Compensatory and obligatory renal growth in rats

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Renal size and function were studied in three groups of rats in an attempt to gain information relating to the control of renal size. One group consisted of normal rats into which a third kidney was transplanted; a second group consisted of unilaterally nephrectomized rats in which a second hypertrophied kidney was transplanted so that each rat had two hypertrophied kidneys immediately following transplant. Rats with three kidneys maintained GFR and RPF approximately 50% greater than control levels, and none of the three kidneys showed any reduction in size. Unilaterally nephrectomized rats showed the usual hypertrophic response. However, when a hypertrophied kidney was transplanted into rats previously unilaterally nephrectomized, both kidneys shrank back to their control size, GFR and RPF. These results are consistent with the hypothesis that compensatory hypertrophy is a growth phenomenon different from normal growth and is reversible, although normal growth is not reversible.

It is well known that a kidney will increase its size and function after contralateral nephrectomy. This renal hypertrophy is seen in humans (3, 8, 14), dogs (15), mice (4), and rats (5). In rats 88% of the original GFR for two kidneys is restored within 2-3 weeks after unilateral nephrectomy (5). An increase in size initially precedes this rise in filtration rate and after 3 days is rapidly outstripped by it.

Despite confusion about the etiology of compensatory renal hypertrophy, most investigators regard it as being similar to the normal process of growth (11, 12). No new nephrons are formed, but there is marked hypertrophy and a lesser hyperplasia, along with a correspondingly sharp increase in RNA and a smaller increase in DNA synthesis (12). Another question is whether this compensatory renal growth is reversible and whether an extra kidney will cause a decrease in renal size and function.

Masson and Hirano (13) constructed the blood flow to one kidney producing atrophy on the constricted side and hypertrophy on the contralateral side. Removal of the constriction on the 20th day did not result in a reversal of either the atrophy or hypertrophy. However, since the animals in this model were all hypertensive and the "hypertrophied kidney" was severely nephrosclerotic, no conclusion could be drawn regarding the reversibility of compensatory hypertrophy.

Klein and Gittes (6) transplanted a third kidney into adult Lewis rats in an attempt to determine if the size of the supernumerary kidney would be altered from normal. In their experiments all transplants, whether into normal or unilaterally nephrectomized rats, showed significant weight loss. The weight loss of kidneys transplanted into unilaterally nephrectomized rats was not significantly different from those transplanted into normal rats. Furthermore, the degree of renal atrophy was proportional to the length of ischemia (up to 2.25 h) suffered during transplant. Thus, their experiments appear to be complicated by technical problems leading to renal atrophy and so make it difficult to determine the effect of a supernumerary kidney on renal size. We have done a series of experiments in which these complications were avoided and in which renal function data were obtained.

Methods

Three kidney rats. An extra or third kidney was transplanted into a group of seven adult male isogenic Lewis rats whose average weight was 500 g. The kidneys were taken from littermates and transplanted into the lower abdomen. The transplantation procedure was that described by Silber and Crudop (17). At the same time littermates of the same sex and weight served as a control group. Thus two groups of rats were obtained from a single litter, one group containing three kidneys and the other a group of normal rats. In addition, both preoperatively and 2 mo after the transplant, renal size as estimated by the length of the longitudinal axis was ascertained by direct measurement as well as intravenous pycography. Simultaneous inulin and PAH clearances (as described below) were performed 2 mo postoperatively on both the three kidney and control rats.

Rats with hypertrophied kidneys. A group of adult male Lewis rats was anesthetized, and one kidney was removed through a midline incision. These rats were then allowed to recover. Four weeks following unilateral nephrectomy, clearance and size measurements were made. In another group of rats which also underwent unilateral nephrectomy, two rats were anesthetized and the hypertrophied kidney was removed from one and transplanted into the other. Thus each rat in this group had two hypertrophied kidneys. At 6 weeks postoperatively clearance and size measurements were made.

Clearance studies. On the day of the experiment the rats were anesthetized with Nembutal given intraperitoneally, 35 mg/kg. The femoral artery and vein were catheterized for the collection of blood and the infusion of appropriate solutions into the animal. The bladder was catheterized with a polyethylene catheter. The priming solution was injected intravenously; it contained 100 mg of inulin.
and 10 μCi of PAH-3H in 4 ml saline. This was followed by a sustaining infusion containing 40 mg of inulin and 2 μCi of PAH/ml at a rate of 0.21 ml/min. Following a 30-min equilibration period, three consecutive 15-min urine collection periods were obtained, with arterial blood collected at the midpoint of each period. The volume of blood collected for each period was less than 0.4 ml and was immediately replaced with an equal volume of saline. Inulin concentrations were measured using the method of Walser, Davidson, and Orloff (20). Radioactivity of plasma and urine was assayed using liquid scintillation spectrometry. Sodium and potassium concentrations of plasma were determined using flame photometry with an internal standard.

RESULTS

Table 1 shows renal function data and the concentrations of sodium and potassium in plasma of each group of rats used. It is readily seen that none of the groups had significantly different concentrations of either Na or K in the plasma. The GFR and RPF of the group of rats containing three kidneys were significantly greater than any of the other groups. They had an average GFR and RPF approximately 50% greater than the control group of littermates. Figure 1 shows an intravenous pyelogram of a rat with an additional kidney. It is evident that the three kidneys are all of similar size and appear to be normal. In addition, the GFR and RPF of the rats containing two hypertrophied kidneys 6 weeks after the transplant were similar to the control and significantly less than twice the value of rats having only one hypertrophied kidney (P < .01). In three kidney rats it is evident from Tables 2 and 3 that the size of donor kidneys before and after transplant was unaltered and was identical to both the recipients' and the control littermates' left and right kidneys. Thus, the transplantation of an extra normal kidney into a normal animal had no effect on the size of that transplanted kidney or the
host's original kidneys. It should also be noted that the possession of a third kidney did not "set" the level of GFR and RPF at the new high value. Removal of the extra kidney did not result in hypertrophy of the two remaining ones. This group of rats had an average GFR and RPF which were not significantly different from control but were significantly less than the values during the period in which they had three functioning kidneys.

From Table 3 one can see that the size of the remaining kidney following unilateral nephrectomy was increased significantly, but when that kidney was transplanted into another animal it and the hypertrophied kidney in the recipient animal both shrank back to a size not significantly different from their original size.

### DISCUSSION

The physiologic changes in renal function after unilateral nephrectomy have been documented in great detail, but no explanation has been found for why it should occur. Increasing the excretory load does not seem to be humorally mediated (1, 2, 9, 10, 18, 19). It is a growth process which usually can be prevented by hypophysectomy, low protein intake, or antimetabolic drugs (1, 7, 16). By manipulation of the nephron population through the technique of transplantation in isogenic animals, we hoped to compare the reversibility of compensatory growth to that of normal growth in adult kidneys.

The addition of an extra or third kidney to an animal might be expected to result in a decrease in GFR, RPF, and size in each one. But these changes did not occur. The host maintained a GFR and RPF which was approximately 50% greater than normal. On the other hand, when two hyper-trophied kidneys were placed in the same host the excess GFR and RPF did not persist. Each kidney returned to its previous state.

Since the presence of a supernumerary kidney results in no decrease in size, but hypertrophied kidneys readily return to normal, there must be a significant difference in the factors stimulating and maintaining normal renal growth and compensatory hypertrophy.

In this context it may be helpful to distinguish between two types of renal growth: obligatory and compensatory. Obligatory growth appears to occur slowly along with the growth of the animal and does not appear to be reversible. None of the kidneys in the three kidney groups showed any reduction in size of function in spite of an elevated GFR and RPF compared to normal animals. Compensatory growth appears to occur rapidly as a result of a decrease in the nephron population below a threshold level and is reversible when the nephron deficit is corrected. It is, therefore, a functional response and its causes appear to be different from those stimulating normal growth as the animal gets older.

If compensatory hypertrophy is due to a humoral factor (19), it could result either from the absence of inhibitor or from an increased level of a trophic hormone. These hormones are not likely to be the same ones which regulate normal obligatory renal growth. Compensatory hypertrophy appears to require a sustained increase in trophic hormone level or decreased inhibitor level. Fully grown adult kidneys, however, maintain their size and function even when the presence of extra kidneys would be expected to decrease the level of trophic hormone or increase the level of inhibitor.

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