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Glomerulotubular Dimensional Readjustments During Compensatory Renal Hypertrophy in the Hypothyroid Rat

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Although growth of tubules is arrested and that of glomeruli retarded by hypothyroidism in rats, unilateral nephrectomy has been found to elicit a vigorous compensatory hypertrophy of the hypothyroid kidney. Microdissection and measurement of the dimensions of glomeruli and proximal convoluted tubules taken from the kidney removed first and from the hypertrophic contralateral organ removed two to three weeks later, disclosed a "normalization" of the typical glomerulotubular dimensional imbalance as a result of greater tubular than glomerular growth. A somewhat more striking but qualitatively identical response was observed in 9 euthyroid animals. Glomerular filtration rate and maximal glucose reabsorptive capacity (Tm_G) increased in both euthyroid and hypothyroid animals in accord with the structural shifts.

Adaptive growth of the nephrons must be evaluated within the complex total context of their growth potential, of their immediate environment and of the more remote extra-renal influences that constantly play upon them and ultimately determine their functions. A lack of precise information on all these factors calls for caution and humility in drawing conclusions regarding the so-called "adaptive" response of renal damage. Youth and old age, at the extremes, certainly endow mammalian tissues with different responsiveness to injury. Likewise, leanness or obesity may exert modifying effects that are just as difficult to define though obviously much easier to control. A much greater difficulty is posed by the inability to assess the local effects of heterogeneous nephron pathology that results in changes in renal architecture, in connective tissue mass and arrangements, and in destruction of some units but not of others. Localized physical and chemical derangements may not only directly affect isolated subpopulations of the nephrons but also give rise to disturbances in the distribution of blood and lymph flows and of pressure gradients. In such a situation, analysis of the role played by extra-renal governing influences that result alone from a deficiency in nephron mass may be impossible. Study of nephron behavior in the normal kidney during compensatory renal hypertrophy following unilateral nephrectomy provides a basis for determining the adequacy and limitations of nephron adaptation within a damaged kidney. In the work to be described here, attention has been focused upon compensatory hypertrophy in the hypothyroid rat in order to determine if interference with growth per se will alter the pattern of adaptive growth response among the nephrons.

Hypothyroidism is associated, in the rat, with a failure of renal growth that is characterized by a reduction in proximal tubular length and mass relative to the

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diameter and volume of the glomerulus in each nephron [1]. The relationship between glomerular size and body weight remains within normal limits indicating a retardation in glomerular growth correlated to that in overall body growth. Tubular growth ceases, however, shortly after thyroidectomy or the administration of a large dose of radioiodine. Even when body weight is well-maintained by dietary means within expected normal limits, tubular growth fails to occur [2]. The resulting dimensional glomerulotubular imbalance does not result in a functional imbalance because a vasoconstrictive reduction in glomerular filtration rate prevents proximal tubular overloading. A tendency to lose sodium [3] may be attributable to distal tubular overloading and may indeed play a role in the pathogenesis of the corrective hypofiltration [4]. All these changes, both structural and functional, have been found to affect the nephron population uniformly in its entirety. A dissociation of glomerular and tubular growth has been observed in the rat and dog also during compensatory hypertrophy [5,6], but in this case, the tubules increase in size more promptly than the glomeruli producing a dimensional tubuloglomerular imbalance that is dominated by the tubules rather than the glomeruli. As in hypothyroidism, the nephron population is uniformly involved and hemodynamic adjustments compensate for the potential functional defect.

To determine if the impulse to hypertrophy could break through the growth-arrest of hypothyroidism, glomerulotubular dimensions were measured directly [7] in samples (25–35 units from superficial, intermediate, and juxtamedullary cortex) of nephrons obtained by microdissection of kidneys removed by unilateral nephrectomy and of the contralateral hypertrophic kidneys removed 2 to 3 weeks later in 9 euthyroid (E) and 3 hypothyroid (H) rats. Function of the hypertrophic kidney was assessed in terms of overall glomerular filtration rate (^{3}H-inulin clearance) and tubular glucose reabsorptive capacity (glucose "titration," threshold, and maximal transport capacity—Tm_G) [8] in 5 euthyroid and 5 hypothyroid rats age-and-weight-matched to the nephrectomized animals. Measurements of nephrons in the right kidney were used as controls for evaluation of change in nephrons dissected from the hypertrophic left kidneys.

Body weight (380 ± SE 35 g in euthyroid—E—and 222 ± 13 g in hypothyroid—H—rats) changed relatively little during the weeks after unilateral nephrectomy but the weight of the kidney (E: 1.33 ± 0.19 g; H: 0.58 ± 0.03 g) increased markedly in both E and H rats (by 92 and 45 percent, respectively) in association with an increase in total proximal tubular length (TPL). The increment in TPL (and presumably tubular mass) affected all segments of the nephron population uniformly—amounting to 34 and 36 percent in superficial (S) and juxtamedullary (JM) units, respectively, in E, and to 28 and 25 percent, respectively, in H rats. The normal difference in S and JM dimensions (JM > S) was observed to persist in hypothyroidism and not to be affected by hypertrophy. During the post-nephrectomy period, glomerular size also increased uniformly throughout the nephron population but by no means as much as tubular size, the glomerular diameter (GD) increasing by 19 percent in the control group and by 9 percent among the H rats. It was evident that the growth response was smaller in both percentile and absolute terms among the hypothyroid animals than among the normals. In both groups, tubular growth appeared to outstrip glomerular and did so to a greater degree among the H rats. Indeed, the change resulted in a tendency to "normalization" of the hypothyroid kidney.

These structural changes were associated with appropriate alterations in glomerular filtration rate (GFR) and TM_G. It should be stressed that renal functional measurements were made for the most part in animals that were not subjected to

anatomical study, but care was taken to compare data from animals with compensatory hypertrophy with control values from animals—both E and H—matched for age and body weight. Though precise structural-functional correlations in the same animal were not possible, the comparative figures should be meaningful. Thus, in accord with the expansion in the glomerular filtering surface evident in the increment in GD, GFR increased in both groups by 38 percent in controls and 22 percent in hypothyroidism. Similarly, both TPL, taken as an index of proximal tubular mass, and Tm_G, taken as an index of maximal proximal tubular reabsorptive capacity, increased more than the corresponding structural and functional equivalents of glomerular activity. On both physiologic and anatomical grounds, therefore, it may be inferred that glomerulotubular balance had shifted with development of a relative tubular dominance. This shift was also evident in the tendency for glucose threshold to rise, presumably as a result of an augmented glucose reabsorptive capacity in the face of a smaller increment in filtration. Of particular interest was the lack of "splay" in any "titration" curve, a finding consistent with the uniform distribution of the hypertrophic response throughout the nephron population. Further evidence of a uniform physiologic adjustment has emerged from a preliminary study of the distribution of single nephron glomerular filtration rates measured by the Hanssen technique [9,10].

The overriding thrust of the hypertrophic response was clearly apparent in the results of this investigation. The strongly suppressive effect of hypothyroidism upon tubular growth was completely overcome throughout the nephron population and every unit was affected. Whether this is always the case is debatable. It seems not unlikely, for example, that bilateral focal nephron loss is as effective as unilateral nephrectomy in eliciting the causative drive, whatever it may be, but the response is necessarily affected by the environment within which it occurs; hence, tubular enlargement within a rigid or contracting fibrous tissue framework or limited segmental responses in discretely injured nephrons may well result in damage or distortion rather than in compensatory improvement of function. Under such circumstances hypertrophy may become a grossly inappropriate "adaptive" response or an "akairial disproportion" as Dickinson W. Richards once called it [11]. Akairia is a fundamental problem in pathophysiology that deserves sharper definition and resolution for it can exert a baneful, perpetuating and intensifying influence upon the course of any acute or chronic disease. The kidney provides an ideal setting within which a variety of "ill-timed, inopportune, inappropriate blundering reactions" can be examined quantitatively in relative isolation. Compensatory hypertrophy may be a particularly suitable tool with which to explore this untouched field that figures so prominently in the manifestations of renal disease. Effective therapy depends, after all, upon understanding and control of harmful "adaptations" as well as beneficial ones.

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