Renal Hypoplasia, From Grossly Insufficient to Not Quite Enough: Consideration for Expanded Concepts Based Upon the Author’s Perspective With Historical Review

Stephen M. Bonsib, MD

Abstract: Hypoplasia is defined in the Merriman-Webster dictionary as “a condition of arrested development in which an organ, or part, remains below the normal size, or in an immature state.” The degree of reduced size is not definitional. Renal hypoplasia, however, has historically been defined as a more marked reduction in renal mass such that presentation in childhood is the norm. There are 3 commonly recognized types of renal hypoplasia, simple hypoplasia, oligomeganephronic hypoplasia (oligomeganephronia), and segmental hypoplasia (Ask-Upmark kidney). They have in common a reduction in the number of renal lobes. A fourth type, not widely recognized, is cortical hypoplasia where nephrogenesis is normal but there is a reduction in the number of nephron generations. Recently there has been great interest in milder degrees of reduced nephron mass, known as oligonephronia because of its association with risk of adult-onset hypertension and chronic kidney disease. Since the last pathology review of this topic was published by Jay Bernstein in 1968, an update of the renal pathology review of this topic was published by Rubenstein et al6 in 1961 as a condition of arrested development in which an organ, or part, remains below the normal size, or in an immature state. Renal hypoplasia may be one of the most misused terms in renal developmental anomalies. Historically, many authorities considered all small kidneys as hypoplastic, thus, the literature is cluttered with a host of diseases, both congenital and acquired, that have in common small overall renal size or limited amount of renal parenchyma, such as pylonephritic, hydronephrotic, and dysplastic kidneys, as well as, truly hypoplastic kidneys. Although overly inclusive definitions of renal hypoplasia noted above have contributed to the confusion, basing the diagnosis on clinical findings, especially imaging studies, rather than having a tissue-based histopathologic diagnosis is equally important. For instance, Eskström1 in 1955 published a radiologic study of 179 cases of “renal hypoplasia.” Forty-six were studied histologically. Only 6 of 46 were small with histologically normal nephrons, conforming to the diagnostic criteria for a hypoplasia as defined by Rubenstein et al in 1961 as a “congenitally decreased amount of histologically normal renal tissue.” The Rubenstein criteria were seminal because they establish a pathologic mandate for a diagnosis of renal hypoplasia.

There are 3 commonly recognized types of renal hypoplasia: segmental hypoplasia (Ask-Upmark kidney), oligomeganephronic hypoplasia (oligomeganephronia), and simple hypoplasia. Although there are gross and microscopic differences between the 3 types of hypoplasia, they have in common a reduction in number of renal lobes. There is a fourth type of hypoplasia, cortical hypoplasia, not codified in most hypoplasia classifications but recognized for many years. It consists of a reduced number of nephron generations resulting in cortical thinning and medullary reduction. Last, there is the concept of reduced nephron number, or reduced nephron endowment, known as oligonephronia (not to be confused with oligomeganephronia), that imparts a predisposition to adult-onset hypertension and chronic kidney disease (CKD). The anatomic basis for oligonephronia and its possible relationship to the known types of hypoplasia has not been characterized.

The most recent review of the pathologic features of renal hypoplasia was by Bernstein in 1968. In this excellent review, he discussed the clinical aspects of the 3 types of hypoplasia and presented details of their gross and microscopic features. He further emphasized that metanephric dysgenesis (renal dysplasia) should not be present, thereby, excluding small dysplastic kidneys, often referred to as hypodysplasia, from renal hypoplasia lexicon. Similarly, the Academy of Pediatrics Committee on Classification, Nomenclature and Terminology in 1989 recognized these same 3 types of hypoplasia, a classification that continues today.

This manuscript will provide a historical review of the 3 commonly recognized types of renal hypoplasia and cortical hypoplasia, discussing their clinical, gross, and histologic features. The renal hypoplasias will then be framed within the modern concept of oligonephronia and its diverse causes and consequences.

HISTORICAL REVIEW OF RENAL HYPOPLASIAS

Segmental Hypoplasia (Ask-Upmark Kidney)

The first type of renal hypoplasia described was segmental hypoplasia reported by Ask-Upmark in a 1929 German publication. It is often referred to as Ask-Upmark kidney. Segmental hypoplasia is rarely diagnosed, or possibly, rarely recognized. Ljungqvist and Lagergren13 in 1962 reported 2 cases in a study of 1000 autopsies and 100 nephrectomies. Segmental hypoplasia is usually identified in children presenting with hypertension (70%) or urinary tract infections. The hypertension is often severe. In Ask-Upmark’s original series, 7 of 8 patients had malignant hypertension. Hypertension is also usually present in patients presenting with urinary tract infection. Vesicoureteral reflux is identified in 70% to 80% of all cases of segmental hypoplasia, whether presenting with infection or hypertension.
Segmental hypoplasia may be unilateral or bilateral and has a marked female predominance (72%). The hypertension appears renin-mediated. Elevated renal vein renin levels have been measured in veins draining the hypoplastic foci. In addition, renin granules have been documented by Bowie stain and by immunohistochemistry, and renin protogranules have been demonstrated by electron microscopy within the hypoplastic foci unrelated to a glomerulus or juxtaglomerular apparatus since neither are present. Surgical excision of the hypoplastic foci has resulted in immediate cure of the hypertension in some, but not all cases. The prospect for a surgical cure is increased in unilateral disease with a single lesion, and when the contralateral kidney is normal. A normal contralateral kidney is most likely if imaging studies are normal, the kidney is enlarged (compensatory hypertrophy), and proteinuria is absent.

The kidney in segmental hypoplasia is usually small, <2 SD from the mean. Renal weight is often <50 g in adult cases and as small as 12 to 25 g in children. The kidney is small because it has a reduced number of renal lobes. It surface is distinctive; having 1 or more transverse grooves that overly a pelvic recess that represent a dilated calyx, or calices (Figs. 1A–D, 2).

**FIGURE 1.** A, This gross photograph of a bivalved kidney from a 19-year-old female with segmental hypoplasia shows a single deep groove characteristic of segmental hypoplasia. The kidney was 7 cm long (normal: 11 to 12 cm). The hypoplastic focus is tan with no evidence of corticomedullary differentiation. The adjacent cortex appears normal. The underlying collecting system shows marked hydronephrosis. B, This gross photograph of a bivalved kidney is from a 33-year-old female with segmental hypoplasia. The kidney was 6 cm long and weighed 38 g (normal: 115 to 125 g). Four hypoplastic foci were present; 3 are visible in this photograph. C, This gross photograph of a bivalved kidney from a 2-year-old female was 2.5 cm long (normal: 5.5 to 7.8 cm) and weighed 3 g (normal: 35 to 50 g). There are several adjacent hypoplastic foci without intervening normal lobes. Two normal lobes are at the top and on the right, respectively. D, This gross photograph of a child with segmental hypoplasia shows the deep circumferential groove characteristic of this entity. Jay Bernstein Consultative Collection, with permission.

**FIGURE 2.** This drawing is from Dr Ask-Upmark’s 1929 article on segmental hypoplasia depicts kidneys with hypoplastic foci. Notice the deep cortical grooves that approximate underlying minor calyces. Reprinted from Ask-Upmark, Fig. 1. With permission from John Wiley and Sons. Copyright John Wiley and Sons, Hoboken, NJ. All permission requests for this image should be made to the copyright holder.
renal parenchyma adjacent to the hypoplastic focus is grossly normal but may be hypertrophied making the groove(s) even more prominent. On cut surface there is a thin strip of parenchyma that consists of attenuated cortex with a rudimentary or absent renal pyramid. The groove appears to represent a renal lobe that failed to form. Evidence of failed or arrested lobar development was provided by Ljungqvist and Lagergren’s microangiographic studies that showed a corticomedullary arterial pattern in the hypoplastic foci with arcuate and interlobular arteries, and anastomoses between efferent and afferent arterioles.

The microscopic features of the hypoplastic focus consist of a sharply delineated lesion bracketed on both sides by normal-appearing cortical parenchyma. The hypoplastic focus contains a few tubules, loose interstitial tissue, with no or only rare glomeruli and little or no inflammation (Figs. 3A–D). There are large dilated veins and thick-walled arteries. Cysts and dysplastic features are absent, although occasional subcapsular immature-appearing cell nests or rarely a small island of fetal cartilage may be seen. Sclerotic glomeruli, atrophic tubules with thick replicated basement membranes and interstitial fibrosis are absent supporting a developmental abnormality rather than a sclerosing or atrophic process.

The underlying medulla is rudimentary and abnormally developed. The limited medullary tissue contains collecting ducts but lacks loops of Henle (Figs. 4A–D). Since loops of Henle are derived from glomeruli their absence is to be expected since glomeruli are absent in the hypoplastic foci. The collecting ducts may be set within a distinctive appearing cellular mesenchymal tissue unlike that of a normal renal pyramid or have collarets of spindle cells, features are often referred to as medullary dysplasia. The medullary stromal cells and collarets of spindle cells often express estrogen and/or progesterone receptor (Fig. 5). Similar aberrant expression has been described surrounding the immature ducts of dysplastic kidneys.

The radiologic and gross differential diagnosis of segmental hypoplasia includes chronic pyelonephritis and chronic pyelonephritis.

**FIGURE 3.** A, This case of segmental hypoplasia from a 2-year-old shows a hypoplastic focus. Notice that the focus is bordered on each side by normal-appearing cortex. The focus is devoid of glomeruli, both intact and sclerotic. It contains large dilated veins, a few tubules, loose connective tissue stroma, and a focus of lymphoid inflammation. Medullary tissue is visible at the bottom of the image. It consists of collecting ducts and cellular stroma. No loops of Henle are present. B, This case of segmental hypoplasia from a 33-year-old shows another hypoplastic focus. The focus is bordered on the left by normal-appearing cortex. The focus itself is devoid of glomeruli, both intact and sclerotic. It contains a large dilated vein, a few tubules, loose connective tissue stroma and several foci of adipocytes. C, This case of segmental hypoplasia from a 22-year-old shows another hypoplastic focus bordered on the right by normal-appearing cortex. The focus itself is devoid of glomeruli, both intact and sclerotic. It contains large dilated veins and loose connective tissue. A few small immature-appearing tubules are noted in the subcapsular region. D, This case of segmental hypoplasia from a 22-year-old shows a distorted appearing hypoplastic focus bordered by normal-appearing cortex on each side. The presumed cortical tissue is on the right side of the hypoplastic focus. On the left side is an oval nodule of rudimentary medullary tissue. To its left is a large artery and large dilated vein.
remote infarct. The renal arteries supplying the hypoplastic foci are small, but patent, and otherwise appear normal. This argues against infarction in the pathogenesis of the lesions. Histologically, a remote infarct contains acellular collapsed glomerular tufts and acellular tubular basement membrane remnants, features not seen in segmental hypoplasia. However, since the renal arteries supplying the hypoplastic foci are small and extrarenal vascular anomalies such as fibromuscular dysplasia or renal artery aneurysm occur in 40% of cases, a role for ischemia in the disease process is possible but further supports developmental contributions to the lesions.22,29,30

Chronic pyelonephritis is particularly challenging radiologically and clinically to distinguish from segmental hypoplasia since pyelocalyceal abnormalities and a history of urinary tract infections may be present in both. However, histologic differences between chronic pyelonephritis and segmental hypoplasia are marked. In chronic pyelonephritis there is a prominent inflammatory component, and sclerotic glomeruli or glomeruli with periglomerular fibrosis are present. In addition, clusters of atrophic tubules with thick replicated basement membranes, atrophic tubules with colloid casts, so-called thyroidization of tubules and dense remote infarct. The renal arteries supplying the hypoplastic foci are small, but patent, and otherwise appear normal. This argues against infarction in the pathogenesis of the lesions. Histologically, a remote infarct contains acellular collapsed glomerular tufts and acellular tubular basement membrane remnants, features not seen in segmental hypoplasia. However, since the renal arteries supplying the hypoplastic foci are small and extrarenal vascular anomalies such as fibromuscular dysplasia or renal artery aneurysm occur in 40% of cases, a role for ischemia in the disease process is possible but further supports developmental contributions to the lesions.22,29,30

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FIGURE 4. A, The medullary tissue of this hypoplastic focus from a 7-year-old contains collecting ducts widely separated by densely cellular stroma. No endothelial-like loops of Henle are visible. Note urothelium at the bottom of the image. B, This hypoplastic focus from a 33-year-old shows a polyploidy-appearing medullary tissue within a urothelial-lined calyx. The medullary tissue consisting of a few ducts within loose edematous-appearing stroma. No loops of Henle are present. C, The medullary tissue in this hypoplastic focus from a 22-year-old contains collecting ducts that have collarettes of spindled cells. No loops of Henle are present. D, This cytokeratin 7 stains highlights the collecting ducts. Notice that no endothelial-like loops of Henle are visible. Immunoperoxidase stain for cytokeratin 7.

FIGURE 5. The medullary stromal cells in this case strongly express estrogen receptor. The progesterone receptor stain was similarly positive. The collecting ducts are negative. Immunoperoxidase stain for estrogen receptor. Please see this image in color online.
interstitial fibrosis are present in chronic pyelonephritis but are not encountered in segmental hypoplasia. However, since vesicoureteral reflux and urinary tract infections are common in segmental hypoplasia, concomitant pyelonephritic changes can be expected in some patients which can complicate recognition of underlying segmental hypoplasia.

The etiology of segmental hypoplasia was originally regarded as congenital in origin, likely due to congenital reflux that damages a ureteric bud branch impairing development of the lobe. Most reported presentations occur in children and neonatal presentations have been described confirming in utero onset in some cases. However, adult presentations also occur as supported by several of the cases reported herein. Furthermore, some cases with typical gross and microscopic features of segmental hypoplasia appear acquired based upon serial imaging studies. Shindo et al. in 1983 reported apparent progression from a normal kidney, to kidneys with the typical radiologic, gross, and microscopic features of segmental hypoplasia. They suggested that segmental atrophy is a more appropriate term at least in some cases. However, imaging studies performed in the 1980s are less sensitive compared with current imaging technology. It is conceivable that the development of a lesion with features of segmental hypoplasia in a previously normal kidney may actually represent a lesion that was initially unable to be imaged. Regardless of whether lesions of segmental hypoplasia have onset in utero, are acquired, or both, vesicoureteral reflux appears to be the common pathogenic insult.

Oligomeganephronia (Oligomeganephronic Hypoplasia)

A second type of hypoplasia, oligomeganephronic hypoplasia, commonly referred to as oligomeganephronia, was first described by Royer and colleagues in 1962 in the French literature. The name oligomeganephronia reflects its distinctive histologic features, a paucity of nephrons which are markedly enlarged. Although several additional reports appeared in French in the 1960s the first detailed description in the English literature was by Bernstein in his 1968 hypoplasia review. The literature on oligomeganephronia is scant and mostly consists of case reports or small series. The only large series was reported by Broyer et al. in 1997, the group who first described the disease in the 1960s. They reported the clinical and pathologic features of 67 patients. Twenty-nine were followed for 3 to 17 years. Twelve patients had renal biopsies and 21 nephrectomies were studied. Their report provides the most comprehensive description of this rare renal disease. Broyer and colleagues’ criteria for a diagnosis of oligomeganephronia were rigorous as follows:

1. Reduction of kidney size with the sum of both kidney lengths ≤ 80% of 1 kidney of a same-sized child.
2. Reduction in glomerular filtration rate to 30% normal.
3. Absence of urinary tract malformations and no evidence of significant vesicoureteral reflux (small amounts of reflux were accepted provided no scars were identified).

As we will see later, many reports of so-called “oligomeganephronia” have employed far more relaxed criteria. Oligomeganephronia as defined above is by definition a pediatric disease. Broyer et al. reported that 29 of 50 patients presented at birth or by 1 year of age, and the remaining 21 patients presented by ages 10 to 15 years. Patients are typically born premature or small for gestational age. Most cases are sporadic, but familial forms occur. It has been reported in twins and in siblings. There is a 3:1 male predominance. The clinical presentation begins with concentrating defects, such as dehydration, polyuria, and polydipsia, in the first few years of life. Hyperfiltration with proteinuria develops later, followed by progression to renal failure, the onset dependent upon the combined renal mass. In Broyer and colleagues’ 1997 series end-stage renal disease (ESRD) occurred between 6 months and 17 years. Hypertension, unlike segmental hypoplasia, is rarely present. Genetic causes of oligomeganephronia have been reported but with more lenient diagnostic criteria. The list includes renal-coboma syndrome (PAX2 mutation), branchioto renal syndrome (EAY1 mutation), acorenal syndrome (RET1 mutation), and chromosome 4 deletion syndrome. These are discussed further below.

Oligomeganephronia is a bilateral disease with kidneys symmetrically affected unless associated with unilateral agenesis, an infrequent association. The kidneys are very small at birth with reduced number of renal lobes, 5 to 6 or fewer, sometimes a few as 1 or 2 lobes. The number of nephrons per lobe is also reduced. Broyer et al. reported that in 21 nephrectomies performed at the time of renal transplantation cortical hypoplasia was present with radial glomerular counts markedly reduced to 2 to 6 rather than the normal of 9 to 10.

Early in the disease the entire nephron including glomeruli, juxtaglomerular apparatus and tubules are markedly enlarged compared with normal nephrons (Figs. 6A-C). Anecdotally, the number of capillary loops also appear markedly increased. In 1969, Fetteman and Habib performed nephron microdissection studies on kidneys from a 13-year-old male. His kidneys weighed 30 and 35 g (normal: 110 g). The mean glomerular diameter and volume were 2 and 12 times normal, respectively. The mean proximal tubular length and tubular cell volume was 4 and 17 times normal, respectively (Fig. 7A). Griffel et al. also performed microdissection studies in an 8.5-year-old with oligomeganephronia and unilateral renal agenesis. Although, they did not report the size or weight of the kidney, their dissections demonstrated markedly enlarged glomeruli, and longer and more voluminous tubules compared with an age-matched control (Fig. 7B). Table 1 lists gross findings and glomerular morphometrics for a number of reported cases of oligomeganephronia demonstrating the marked glomerular enlargement.

In a renal biopsy the diagnosis of oligomeganephronia can be challenging since knowledge of kidney size is required if the stringent criteria of Broyer et al. are applied. In addition, information on the number of renal lobes would be particularly helpful. Unfortunately, both data points are usually lacking. Histologically, there is marked enlargement of glomeruli and tubules (Figs. 6A, B). Because of hypertrophy of both glomeruli and tubules, the glomerular density is decreased resulting in fewer glomeruli per millimeter of cortex compared with a normal biopsy in a patient of similar age. In an uncomplicated scenario, the combination of bilateral small kidneys, very large nephrons and absence of nephrosclerosis eliminates acquired atrophy with secondary nephron hypertrophy from consideration. However, with disease progression, segmental, and global glomerulosclerosis with tubulointerstitial scarring develops complicating the histologic recognition of oligomeganephronia. For a diagnosis of oligomeganephronia in this situation a specific underlying disease, glomerulonephritis, pyelonephritis, etc., should be excluded and the renal size should be markedly reduced, beyond that expected from ESRD of other causes, a difficult determination.

The literature on oligomeganephronia is quite limited and muddled with questionable cases. Excluding Broyer and colleagues’ large series, <30 nonsyndromic cases have been
Many reported cases fall short of fulfilling Broyer and colleagues’ criteria. For instance, cases have been reported in children with renal sizes in the 7.5 to 10 cm range, significantly exceeding Broyer and colleagues’ size criteria. Cases have also been reported in adults with advanced CKD, despite oligomeganephronia, by definition, representing a pediatric disease with such severe reduction in nephron mass that ESRD develops in childhood or adolescence. Although the kidneys were smaller than normal in adult cases reported, in the range of 7 to 8.5 cm, CKD was also present. Therefore, the original kidney size would have been significantly larger before onset of atrophic changes. Acquired atrophy with secondary nephron hypertrophy is more likely in these cases rather congenital oligomeganephronic hypoplasia.

**Simple Hypoplasia**

The third type of hypoplasia is simple hypoplasia. The affected kidneys have been referred to in the older literature as a doll’s kidneys, dwarf kidney, miniature kidney or “trop petit rein.” The diagnostic criteria for simple hypoplasia were defined by Rubenstein et al in 1961 as 1 kidney weighing 50% or less than expected, or if both kidneys were small, their combined weight was <33% of that expected. Kissane further opined in 1966 that “more important than … mass is enumeration of renal lobules” (Figs. 8, 9A–D). He was referencing renal lobes. “A truly hypoplastic kidney possesses a markedly reduced number of reniculi and calyces, 5 or fewer, in contrast to the normal complement of 10 or more.”

Simple hypoplasia is often associated with hypertension, and if bilateral, progressive renal insufficiency. When unilateral, the contralateral kidney may be hypertrophied and renal function normal. Simple hypoplasia may be an isolated abnormality but is most often associated with other extrarenal anomalies. In simple hypoplasia the kidney, other than its small size, is normal in all other aspects. Radiologic assessment is not adequate for the diagnosis which can reveal small size but not normal histology. Histologically, in simple hypoplasia the nephrons are normal (Figs. 9A, B). The issue of nephron size is not addressed in most reports which were all published many years ago, but nephron enlargement should not be present since it is the single definitional criteria in distinguishing simple hypoplasia from oligomeganephronia. Furthermore, there should be no cysts or renal dysplasia. Simple hypoplasia is most obvious in the young patient with unilateral disease. With bilateral disease, acquired injury due to low nephron mass and progressive CKD with aging makes it more difficult to histologically distinguish atrophy in a hypoplastic kidney, from atrophy in a developmentally normal kidney.
When strict anatomic criteria are applied, simple renal hypoplasia is very rare. Rubenstein et al\(^6\) in a 1961 review of 2153 pediatric autopsies, found only 58 cases (0.27%) of hypoplasia. All were simple hypoplasia. Fifty-six cases were bilateral and 32 of these cases had malformations of other organ systems raising the prospect of a genetic cause. Similarly, in 1975, Risdon et al\(^5\) in a radiologic study of 49 small kidneys with pathology correlation identified only 2 cases of hypoplasia, both were examples of simple hypoplasia. No examples of oligomeganephronia or segmental hypoplasia were identified in either study.

**Cortical Hypoplasia**

A fourth type of hypoplasia, cortical hypoplasia, was introduced in a renal hypoplasia classification by Bonsib\(^5\) in 2012 but has been known for many years. Cortical

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**TABLE 1. Oligomeganephronia—Autopsy and Biopsy Findings**

| Age     | Patient’s Renal Weight (g) | Normal Renal Weight (g) | Glomerular Diameter (µm) | Control Diameter (µm) | Other Findings                        | References |
|---------|----------------------------|-------------------------|--------------------------|-----------------------|---------------------------------------|------------|
| 0-15 y  |                            | 250-300                 |                          | <150                  | Malformations in some                  | 41         |
|         |                            |                         |                          |                       | Reduced RGC in 21 nephrectomies        |            |
| 13 y    | 30, 35                     | 95-120                  |                          |                       |                                       | 46         |
| 12 y    | 9, 22                      | 90-110                  |                          |                       |                                       | 48         |
| 18 y    | 35                         | 115-135                 |                          |                       |                                       |            |
| 4.5 y   | 9, 10                      | 50-65                   | 237                      | 142                   | 3-4 lobes                             | 35         |
| Term    | 1.4—L+R                    | 11-16                   | 69                       | 56                    | 2 lobes/kid                           | 36         |
| 2 mo    | 2                         | 15-22                   | 79                       | 62                    | RGC of 3                              | 36         |
| 2.25 y  | 9, 12                      | 16-24                   | 266                      | 102                   | Acrorenal syndrome                    | 37         |
| 8 d     | 1.5, 1.6                   | 12-18                   | 87.5                     | 70.5                  | 2 siblings                            | 38         |
| 11 d    | 2.5, 2.6                   | 12-18                   | 116                      |                       | Few lobes                             |            |
| 8.5 y   | Biopsy                     | NA                      | 340                      | 120                   | 4p del syndrome                       | 47         |

L+R indicates left and right kidneys combined; NA, not applicable; RGC, radial glomerular count.

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hypoplasia was first described in dogs in 1957.39 Bernstein and Meyer in the 1960s discussed cortical hypoplasia in humans.7,8 In this form of hypoplasia, there are reduced numbers of nephron generations (Figs. 10A–C). Cortical hypoplasia presumably represents premature cessation or arrest of nephrogenesis resulting in fewer nephron generations than normal, and therefore, smaller overall renal size. Medullary rays are smaller as are the renal pyramids. Cortical hypoplasia may, rarely, occur alone as noted in 1 of 18 cases reported above. It is often associated with other forms of renal hypoplasia. In Broyer et al41 large series of oligomeganephronia reduced radial glomerular counts were identified in 21 nephrectomy cases. In the 18 cases of hypoplasia reported herein, 3 of 9 cases of segmental hypoplasia and 5 of 8 cases of simple hypoplasia also showed reduced radial glomerular counts. There are also other clinical associations (Table 2) most related to developmental abnormalities of ampullary buds. In 1980 Henneberry and Stephens69 published an autopsy study of renal hypoplasia and dysplasia in 19 patients with urethral valves. They noted that in the mildest forms of urethral ectopia near normal renal histology may be observed but associated with reduced radial glomerular counts. In a second study of 32 autopsies and 11 surgical nephrectomies in patients with partial ureteral obstruction and vesicoureteral reflux, Sommers and Stephens61 identified reduced radial glomerular counts to 6 generations, or less. Hinchcliffe et al62 showed that reduced radial glomerular counts are commonly present in nonscared lobes in patients with vesicoureteral reflux-associated chronic pyelonephritis. They graded cortical hypoplasia based upon radial glomerular counts as follows: none >10, minimal 8 to 10, moderate 4 to 8, severe <4. Severe hypoplasia was identified in 47 of 86 patients.

THE AUTHOR’S PERSONAL EXPERIENCE WITH 18 CASES

Eighteen cases of renal hypoplasia have been collected by the author over many years while practicing at several medical centers. The 18 cases comprise 9 cases of segmental hypoplasia with or without cortical hypoplasia, 8 cases of simple hypoplasia with or without cortical hypoplasia, and 1 case of cortical hypoplasia (normal number of renal lobes). No cases of oligomeganephronia are included. Limited demographic data was available on each case primarily consisting of age and sex. Most cases included renal size and/or weight. The diagnostic criteria employed in this study for each type of hypoplasia are listed in Table 3. The cases satisfy the criteria for hypoplasia as defined by Rubinstein and colleagues.6,8

The number of nephron generations was estimated by the Radial Glomerular Count Method which employed sections oriented along medullary rays.63 The glomerular layers on each side of the medullary ray were counted. The normal number of nephron generation ranges from 12 to 14, although usually no >10 generations can be observed in optimally oriented sections. Cortical hypoplasia is defined by radial glomerular counts of ≤8 nephron generations.63 The age-related normal ranges for renal weights and sizes utilized published data from several sources.64–66

Nine cases of segmental hypoplasia were reviewed (Table 4). The patient ages ranged from 11 months to 44 years. Five were 19 years of age, or less. All 9 cases were unilateral. One patient presented with malignant hypertension, blood pressure 220/120, which was cured by nephrectomy. Two patients had ureteral ectopia. Two other kidneys were hydropnephrotic. One other patient presented with a urinary tract infection.

All 9 cases of segmental hypoplasia were diagnosed on a nephrectomy specimen. The kidneys in 8 cases were much smaller in size and/or weighed much less than that expected for the patient’s age (Table 4). In 1 case the kidney size and weight were not available. Grossly, from 2 to 5 hypoplastic foci were identified by external examination. The hypoplastic foci were deeply indented and often sharply delineated on each side by normal-appearing cortex (Figs. 1A, B). In cases with multiple adjacent hypoplastic foci, the foci merged resulting in a very small kidney with an irregular profile (Fig. 1C). In a bivalved kidney the hypoplastic foci grossly appeared gray-white in contrast to the adjacent red-brown normal cortex. No grossly discernable corticomedullary differentiation was present in the hypoplastic foci.

Microscopically the “cortical” tissue contained small foci of small tubules (Figs. 3A–D). There were multiple large dilated veins and thick-walled arteries which permitted identification of the tissue as cortical since large veins and arteries are not present in the medulla. The cortical stroma was loose without dense fibrosis. Focal lymphocytic inflammation and foci of adipocytes (not present in the normal cortex) were present in several cases. No intact or sclerotic glomeruli were noted in the hypoplastic foci in 8 cases. One hypoplastic focus in 1 kidney contained several normal-appearing glomeruli without tubular segments. One kidney contained a few immature-appearing or embryonal-like cell nests and tubules in the immediate subcapsular area. No cortical cysts, cartilage, or immature/dysplastic ducts were present as seen in dysplastic kidneys.

All hypoplastic foci histologically contained medullary tissue (Figs. 3A–D, 4A–D). The medullary tissue was much smaller in quantity compared with the adjacent normal renal pyramids. It was usually deep to the cortex as expected but appeared isolated from the cortical tissue and not connected to the scattered cortical tubules. Specifically, no medullary rays were present, the usual route of corticomedullary tubular connection. Occasionally, medullary tissue was off-set, adjacent to, lateral to, the cortex or (Fig. 3D). The medullary tissue contained collecting ducts. However, loops of Henle were absent, as expected since they would be derived from glomeruli which were not present in the hypoplastic cortex (Figs. 4A–D). The absence of loops
of Henle was readily demonstrated by cytokeratin 7 staining in which variably-sized collecting duct cuboidal to columnar cells are seen with no intervening endothelial-like thin loops of Henle cells (Fig. 4D). Most medullary tissue had a cellular immature-appearing stroma unlike the stroma of normal renal pyramids. In 2 cases the medullary collecting ducts had collarets of spindled cells (Fig. 4C). The stromal cells and collecting duct collarets strongly expressed estrogen receptor in 5 of 5 cases stained and progesterone receptor in 2 of 5 cases stained (Fig. 5). This combination of findings is often referred to as medullary dysplasia (Table 2).

The cortex adjacent to the hypoplastic foci contained histologically normal nephrons in 7 cases. In 2 cases, segmental glomerulosclerosis (31 and 35 y old) was noted affecting some glomeruli. Although histologically normal nephrons were present in nonhypoplastic lobes in all 9 cases, in 4 cases multiple lobes showed cortical hypoplasia with reduced radial glomerular counts (Figs. 11A, B). The radial

FIGURE 9. A, This gross photograph from a 50-year-old female shows a simple hypoplastic kidney. The kidney weighed 50 g and was 6 cm in length. There is a marked reduction in number of renal lobes; only 5 renal pyramids are visible in this bivalved specimen. B, Histology from the kidney in (A) is normal. There is no atrophy, cysts or dysplastic features. The number of nephron generations counted in several lobes ranged from 9 to 10. Periodic-acid Schiff stain. C, This gross photograph of a simple hypoplastic kidney from an adult appears somewhat distorted. Only 4 lobes and 3 renal pyramids are noted in this bivalved specimen. D, Histology from the kidney in (C) is normal. There is no atrophy, cysts, or dysplastic features. The number of nephron generations counted in several lobes ranged from 9 to 10. Periodic-acid Schiff stain.
glomerular counts in 3 cases were severely reduced to 2 to 3 nephron generations and in 1 case the radial glomerular counts were moderately reduced to 6 to 7 generations, compared with 9 to 10 nephron generations in the other cases (Table 4). In addition, in 1 case the medulla underlying normal-appearing cortex (2 y old) had cellular immature-appearing stroma similar to the medullary changes in the hypoplastic foci. Estrogen and progesterone receptor stains were negative in that case.

Nine cases of simple and/or cortical hypoplasias were studied (Table 4). They consisted of 1 case of cortical hypoplasia, 3 cases of simple hypoplasia and 5 cases of combined simple and cortical hypoplasia. The patients ages ranged from 17 days to 50 years old. Seven were pediatric cases. All cases were unilateral. The tissue reviewed consisted of 4 autopsies and 5 nephrectomies.

The single case of isolated cortical hypoplasia occurred in a 17-day-old female (Table 4). The kidney was grossly reniform and modestly reduced in weight at 9.8 g (normal: 13 to 19 g). The contralateral kidney was of normal size, 16.5 g. On cut surface corticomedullary differentiation was present in the hypoplastic lobes but the cortex appeared thin and the renal pyramids small. The cortex in the hypoplastic foci contained predominately histologically normal nephrons without glomerulosclerosis, tubulointerstitial scarring, or arterial sclerosis (Figs. 10A, B). However, immediately beneath the capsule a few scattered small dysmorphic

TABLE 2. Clinical Contexts Associated With Cortical Hypoplasia/Reduced Radial Glomerular Counts

| Isolated finding       | Segmental hypoplasia | Oligomeganephronia | Simple hypoplasia | Prematurity | Vesicoureteral reflux | Ureteral ectopia | Urethral valves |
|------------------------|----------------------|--------------------|-------------------|-------------|-----------------------|----------------|----------------|

FIGURE 10. A, This case of isolated cortical hypoplasia is from a 17-day-old with a 4 cm/9.8 g kidney (normal: 4.5 to 6 cm/13 to 19 g). The cortex contains 3 to 5 nephron generations. The medullary tissue at the bottom is normal. B, This is another lobe from the above case has 3 normal nephron generations and fourth generation of aberrantly formed glomeruli just beneath the renal capsule at the top of the image. C, In several lobes from the above case the medullary tissue contained collecting ducts within a dense cellular stroma. Loops of Henle were not present.
glomeruli and occasional small immature-appearing tubules were present. The normal nephrons in the hypoplastic focus were not enlarged. Medullary rays were absent or only minimally developed since the number of nephron generations, and therefore, descending and ascending tubules that populate the medullary rays, were few. Radial glomerular counts ranged from 3 to 5 (Table 4). The underlying renal medulla appeared normal in some lobes (Fig. 10A) while in other lobes medullary dysplasia was present consisting of collecting ducts widely separated by cellular stroma with few loops of Henle (Fig. 10C).

Three cases of simple hypoplasia were reviewed (Table 4). Two cases were from adults and 1 was from a 17-year-old. All were unilateral. In 2 cases, the kidney was one third smaller in size and weight compared with a normal kidney (Table 4). The kidney in 1 case was 50% or less, smaller or lighter, than normal (Figs. 9A, C). The number of renal foci where foci were counted were 6 and 7 lobes, respectively. The nephrons were histologically normal (Figs. 9B, D). Specifically, no glomerulosclerosis, tubulointerstitial scarring, vascular sclerosis, cysts, or dysplastic development were noted in any case. The glomerular diameter in 1 adult case was normal. The glomerular diameters in

| TABLE 3. Renal Hypoplasia Diagnostic Criteria |
|-----------------------------------------------|
| Segmental hypoplasia | Transverse cortical groove(s) overly expanded calix(es) |
| Cortex—absence of glomeruli both normal and atrophic |
| Medulla—absent to rudimentary with medullary dysplasia (see below) |
| Oligomeganephronia | Bilateral, unless associated with unilateral agenesis |
| Reduced number of renal lobes to <5-6 |
| Morphologically normal, but markedly enlarged nephrons |
| Simple hypoplasia | One kidney <50% normal, or both kidneys <30% normal |
| Normal histology, nephrons not enlarged |
| Cortical hypoplasia | Radial glomerular count ≤6 |
| Medullary dysplasia | Medullary tissue contains collecting ducts and cellular stroma |
| No, or few, loops of Henle, and peritubular capillaries |
| Stroma cells often estrogen and/or progesterone receptor positive |

| TABLE 4. Renal Hypoplasia—Clinical and Pathologic Features of 18 Cases |
| Age | Type of Hypoplasia/Other Findings | Size/Weight | Normal Size/Weight | # of Foci | RGC | Medullary Dysplasia | ER/PR |
|-----------------------------------------------|
| Segmental hypoplasia | Segmental and cortical/ectopic ureter/cryptorchid |
| 11 mo/male | 3.9 cm | 5-7 cm | 4 | 6-7 | + | +/− |
| 2 y/female | 2.5 cm/3 g | 5.5-7.8 cm/35-50 g | 4 | 9-10 | + | +/+ |
| 7 y/male | 4.5 cm/16 g | 7-8 cm/55-80 g | 3 | 2-3 | +/− |
| 11 y/male | 6.5 cm | 8.5 cm | 5 | 2-3 | + | +/+ |
| 19 y/female | 7 cm | 11-12 cm | 4 | 2-3 | + | +/− |
| 22 y/female | 5.5 cm | 11-12 cm | 2 | 9-10 | + | +/+ |
| 31 y/female | 9 cm | 11-12 cm | 2 | 9-10 | + | NP |
| 33 y/female | 6 cm/38 g | 11-12 cm/115-125 g | 2 | 9-10 | + | NP |
| 44 y/female | 5.5 cm | 11-12 cm | 2 | 9-10 | + | NP |

| Age | Type of hypoplasia | Size/weight | Normal size/weight | RGC | Other findings | ER/PR |
|-----------------------------------------------|
| Segmental and/or cortical hypoplasia | Cortical |
| 17 d/female | Right = 4 cm/9.8 g | 4.5-6 cm/13-19 g | 3-5 | Medullary dysplasia | −/− |
| 3 wk/female | Right = 8 g | 13-20 g | Right = 5-6 | Medullary dysplasia | −/− |
| 5 mo/male | Right = 34 g | 5-6.5 cm | 3-5 | Medullary dysplasia | +/− |
| 14 mo/male | Right = 10 g | 5-6.5 cm | 3-4 | Medullary dysplasia | +/− |
| 17 y/male | Right = 4 cm/15.6 g | 7-8 cm/65-85 g | 2-3 | Medullary dysplasia | +/− |
| 11 y/male | 7.5 cm/40 g | 9-10 cm/80-105 g | 3-4 | Glomeruli up to 300 μm | NP |
| 17 y/male | 8 cm/94 g | 11-12 cm/115-125 g | 9-10 | Glomeruli up to 350 μm | NP |
| 50 y/female | Simple | 6 renal lobes | Left = 11 cm/130 g | 11-12 cm/115-125 g | 9-10 | Glomeruli up to 250 μm | NP |

ER indicates estrogen receptor; FSGS, focal segmental glomerulosclerosis; NP, not performed; PR progesterone receptor; RGC, radial glomerular count.
2 cases were enlarged. The largest glomeruli were 300 and 350 µm compared with a normal adult glomerulus of 200 to 250 µm. Nephron generation ranged from 9 to 10. The medullary tissue was histologically normal.

Combined simple and cortical hypoplasia was identified in 5 cases (Table 4). The patient ages ranged from 3 weeks to 11 years. All cases were unilateral. The hypoplastic kidney sizes were markedly decreased to one third of normal in 1 case, and to less than one fourth of normal in 4 cases (Fig. 12A, Table 4). The contralateral kidney was reported as normal in size in all cases. The nephrons were histologically normal and not enlarged (Figs. 12B, 13A, D). No glomerulosclerosis, tubulointerstitial scarring or vascular sclerosis were present. In addition, no cysts or dysplastic development was present. However, a single island of cartilage that was noted among normal nephrons in 1 case (Fig. 13B). The medullary rays were inconspicuous and poorly developed (Fig. 13C). The nephron generations ranged from as low as 2 to 3, to a maximum of 5 to 6. The medulla was dysplastic in 2 cases containing collecting ducts within cellular immature stroma with only a few loops of Henle identified (Fig. 13D). No medullary abnormalities were noted in the other 3 cases.

Genetic Causes of Hypoplasia

Normal nephrogenesis is dependent upon proper ampullary bud formation and arborization, and subsequent nephron induction. This is a complex process that requires
the intricate coordination, expression, and interaction of many genes. Some of the most important currently known genes are PAX2 (paired box 2), RET (receptor tyrosine kinase), GDNF (glial-derived neurotrophic factor), WT1 (Wilms tumor 1), and wnt-4, to name a few.67,68 Mutation of 1 or more of these genes can affect ampullary bud function leading to “congenital anomalies of the kidney and urinary tract”, a family of mutations of which renal hypoplasia is one of its members. Table 5 lists many of the other malformations.

Genetic causes of renal hypoplasia are discussed separately, herein, because most reports of simple and oligomeganephronic hypoplasia appeared before the availability of genetic testing. Many would likely have a genetic basis if tested today. Many genetic causes of small kidneys cannot be placed within the known anatomic types of hypoplasia since they lack documentation of renal size, renal weights, and/or histologic evaluation (Table 6). Even when such documentation has been provided, cases often fail short of the stringent criteria established for simple and oligomeganephronic hypoplasia by Rubenstein and colleagues.6,8

One of the most important and widely studied genes in renal hypoplasia is PAX2. PAX2 is a nuclear transcription factor critical to formation of the nervous system and genitourinary tract.67,68 It is a master organizer and one of the first genes activated during fetal development. It is expressed

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TABLE 5. Congenital Abnormalities of the Kidney and Urinary Tract Malformations

| Malformation                                                |
|-------------------------------------------------------------|
| Renal agenesis                                              |
| Renal hypoplasia                                            |
| Renal dysplasia                                             |
| Renal fusion, ectopia, and duplication                      |
| Ureteral-pelvic junction and ureterovesical junction obstruction |
| Vesicoureteral reflux                                       |
| Ureteral duplication and ectopia, and ureterocele            |
| Bladder extrophy, persistent cloaca, and rectal-vesical fistula |
| Urethral atresia and posterior urethral valves               |

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FIGURE 13. A, This example of simple and cortical hypoplasia is from a 3-week-old. The kidney weighed 8 g. The opposite kidney weighed 34 g. The histology of both cortex and medulla is normal. However, only 5 to 6 nephron generations are present. B, Although no cysts or dysplastic developmental abnormalities were noted in the above case a single focus of cartilage was noted among otherwise normal nephrons. C, Immunoperoxidase staining for epithelial membrane antigen on the case in Figures 11A and B shows poorly developed medullary rays in the center with only a few distal tubules and collecting ducts. D, This is a case of mixed simple and cortical hypoplasia from a 7-year-old. The kidney weighed 15.6 g (normal for age: 65 to 85 g). The histology of the cortex is normal but only 2 nephron generations are present in this lobe. The underlying medullary tissue at the bottom of the photograph shows collecting ducts in a densely cellular stroma. A few loops of Henle were present but not readily seen in this image.
in the nephric duct, ampullary bud and metanephric mesenchyme. Small kidneys have been reported with PAX2 mutations in a sporadic setting, as well as syndromically, specifically the renal-coloboma syndrome (pseudolema-renal syndrome).

Porteous et al.\(^6^9\) in 2000, studied 29 patients (5 children and 24 adults) with renal-coloboma syndrome. Radiologic evidence of small but otherwise normally formed kidneys was the most common renal abnormality found in 17 patients. Salomon et al.\(^4^2\) also studied 9 patients with small but radiologically normal-appearing kidneys. Three of the 9 patients were found to have PAX2 mutations. In retrospect, minor ocular abnormalities were detected in 2 of 3 patients suggesting that they may have a mild form of renal-coloboma syndrome. Kidney sizes were not provided in either study. Salomon and colleagues also reviewed the literature on PAX2 mutations and found 32 cases;\(^1^8\) cases were labeled as having renal hypoplasia. Subtle forms of renal disease may also be caused by PAX2 mutations. Quinlan et al.\(^7^0\) in a study of 168 newborns measured kidney volumes by ultrasound. They identified a PAX2 haplotype (AAA) present in 18.5% of newborns that was associated with a 10% reduction in renal volume compared with the most common haplotype (GGG/GGG). Unfortunately, histology was not part of these 3 studies.

Histology was part of 2 PAX2 mutation and renal hypoplasia studies. Nishimoto et al.\(^4^3\) tested for PAX2 mutations in 20 patients with radiologically small kidneys. Only 2 patients harbored PAX2 mutations, ages 4 and 8 years. Their kidneys were 67% to 78% of normal size, much larger than the original definition for both simple and oligomeganephronic hypoplasia. Renal biopsies were performed in 11 patients. Ten had “oligomeganephronia” based upon having the combination of small kidneys and normal but greatly enlarged nephrons. One patient was classified as having simple hypoplasia. The size of the kidneys and patient ages in 18 of 20 cases with small kidneys but lacking PAX2 mutations were not provided. The latter is important since oligomeganephronia as classically defined is a pediatric disease with marked reduction in renal size. Martinovic-Bouriel et al.\(^3^4\) reported autopsy findings in 2 fetuses with renal-coloboma syndrome. One fetus, 24 weeks of gestational age, had unilateral renal hypoplasia with kidney weight 10% of normal and a contralateral cystic dysplastic kidney. The other fetus, 18 weeks of gestational age, had kidneys with a combined weight 50% normal for gestational age. Histology showed a scant nephrogenic zone. Collectively, these 5 studies indicate that PAX2 mutation can cause small kidneys, widely variable in size, but PAX2 mutation accounts for only a small percentage of small but radiologically normal kidneys.

Several other mutations have been identified associated with smaller than normal kidneys. Zhang et al.\(^7^1\) studied 136 normal newborns and identified a RET single nucleotide polymorphism (RET 1476A allele) in Caucasian newborns. Affected patients had 10% smaller renal volumes and 9% less cystatin C levels (a measure of renal function). So-called oligomeganephronia was identified in some patients with branchio-oto-renal syndrome due to EYA1 gene mutation and in Townes-Brocks syndrome due to SALL1 mutation.\(^7^2,7^3\) Finally, Anderson et al.\(^4^5\) identified small kidneys, 6.8 and 7.7 cm, and large glomeruli on biopsy, in patients with Seckel syndrome and chromosomal abnormalities.

**Oligonephronia**

All types of hypoplastic kidneys have in common reduced nephron number. However, nephron quantifications have demonstrated that even patients with putatively normal kidneys may have too few nephrons, referred to as oligonephronia. Nephron quantifications were first performed almost 100 years ago.\(^5,7^6\) It was discovered from the beginning that there is broad range of nephron number in the “normal” kidney, that is, a kidney that is grossly and histologically normal, in a patient with normal renal function. The broad range in nephron number in otherwise normal individuals has received attention over the past few decades because of the association of congenitally low nephron number with adult-onset hypertension and CKD.\(^8^0,7^7-7^8\) Although methodologies have varied, modern glomerular quantifications consistently show a Gaussian distribution in nephron numbers in the normal population. The “average” kidney contains ∼900,000 to 1,000,000 nephrons.\(^7^7-8^2\) However, nephron numbers range from as low as 210,000, to as high as 2,700,000, almost a 12.9-fold range (Table 7).

Glomerular number is known to be influenced by many factors (Table 8).\(^4^2,4^5,6^7-1^0^5\) Gestational causes of oligonephronia, maternal, and intrauterine, are particularly important because of their prevalence. Maternal factors include smoking, gestational hyperglycemia, nutritional deficiencies, drug and alcohol abuse, and chronic infections.\(^8^6-9^0\) Although potentially preventable,

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**Table 6. Genetic Studies of Renal Hypoplasia**

| Genetic Disease | Gene | Hypoplastic Features | References |
|-----------------|------|----------------------|------------|
| Renal-coloboma syndrome | PAX2 | 17/29 patients had “small kidneys” | 69 |
| | | No size given, no histology performed | |
| Hypoplastic kidneys diagnosed as oligomeganephronia | PAX2 | 9 patients had kidneys 25%-70% of normal size—5/9 had biopsies | 42 |
| | | 3/9 had PAX2 mutations—kiddie size was 60%-70% of normal kidneys | |
| Hypoplastic kidneys diagnosed as oligomeganephronia | PAX2 | 20 patients had “small kidneys” | 43 |
| | | 10/20 biopsies showed nephron hypertrophy | |
| | | 2/20 had PAX2 mutation—kiddie size was 60%-78% of normal kidneys | |
| Normal term infants | PAX2 | 31/168 patients had PAX AAA haplotype | 70 |
| | | Kidney volume was 10% less than normal kidneys | |
| Normal term infants | RET | 17/136 normal newborns had AAA and 1476A allele | 71 |
| Branchio-oto-renal syndrome | EYA1 or SIX1 | Renal agenesis, renal hypoplasia, “oligomeganephronia” | 68,72 |
| | | Kidneys size was 9% smaller than normal kidneys | |
| Townes-Brocks syndrome | SALL1 | Renal hypoplasia, “oligomeganephronia” | 73 |
| | | Chromosome 4 mutation | 45 |
| Seckel syndrome | | Small kidneys—7-8 cm and large nephrons | |

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maternal factors represent enormous social and economic issues not easily addressed in the United States but especially challenging in Third World Countries. The World Health Organization estimates that worldwide there are 1.22 billion smokers and 422 million adults living with diabetes, while the United Nation's Food and Agriculture Organization estimated that the incidence of malnutrition worldwide in 2014 was 795 million.88

Intrauterine factors such as prematurity and growth retardation/small for gestational age are major sources of oligonephronia.11,78–81,86–102 It has been demonstrated that there is a direct linear correlation between birth weight and nephron number80,81 (Fig. 14A). For each kilogram increase in birth weight there is an increase in 185,000 to 300,000 nephrons per kidney.81 Like maternal factors, intrauterine factors are extremely prevalent worldwide. The World Health Organization (WHO) estimated that in 2010 that 14.9 million, or 11.1% of all births worldwide, were preterm defined as birth occurring at 37 weeks, or less.88

### Table 7. Glomerular Numbers—Range and Average in Adults

| Study Group          | Number Studied | Range in Glomerular Number | Mean Glomerular Number | References |
|----------------------|----------------|---------------------------|------------------------|------------|
| Adults               | 79             | 150,000-1,360,000*        | 700-800,000*           | 75         |
| 15% hypertension     | 37             | 331,000-1,400,000         | 617,000                | 83         |
| 33% hypertension     | 28             | 655,000-1,354,000         | 1,107,000              | 84         |
| 100% hypertension    | 78             | 210,000-1,825,000         | 1,429,000              | 85         |
| Adults               | 45             | 227,000-1,825,000         | 874,000                | 86         |
| Males: infants to adults | 20     | 513,000-1,950,000         | 1,074,000              | 77         |
| Females: infants to adults | 10    | 1,429,000                | 702,000                |            |
| Ethnicity            |                |                           |                        |            |
| African Americans    | 176            | 210,000-2,700,000         | 899,000                | 78,81      |
| United States Caucasians | 132      | 227,000-1,660,000         | 894,000                |            |
| Australian Aborigines| 19             | 364,000-1,129,000         | 713,000                |            |
| Australian Caucasians| 24             | 380,000-1,494,000         | 861,000                |            |
| African Senegalese   | 47             | 536,000-1,764,000         | 988,000                |            |

*Estimated from publication figure #5.

### Table 8. Causes of Oligonephronia

| Clinical Features                        | Renal Findings                                                                 | References |
|-----------------------------------------|--------------------------------------------------------------------------------|------------|
| Demographic                             |                                                                               |            |
| Sex                                     | Females 9%-12% less than males                                                | 78,80      |
| Adult height                            | Increase of 28,000 glomeruli/1 cm increase in height                           | 78         |
| Aging                                   | Decrease of 3676 glomeruli/kidney/year of age > 18 y                           | 78         |
| Ethnicity                               | Decrease in glomerular numbers for Australian Aborigines compared with United States Caucasians and African Americans | 78,85,87   |
| Maternal                                | Decrease in glomerular numbers                                                | 88–90      |
| Malnutrition, smoking, gestational hyperglycemia, chronic infections, drugs, chronic illness, nos | Decrease in radial glomerular counts                                           |            |
| Intrauterine                            |                                                                               |            |
| Low birth weight (<2500 g)              | Decrease in glomerular numbers (increase of 300,000 glomeruli in Caucasians and 185,000 glomeruli in African Americans/kilogram increase in birth weight) | 11,78–81,86–102 |
| Small for gestational age               | Increased risk of adult hypertension and chronic kidney disease                |            |
| Prematurity                             |                                                                               |            |
| Kidney volume or size                   | Kidney size or volume at birth                                                | 70,71,81,83,88 |
| Urinary abnormalities                   |                                                                               |            |
| Vesicoureteral reflux, ureteral ectopia, obstruction | Increase of 23,459 glomeruli/gram of kidney tissue                             | 60–64      |
| Genetic mutation                        |                                                                               |            |
| PAX2 mutations—sporadic and renal-coloboma syndrome | Oligomeganephronia, Decrease in radial glomerular counts AAA allele associated with a 10% decrease in nephron numbers | 42,43,67–70,74 |
| RET1 mutation                          | 10% decrease in nephron numbers                                               | 71         |
| E471 mutation—branchiootorenal syndrome | Small kidneys                                                                | 72         |
| Chromosome 4 mutation                   | Small kidneys                                                                | 44,45      |

nos indicates not otherwise specified.
Furthermore, a daunting 36% of live births are either preterm, low birth weight as defined as <2500 g, small for gestational age, or a combination, underscoring the massive global potential for CKD due to oligonephronia.

The developmental defect underlying prematurity-associated oligonephronia is premature cessation of nephrogenesis leading to cortical hypoplasia. Glomerular number is a biological variable fixed at birth in the normal individual; no new nephrons are formed after 34 to 36 weeks gestational age. Most nephron are formed in the third trimester; no new nephrons are formed after 34 to 36 weeks gestational age. Most nephron are formed in the third trimester; no new nephrons are formed after 34 to 36 weeks gestational age. Most nephron are formed in the third trimester; no new nephrons are formed after 34 to 36 weeks gestational age. Most nephron are formed in the third trimester; no new nephrons are formed after 34 to 36 weeks gestational age.

FIGURE 14. A, The relationship between birth weight and total glomerular number among all cases that includes infants, children, and adults. Number of glomeruli versus birth weight (○); number of glomeruli versus birth weight regression (---); 95% regression confidence interval (---); regression prediction interval (----). The regression coefficient predicts a gain of 257,426 glomeruli/kg increase in birth weight ($r = 0.423; P = 0.0012; N = 56$). Reprinted from Hughson et al. Fig. 4 with permission from Elsevier. B, Relationship between glomerular number and glomerular volume. Reprinted from Hughson et al. Fig. 6 with permission from Elsevier. Copyright Elsevier, Amsterdam, Netherlands. All permission requests for this image should be made to the copyright holder.

that glomerulogenesis can continue up to 40 days of life postterm in premature babies but only 1 nephron generation is formed per month rather than the 3 to 4 generations per month in the later stages of a normal gestation. Very premature infants also have reduced renal function. Kandassamy et al. found that babies born <32 weeks when studied at term corrected age (preterm age plus extrauterine age) compared with term babies have a lower glomerular filtration rate. They also have a smaller kidney volume, a surrogate for nephron number.

There are many other causes of oligonephronia which includes genetic factors, ethnicity, possibly sex, and even height. Recently, it has been shown that United States Caucasians and Australian Aborigines have much larger range than Caucasians. Both groups have average nephron numbers that are much greater than Australian Aborigines. Japanese have been found to have smaller kidneys than United States Caucasians at autopsy, presumably due to low nephron number which may partially explain their higher incidence of hypertension. Hoy et al. found that males have 9% to 12% more nephrons than females. Curiously, taller individuals have been shown to have more nephrons than shorter individuals with an increase of >28,000 glomeruli per centimeter increase in height.

Oligonephronia and the Fetal Origin of Essential Hypertension

Twenty-three percent of American adults develop essential hypertension which places them at risk for CKD. Although the pathogenesis of hypertension is heterogeneous, the kidneys appear to be the primary culprit in many cases. Studies of transplant patients have shown that when a normotensive recipient receives a transplant from a hypertensive donor he/she is more likely to develop hypertension than a recipient who receives a kidney from a normotensive patient. Conversely, a hypertensive recipient who receives a kidney from a normotensive patient is more likely to become normotensive than if he/she receives a kidney from a hypertensive donor.

In 1988 Brenner et al. postulated that essential hypertension in many patients may result from reduced nephron endowment. They argued that low nephron number results in a decrease in total glomerular filtration surface area, that leads to elevated glomerular capillary pressure and hyperfusion injury, that culminates in glomerulosclerosis. The Brenner hypothesis of an inverse relationship between nephron number and hypertension has been confirmed in multiple studies.

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controls. In addition to hypertension and CKD, the diminished renal reserve of low nephron numbers may negatively affect the renal outcome when other primary renal diseases are superimposed. This includes not only potentially progressive diseases such as IgA nephropathy, focal segmental glomerulosclerosis, and autosomal dominant polycystic kidney disease, but diseases generally regarded as not progressive such as minimal change disease.106–113

GLOMERULAR HYPERTROPHY AND CHRONIC KIDNEY DISEASE

The hypertensive diathesis of low nephron number and risk of CKD is associated with nephron hypertrophy. Nephron hypertrophy is regarded as an indication of adverse glomerular hemodynamics and maladaptation due to the stress of low nephron number. The resultant decrease in total glomerular filtration area leads to glomerular hypertension, hyperfiltration, and nephron enlargement that culminates in nephron sclerosis. Numerous studies have demonstrated an inverse correlation between nephron number and glomerular volume in normal adults, premature infants and small for gestational age/growth retarded infants, and in ethnic groups with high incidences of hypertension and CKD such as Native Americans, African Americans, and Australian Aborigines (76 to 83, 85 to 88, 92, 93) (Fig. 14B). Large glomerular volume is also seen in other conditions associated with elevated risk of CKD such as diabetes mellitus, smoking, gout, and obesity114–117 (Table 9).

RENAI HYPOPLASIA: AN CONTEMPORARY PERSPECTIVE BASED UPON HISTORICAL REVIEW AND THE AUTHORS’ PERSONAL EXPERIENCE

Our understanding of renal hypoplasia has evolved considerably since the definitions were first proposed many decades ago. Simple hypoplasia and oligomeganephronia as described by Rubenstein and colleagues,6–8 restricted the diagnosis to the most extreme degrees of nephron deficit such that presentation in childhood was inevitable in those with bilateral disease. Although, the current definitions of hypoplasia remain as originally proposed, in practice, more relaxed definitions are now often employed that accommodate the anatomic continuum in number of renal lobes, number of nephron generations and absolute nephron numbers. This is in accord with dictionary definitions of the general term, hypoplasia, which are not restrictive. For instance, in the Merriman-Webster dictionary hypoplasia is defined as “a condition of arrested development in which an organ or part, remains below the normal size, or in an immature state.”118x The degree of reduced size is not definitional.

Even with the strict original definitions of renal simple and oligomeganephronic hypoplasia there is a spectrum of lobar reduction from 1 to 5 lobes, and a broad range of the resultant nephron deficit. Interposed between the extreme degrees of nephron deficit of classic simple and oligomeganephronic hypoplasia and “normal” nephron numbers of 900,000 to 1,000,000, are milder degrees of clinically important nephron deficiency. For instance, nephropathologists on occasion encounter an adolescent whose kidneys are significantly smaller than normal (for instance 7 to 9 cm) presenting with proteinuria and/or renal insufficiency. A biopsy may show marked nephron enlargement with normal histology excluding atrophy as a cause for small renal size and renal impairment. Although the kidneys are larger than classically defined for hypoplastic kidneys, the patient has clinical (proteinuria and/or renal insufficiency) and has biopsy (nephron hypertrophy) features associated with reduced nephron mass. The anticipated renal prognosis is progressive renal disease. Patients with this scenario merge with the lower end of the oligomeganephronia spectrum, such as those with <700,000 nephrons, in which hypertension and CKDs are inevitable, but delayed until adulthood unless additional stress or renal injury is imposed. This anatomic continuum of kidney size and nephron number defy specification of a diagnostic threshold for renal hypoplasia since the consequences of a nephron deficit may present in a neonate, infant, adolescence, or be delayed until adulthood dependent upon nephron endowment.

The 3 classic forms of hypoplasia, segmental, oligomeganephronic and simple, have in common a reduced number of renal lobes that implicates early ampullary bud abnormalities in development. The finding that several genes important in ampullary bud arborization are associated with renal hypoplasia in humans and experimental demonstration in animals, and that mutation of these same genes enhance ampullary bud apoptosis and reduces ampullary bud branching leading to low nephron number, supports this postulate.107–74,119–121 Reduced ampullary bud branching may also be associated with cortical hypoplasia in otherwise normal-appearing lobes although premature cessation of nephrogenesis could also be primary, especially in the intrauterine causes.

Segmental hypoplasia differs from simple hypoplasia and oligomeganephronia in that there is nearly complete lobar failure of 1, or more lobes, with normal, or near normal, development of most other lobes. Although nephrogenesis is lacking in the hypoplastic lobes rudimentary medullary differentiation is present indicative of limited ampullary bud activity. The seemingly normal-appearing lobes, however, may not completely escape ampullary bud injury since some lobes demonstrate varying degrees of cortical hypoplasia with reduced nephron generations. Interestingly, in several closely related ampullary bud-associated developmental defects such as vesicoureteral reflux, ureteral ectopia, and urethral valves, cortical hypoplasia may also occur.10–62

The main anatomic difference between simple hypoplasia and oligomeganephronic hypoplasia is the presence or absence of nephron hypertrophy. However, this definitional difference may be a matter of circumstance, or timing, rather than a fundamental difference in the disease process. The scattered reports of bilateral simple hypoplasia are often in a neonate or very young infant at autopsy.1–6,53–56 Should these patients have survived longer; nephron hypertrophy due to maladaptation to low nephron number may have developed, thereby, qualifying as oligomeganephronia. In addition, nephron hypertrophy was usually not addressed these reports since most cases occurred before

| TABLE 9. Causes of Nephron Hypertrophy |
|----------------------------------|
| Oligonephronia                  |
| Oligomeganephronia             |
| Single kidney                  |
| Diabetes mellitus              |
| Obesity                        |
| Hyperuricemia/gout             |
| Cyanotic congenital heart disease |
| Chronic kidney disease, nos    |

nos indicates not otherwise specified.
the description of oligomeganephronia in the late 1960s and 1970s.

The most important type of renal hypoplasia because of its prevalence is oligomeganephronia although it is not formally included in hypoplasia classifications. The anatomic basis for many causes of oligomeganephronia are not known, that is, how kidneys in the lower quartile of nephron numbers relate to simple, oligomeganephronic, and cortical hypoplasia. A reduced number of renal lobes, a reduced number of nephron generations, or a combination, must be present since these are the only mechanisms in which low nephron numbers can occur. Unfortunately, the number of renal lobes or nephron generations in oligomeganephronic kidneys were not addressed in studies of nephron quantification.15-80 These features may not have been of interest to the investigators, or the quantification techniques may not have allowed determination of renal lobe number or performance of radial glomerular counts.

Maternal and intrauterine causes of oligomeganephronia are particularly of concern on a global scale as previously discussed. The magnitude of genetic contribution to oligomeganephronia has yet to be defined. Although several genes have been associated with small kidneys and renal hypoplasia, many other genes may ultimately be described. Many patients with a genetic cause would not qualify for the classic definition of simple hypoplasia or oligomeganephronic hypoplasia, but they have smaller kidneys than normal and many have nephron hypertrophy, features know to predispose to hypertension and CKD.

In summary, the initial descriptions of a disease entity invariably identify the most severe cases. Establishing a diagnostic threshold for a disease is often problematic, somewhat arbitrary and may become a moving target. Such is true for renal hypoplasia. Many other genes may ultimately be described. Many patients with a genetic cause would not qualify for the classic definition of simple hypoplasia or oligomeganephronic hypoplasia, but they have smaller kidneys than normal and many have nephron hypertrophy, features know to predispose to hypertension and CKD.

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