult rats, one might expect the single kidney in the adult that underwent nephrectomy in youth to be bigger than that of the adult that underwent nephrectomy in adulthood. This did not appear to be the case. In both baby and adult kidneys, the increase in volume attributable to compensatory hypertrophy was about 70%.

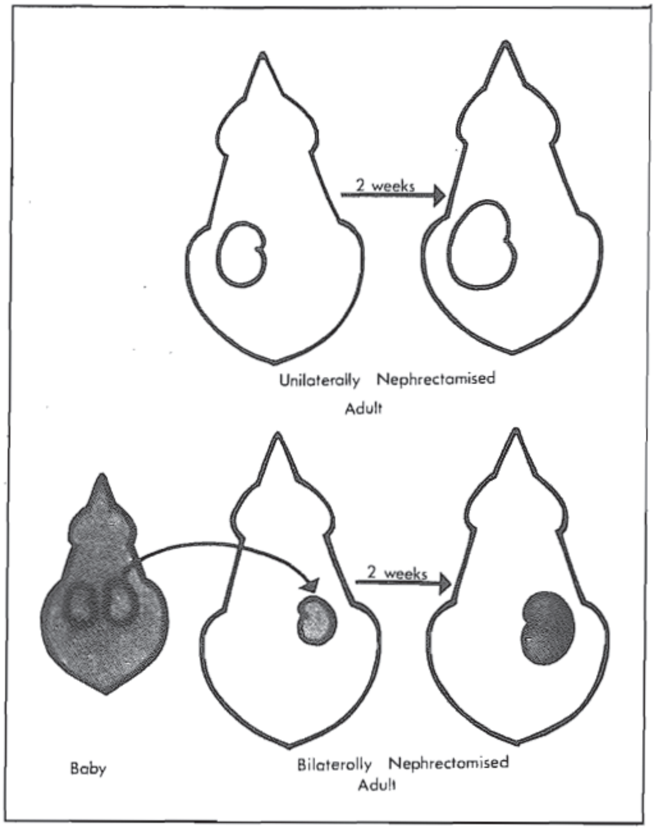

Fig 1.—Experimental renal transplants in group 1 (top) and group 2 (bottom).

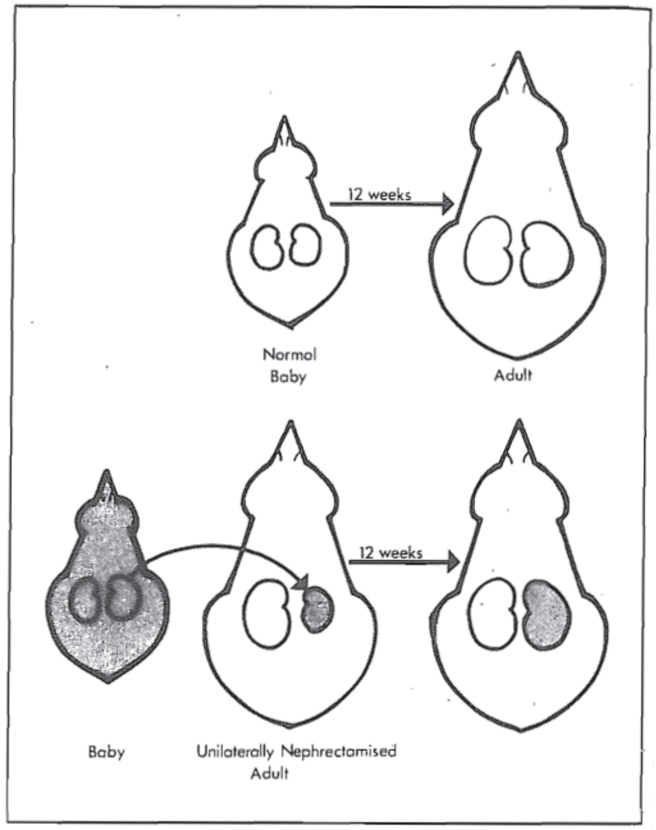

Fig 2.—Experimental renal transplants in group 4 (top) and group 5 (bottom).

Table 1.—Growth and Hypertrophy of Baby Kidneys in Babies vs Adults

	Rat Age, Weeks	Kidney Age, Weeks	Kidney Size, cm*
Baby rat unilaterally nephrectomized at 4 weeks	4	4	1.27 ± 0.10
	7	7	1.80 ± 0.10
	12	12	2.05 ± 0.13
Baby kidney at 4 weeks transplanted into bilaterally nephrectomized adult rat	12	4	1.30 ± 0.15
	15	7	1.88 ± 0.12
	20	12	2.10 ± 0.14

* All values expressed as ± 1 SD.

Table 2.—Growth (Without Hypertrophy) of Baby Kidneys in Babies vs Adults

	Rat Age, Weeks	Kidney Age, Weeks	Kidney Size, cm*
Control, two-kidney baby rats	4	4	1.32 ± 0.15
	7	7	1.68 ± 0.18
	12	12	1.78 ± 0.16
Baby kidney at 4 weeks transplanted into unilaterally nephrectomized adult rat	12	4	1.35 ± 0.14
	15	7	1.70 ± 0.12
	20	12	1.80 ± 0.18

* All values expressed as ± 1 SD.

COMMENT

In comparing the growth of a single baby kidney in growing baby rats to that of a baby kidney transplanted to a fully grown adult that had been bilaterally nephrectomized, it is apparent that the kidney grows at the same rate, regardless of whether it is in a baby or an adult. There is an initial period of compensatory hypertrophy, but it is the same in both groups.

Similarly, in comparing the growth of baby kidneys in nonnephrectomized, growing baby rats to that of a baby kidney transplanted into a fully grown adult that had been only unilaterally nephrectomized (in order to minimize compensatory hypertrophy of the baby kidney), it is again apparent that the baby kidney grows at the same rate and to the same size, regardless of whether it is in a baby or an adult. Of course, in these latter two groups, renal size is consistently less than in the former two groups because there is little or no compensatory hypertrophy.

In studies that have demonstrated an increased capacity for compensatory renal hypertrophy in babies, the rats were under 4 weeks of age.[7-9] Our transplant technique could not easily be applied to rats under 4 weeks of age, and this may explain why the adult kidneys in our study became hypertrophic to as great an extent as did the baby kidneys. Our baby rats were not quite young enough to demonstrate this phenomenon of increased compensatory growth in the very young.

Table 3.—Normal Hypertrophy of Adult Kidneys

	Rat Age, Weeks	Kidney Age, Weeks	Kidney Size, cm*
Adult rat unilaterally nephrectomized at 12 weeks	12	12	1.80 ± 0.15
	14	14	2.13 ± 0.17
	17	17	2.20 ± 0.13

* All values expressed as ± 1 SD.

This study seems to indicate that obligatory growth for the kidney occurs at a standard rate, despite the age or size of the host. This means that kidney grows at its own programmed rate, independent of its environment. Compensatory hypertrophy can occur in addition to this standard obligatory growth rate, and can be distinguished by the fact that it is reversible when the extra "need" is removed. Therefore, when an extra baby kidney is transplanted into an adult whose original kidneys are left in place, any stunting of its growth (as noted in our previous work) should be due to the counterbalance effect on a slightly damaged kidney, as postulated by Klein and Gittes.[4] This study excludes the possible explanation of a renal growth stimulus in the growing baby rat that is absent from the adult.

There have been few such transplantation studies on growth for other organs, but results similar to ours have been found with thymus grafts. The growth capacity of individual thymus grafts is not affected by the presence or absence of the host's own thymus or by the presence of other thymus implants.[10-12] In addition, newborn thymus, when grafted to adults, grew at the same rate and involuted at the same time as those that remained in the newborn. A thymus graft from a 1-week old mouse, when transplanted to an adult mouse, gained and then lost weight in the same time interval as thymus weight gain and involution in the intact baby. The age of the host had no effect on the growth and development of the thymus.

There are a number of important clinical applications to this concept of compensatory and obligatory renal growth:

1. A baby kidney used for transplantation to an adult will become dramatically hypertrophic, but no faster obligatory growth will occur just because the kidney is in an adult.[13] It would appear that the baby kidney transplanted into the adult may become dramatically hypertrophic, even to the size of an adult kidney, but not to the size of an adult hypertrophic kidney. This extra obligatory growth should occur at a slower rate, as it would if left in the baby donor.

2. Adults with duplication anomaly of the kidneys that exhibit no pathologic changes can be expected to have more nephrons and more renal function than the normal person with the usual allotment of nephrons. The excess endowment of nephrons at birth will not have suppressed renal growth.[14]

3. Since the body grows at a greater rate than the kidneys, and the rate of renal growth is preset, the condition of a child with moderately poor renal function may get worse as he continues to grow at a greater rate than his kidneys.[14,15]

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References

1. Silber S, Malvin R: Compensatory and obligatory renal growth in rats. *Am J Physiol* 226:114-117, 1974.
2. Silber S, Crudup J: The three-kidney rat model. *Invest Urol* 11:466-470, 1974.
3. Silber S: Compensatory and obligatory renal growth in babies and adults. *Aust NZ J Surg* 44:421-423, 1974.
4. Klein TW, Gittes RF: The three-kidney rat: Renal isografts and renal counterbalance. *J Urol* 109:19-27, 1973.
5. Silber S, Crudup J: Kidney transplantation in inbred rats. *Am J Surg* 125:551-553, 1973.
6. Shanks SC, Kerley P (eds): *A Textbook of X-ray Diagnosis by British Authors in Six Volumes*, ed 2. Philadelphia, WB Saunders Co, 1970, vol 5, p 302.
7. McCreight CE, Sulkin NM: Cellular proliferation in the kidneys of young and senile rats following unilateral nephrectomy. *J Gerontol* 14:440-443, 1956.
8. MacKay EM, MacKay LL, Addis T: The degree of compensatory renal hypertrophy following unilateral nephrectomy: I. The influence of age. *J Exp Med* 56:255-265, 1932.
9. Barrows CH Jr, Roeder LM, Olewine DA: The effect of age on renal compensatory hypertrophy following unilateral nephrectomy in the rat. *J Gerontol* 17:148-150, 1962.
10. Pepper FJ: Transplantation of thymic tissue in the inbred strains of mice. *J Endocrinol* 22:349-359, 1961.
11. Metcalf D: The autonomous behavior of normal thymus grafts. *Aust J Exp Biol Med Sci* 41:437-447, 1963.
12. Metcalf D: The thymus and lymphopoeisis, in Good RA, Gabrielsen AE (eds): *The Thymus in Immunobiology*. New York, Hoeber-Harper, 1964, p 150.
13. Silber S: Renal transplantation between adults and children: Differences in renal growth. *JAMA* 228:1143-1145, 1974.
14. Silber S: Extra renal function in patients with duplication anomaly: Obligatory and compensatory renal growth. *J Urol* 112:423-424, 1974.
15. Kaufman JM, Di Meola HJ, Siegel NJ, et al: Compensatory adaptation of structure and function following progressive renal ablation. *Kidney Int* 6:10-17, 1974.

Editorial Comment

This is exciting work that has been made possible by the availability of isologous animals and the development of microsurgical technique. The author's careful dissection of the two separate types of kidney growth, obligatory and compensatory, is extremely useful. It will be welcomed by all who have been fascinated by the riddle of what controls growth rate in mammalian tissues.

It is now established that if ischemic or other parenchymatous damage is avoided with optimal surgical technique and the use of a live donor, additional kidneys transplanted into normal rats will not experience trophic failure. If the kidney is infantile and obligatory growth has not yet been attained, the kidneys will grow as they would have in the donor. We have studied a large number of four-kidney rats in our laboratory.

When clinicians consider the transplantation of an extra kidney into a patient with a congenital metabolic disorder with normal renal function, as in the Lesch-Nyhan syndrome, it must be expected that the conditions for success will be very demanding. It would be expected that the ischemia and intrinsic damage associated with the use of a cadaver kidney would result in hypotrophy of the added kidney, with major impairment of its function.

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