The Role of Renal "Work"
in Compensatory Kidney Growth

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In a series of studies designed to test the role of renal "work" in compensatory kidney growth we examined the relationship between absolute sodium reabsorption—which constitutes the bulk of renal energy expenditure, and growth of the remaining kidney at various intervals after contralateral nephrectomy.

The increase in weight of the remaining kidney preceded the rise in sodium reabsorption and these two processes took place at different rates between 24 hours and 21 days after uninephrectomy.

Absolute sodium reabsorption did not change during the first hours after contralateral nephrectomy, at a time when biochemical alterations are known to occur.

The rate of [^{14}C] choline incorporation into renal phospholipid, an early biochemical indicator of compensatory kidney growth, increased significantly one hour after contralateral nephrectomy but remained unchanged after sham-nephrectomy, regardless of the magnitude or direction of the concomitant change in absolute sodium reabsorption ("kidney work").

These results indicate that renal work expended in the reabsorption of glomerular filtrate is neither the initiating, nor the primary controlling factor, of the compensatory kidney growth that follows unilateral nephrectomy.

The mechanisms that initiate and sustain the growth of the remaining kidney after removal of its mate are still unknown. During nearly a century of research into the nature of this phenomenon, two hypotheses have been most frequently proposed: According to the first, the enlargement of the remaining kidney is due to the increased work load that the smaller renal mass is now called upon to perform—an example of "work hypertrophy." The alternative theory attributes compensatory kidney growth to changes in the concentration of an organ-specific humoral factor which controls renal mass via a negative feedback mechanism. This paper reviews our studies designed to test the former hypothesis.

The origin of the "work hypertrophy" theory can be traced back to Sacerdotti [1], who suggested that the stimulus to continued enlargement of the remaining kidney after contralateral nephrectomy was the requirement for increased work to rid the body of an increased quantity of chemicals via the urine. This concept was first mentioned in the English literature 30 years later [2], and was the prevailing view during the first half of this century.

The hypothesis that an increased work load on the remaining kidney stimulates its compensatory growth gained impetus from observations that feeding diets enriched with protein [3,4,5,6,7], or its metabolic end product, urea [8,9,10], enhanced renal growth. Since the excretion of urea was believed to require renal work [11], it was argued that the growth of normal kidneys [3,5,6,7,8], or of the compensating kidney after uninephrectomy [4,10] in rats fed protein- or urea-enriched diets was augmented by the increased work required for urea excretion. Others believed that the amount of

osmotic work necessary to concentrate the glomerular filtrate, or the work required for the excretion of urine, directly determined renal size—so that decreases in renal mass brought about by disease or surgical extirpation were followed by the demand for more renal work, which was met by an increase in renal size [12,13]. In some of these older studies, feeding diets rich in "salts" had no effect on renal growth [3,8,10], which only served to reinforce the prevailing misconception that the renal handling of nitrogenous waste products, but not of salt, required kidney work. Now that urea excretion is known to be passive, its role in the theory has been replaced by the concept of increased functional demand for reabsorption of solutes from the glomerular filtrate [14].

A number of studies have been performed to test the hypothesis that the magnitude of the excretory work load is the determinant of renal mass. An interesting experiment was done some 25 years ago by Paul Weiss [15] who extirpated one embryonic metanephros in a prefunctional stage and noted a marked increment in mitotic activity of the remaining kidney, even though it was not subjected to functional overload. Other investigators have induced increased excretory work by experimental ureteroduodenostomy [16] and ureteroperitoneostomy [17,18,19] and a decrease in the excretory solute load was effected by starvation [20]. The results of these studies failed to demonstrate that an increased excretory or reabsorptive load augmented renal growth, or that a decreased load prevented the increment in the renal RNA:DNA ratio which occurs during compensatory growth after uninephrectomy [21]. It should be pointed out, however, that experiments based on urine diversion are technically demanding and their conclusions are valid only if the diverted kidney does not undergo obstructive or infectious changes.

As the bulk of renal energy expenditure is invested in the reabsorption of sodium chloride from the glomerular filtrate, we chose a different approach and evaluated the role of the renal work load in compensatory kidney hypertrophy by examining the relationship between sodium reabsorption and growth of the remaining kidney at various intervals after contralateral nephrectomy. In the first study [22], absolute sodium reabsorption and kidney weight were correlated in rats one to 21 days after uninephrectomy. The increase in weight preceded the rise in sodium reabsorption and was highly significant statistically at 24 hours (Fig. 1), when absolute sodium reabsorption was not different from that calculated for one kidney in the intact animal. There was a further increase in kidney weight at 7 days, the remaining kidney now being 39 percent heavier than the control. Thus a considerable fraction of the compensatory increase in kidney weight took place in the first day after uninephrectomy. However, the rise in GFR and absolute sodium reabsorption in the remaining kidney followed a different pattern. These functions were unchanged one day after nephrectomy, but increased by 30 percent at 3 days and continued to rise for the next three weeks. The different rates at which the increases in kidney size and in sodium reabsorption occurred in the remaining kidney are evident when expressed as sodium reabsorption (T_{Na}) per gram of kidney, which was lower than the control value at 24 hours, unchanged at three days, and higher only after one week (Fig. 1). Thus the increase in sodium reabsorption appeared later, was more marked and reached its maximum after the increase in kidney weight. The lack of both a quantitative and chronologic correlation between the changes in sodium reabsorption and in kidney size did not support the concept that an increased reabsorptive work load per unit mass of kidney tissue is the stimulus for compensatory renal hypertrophy.

It is well known that biochemical and structural alterations occur shortly after contralateral nephrectomy: renal RNA [21] and protein [23] content increase after 14
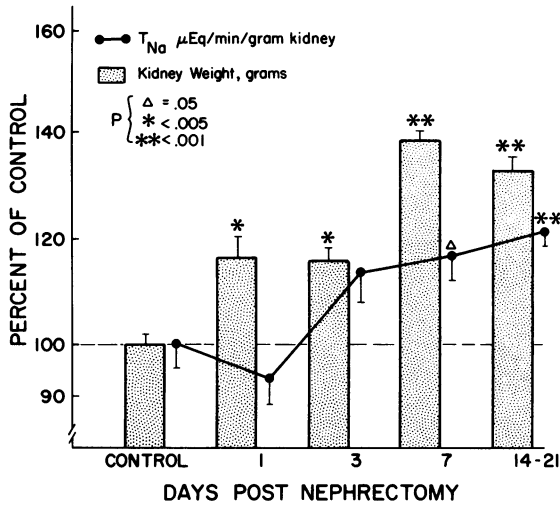
FIG. 1.   Absolute sodium reabsorption (T_{Na}) and weight of the remaining kidney one to 21 days after contralateral nephrectomy in rats. The increase in weight preceded the increase in sodium reabsorption. From [22]. Reproduced by permission.

hours, and changes in RNA metabolism may be detected in the compensating kidney within one hour [21,24]. Even earlier alterations, which can be detected after 5–15 minutes, occur in cell membrane metabolism [25] and in the levels of cyclic nucleotides [26,27]. Since the earliest phase of compensatory hypertrophy was not included in the study just described, it is conceivable that changes in renal function which might play a role in initiating compensatory growth occur shortly after one kidney is removed but are too transient to be detected 24 hours later. To evaluate this possibility we measured renal function during the first hours after unilateral nephrectomy [28]. As compensatory growth is affected by the animal's age [29,30], we determined absolute sodium reabsorption in the remaining kidney in both young and adult rats. The results of this study indicated that tubular reabsorption of sodium in the remaining kidney does not change appreciably during the first hours after removal of its mate, in either young or adult animals (Fig. 2).

While these two studies cast serious doubts about the "work hypertrophy" theory, we felt that more definitive evidence was necessary in order to disprove it. This required the solution of a recurrent problem in renal physiology, namely the limited precision of the measurement of GFR, on which the determination of absolute sodium reabsorption is based. It can be argued—as it was for many years before de Wardener's studies [31] on the mechanisms of natriuresis during saline loading—that an increase in GFR does occur yet it is too small to be detected with available techniques. If such an increment occurs after nephrectomy, the parallel rise in sodium reabsorption (work) could in theory trigger the sequence of biochemical events leading to compensatory kidney growth. Indeed, some authors suggest that this is the case [14], and imply that the postnephrectomy rise in GFR may not always be apparent because of the effects of surgery or volume contraction [32].

The last series of experiments [33] was addressed to these points. Fluid intake was enhanced preoperatively and the experiments were done in animals which were undergoing a water diuresis produced by hypotonic saline and were mildly volume expanded. More important, to preclude the possibility that a slight increase in GFR
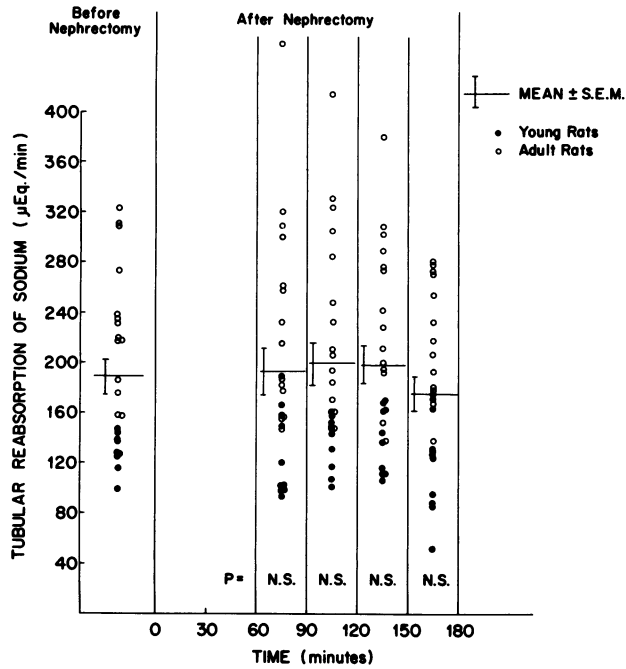
FIG. 2. Absolute sodium reabsorption measured before and immediately after unilateral nephrectomy in the same rats. Absolute T_{Na} did not change after nephrectomy. From [28]. Reproduced by permission.
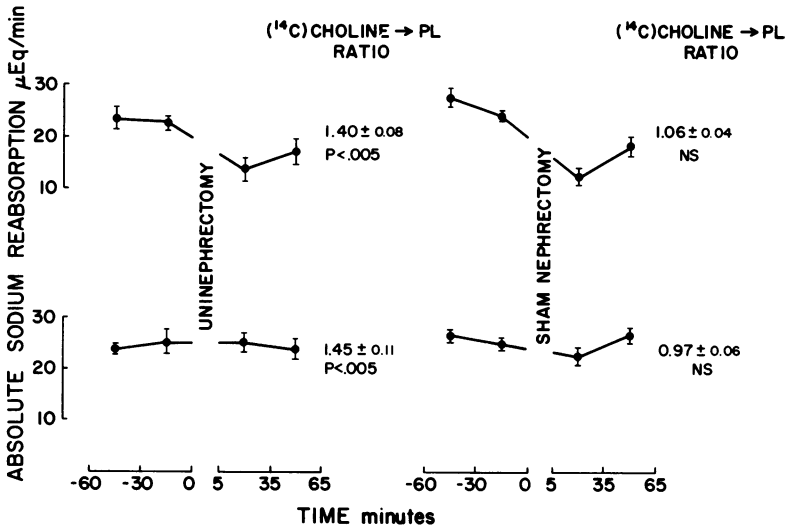

FIG. 3. Absolute sodium reabsorption and ratios of [14C] choline incorporation rates into renal phospholipid in mice. Sham-operated and uninephrectomized animals with decrements in T_{Na} during the second hour (*upper panel*) are compared with mice in which this function did not change (*lower panel*). Incorporation increased only in the compensating kidney of uninephrectomized animals, and was independent of the concurrent change in sodium reabsorption.

and absolute sodium reabsorption might occur but remain undetected because of methodologic limitations, we deliberately produced a large *decrement* in these two functions by raising the hydrostatic pressure in the lower urinary tract after nephrectomy. Searching for a reliable early biochemical indicator of compensatory kidney growth, we took advantage of the observation that an increase in the rate of [^{14}C] choline incorporation into phospholipid of the remaining kidney can be detected in mice as early as 5 minutes after contralateral nephrectomy and reaches a plateau after one hour [25]. Inulin and [^{3}H] p-aminohippurate clearances and sodium reabsorption were measured in mice for one hour before and one hour after unilateral nephrectomy and sham uninephrectomy. Both the nephrectomized and the sham-operated animals were divided into two groups: In one, the bladder catheter was left undisturbed, and in the other group it was raised 10 cm above the level of the animal during the hour following nephrectomy or sham operation. The rate of [^{14}C] choline incorporation was measured in the left (resting) kidney removed at nephrectomy, the right (compensating) kidney removed one hour later, and in both kidneys of the sham-operated controls. Values are expressed as a ratio of the rate of incorporation in the compensating kidney to that in the animal's own resting kidney.

Effective renal plasma flow averaged 0.75 ml/min in the control periods, and did not change significantly after nephrectomy or sham nephrectomy when the ureteral pressure was not increased. GFR, which averaged 0.18 ml/min, also remained unchanged after surgery in both groups of animals. When the bladder catheter was raised, the ERPF and GFR decreased significantly in both nephrectomized and sham-operated mice. This decrease was more pronounced in the first 30 minutes and both measurements tended to return toward normal in the second half hour, a pattern also observed after increasing the ureteral pressure in dogs [34].

Absolute sodium reabsorption followed the same pattern (Fig. 3). T_{Na} was constant before and after uninephrectomy if the bladder catheter was left undisturbed, but decreased substantially in animals in which the catheter was raised after nephrectomy. This decrease averaged 34 percent ($P<.001$). Nevertheless, the rate of choline incorporation into phospholipid in the remaining kidney of these animals was 40 percent higher than in the kidney removed one previously ($P<.005$), and was not different from that measured in mice in which T_{Na} was unaltered (45 percent). In sham-nephrectomized animals sodium reabsorption also remained unchanged in the control group and decreased markedly, this time by 41 percent ($P<.001$), in mice with elevated lower tract pressure. However, in contrast with the results in nephrectomized animals, the rate of choline incorporation was unaffected by sham nephrectomy, the ratio between the rates of incorporation in the two kidneys being not different from unity in either group (Fig. 3). Thus, the rate of choline incorporation increased only in the compensating kidneys of mice whose resting kidney was removed one hour before, whether sodium reabsorption increased or remained unchanged after nephrectomy, while in sham-nephrectomized mice in which renal mass was not reduced, the rate of incorporation did not increase at either level of sodium reabsorption.

The relationship between ratios of choline incorporation rates into phospholipid and absolute sodium reabsorption in all animals is illustrated in Fig. 4. Ratios increased markedly in nearly all uninephrectomized mice (solid circles), but clustered around unity in sham-nephrectomized controls (open circles), and were unrelated to the direction or the magnitude of the concomitant change in sodium reabsorption.

The reabsorption of sodium chloride accounts for most of the energy expenditure by the kidney, and elevation of ureteral pressure has been shown to decrease T_{Na} and
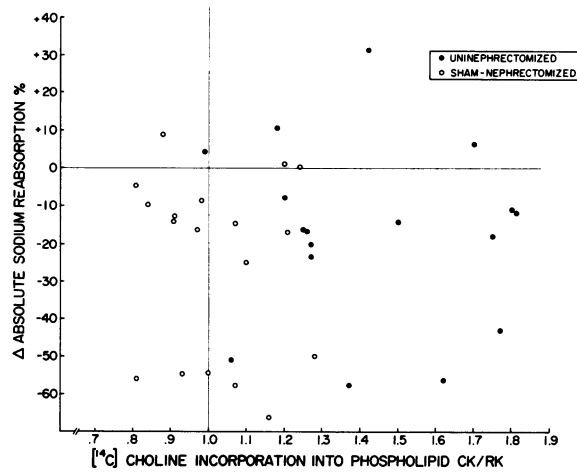
FIG. 4. Relationship between ratios of [^{14}C] choline incorporation and changes in sodium reabsorption in all animals. Ratios increased markedly in uninephrectomized mice and clustered around unity in sham-nephrectomized animals regardless of magnitude or direction of concomitant change in sodium reabsorption. CK, compensating kidney; RK, resting kidney. From [33]. Reproduced by permission.

renal oxygen consumption in parallel [35]. The remaining energy is spent chiefly in the reabsorption of other solutes from the glomerular filtrate, but the reabsorption of sugars and amino acids is closely linked to that of sodium [36,37]. Thus, by decreasing GFR and filtered load after uninephrectomy, the energy required for the reabsorption of sodium, and probably of other solutes, was reduced, Nevertheless, biochemical evidence of renal growth was demonstrated, and was not different from that observed in uninephrectomized animals in which filtrate reabsorption was not altered. It should also be noted that the rate of choline incorporation increased after nephrectomy despite a significant reduction in effective renal plasma flow (−20 ± 7%, $P < .05$), suggesting that increased delivery of substrates is also not essential for this phenomenon. Based on these observations we conclude that compensatory kidney growth is not triggered by an increase in renal work expended in the reabsorption of solutes from the glomerular filtrate; in fact, it can occur when reabsorptive work is substantially decreased.

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