Renal obstruction is well recognized as causing renal dysfunction and can be reliably repaired, so why is there still a fuss about UPJ obstruction sufficient to prompt many laboratories, particularly Dr. Chevalier’s, to invest significant time and effort in trying to define this common entity [1]? The crux of this issue involves the many neonates with renal dilation, usually detected prenatally, who have no obvious clinical problems and seem to grow and thrive. While we know that some might have demonstrable deterioration of renal function over time, we clearly do not know who these children may be. The controversy regarding congenital obstructive uropathy remains lively and shows no sign of being readily resolved [2]. Two camps have emerged in the ongoing debate, the “watchers” and the “fixers.” The “watcher” assumes that the incidence of renal functional deterioration can be accurately measured, promptly detected, and corrected with specific intervention in these children [3, 4]. The “fixer” feels that renal deterioration is slowly ongoing, inaccurately measured, and by the time intervention is undertaken, may be irreversible to some degree. These different perspectives seem to follow some cultural and institutional lines, but are often quite unpredictable. This paper attempts to shed further light on this murky debate.

Broadly put, this paper helps us recognize the spectrum of hydronephrosis and obstruction. The relationship between the degree of obstruction and its consequences is not necessarily linear, and there may be a threshold of impact below which the kidney can maintain a homeostatic compensation without deterioration, albeit for an indeterminate time. While we all recognize the presence of that spectrum, the relationship to the impact of obstruction on the kidney is less well understood. It is also clear that obstruction, which may not appear to be very severe, can yet produce abnormal development and loss of function in the developing kidney. Glomerular loss is not a trivial issue and must be viewed as a high-risk occurrence with obstruction. This paper also identifies possible potential mechanisms for renal functional loss. These observations offer potential for both diagnosis and therapy.

Is it appropriate to simply accept this paper as a reflection of the infant with asymptomatic UPJ obstruction? Several concerns should be considered in the interpretation of this paper. The critical question is whether this model is relevant. There have been many models of urinary obstruction, and all have limitations. This model is in an early neonate in whom nephronogenesis is ongoing. The assumption is that this is not markedly different, in terms of renal response, to the fetal kidney with presumably slowly progressive obstruction. Even when the kidney is still developing nephrons, after birth it has become active in the renal work of filtration and homeostasis, which the fetal kidney does not need to do while the placenta is healthy; therefore, its responses to obstruction may be distinct. This obstruction is rather abrupt in contrast to naturally occurring obstruction. This obstruction stays fixed, which might be the human pattern, but is not really known. It has been argued that the technique of burying the ureter in the psoas [5] is a more realistic method of obstruction in that it “grows” with the animal. We do not know if this is the actual case in humans. This model shows apparent progressive hydronephrosis, with increasing apparent renal functional loss over time. This is certainly logical and intuitive, but it is uncommon to see increasing hydronephrosis in patients with severe unilateral hydronephrosis. Progressive hydronephrosis may be a very different entity in this animal and may explain the observed results, but may not apply to many humans. The observation of somatic growth impairment in the obstructed animals is also challenging to interpret, as this is not an observed occurrence in human. The authors suggest the possibility of subtle tubular dysfunction, leading, perhaps, to acidosis, and indeed this might be the case, assuming the rodent is more sensitive to these changes than the human. Tubular loss is indeed suggested in this experiment, and has been identified in human studies as well [6]. This hypothesis raises the important question of whether human unilateral obstruction can induce tubular dysfunction that is not readily measured using current clinical studies, such as radionuclide renography. This may cause dysfunction, which, while compensated for during childhood, may become a clinical problem with time. Broadly viewed, the model is imperfect, but more perfect than most others. It focuses on what is clinically relevant, which is high-grade unilateral renal obstruction early in development. Identification of a threshold effect of obstruction on function is a critically important concept that
has direct clinical bearing, as well as suggesting pathophysiologic mechanisms. The observation of progressive functional loss, impaired growth, and development should send a strong message of caution to anyone considering observational management in these patients, although it cannot yet justify universal early surgical intervention. Only if we can identify those kidneys at risk of obstructive nephropathy will we be able to rationally select those for intervention.

Identification of the specific mechanisms of congenital obstructive nephropathy offers the potential to interrogate those mechanisms for more precise diagnosis and prognosis. Further, manipulation of those mechanisms may ultimately permit therapeutic interventions more specific than simple surgery. Adjunctive therapy with surgery might also be a possibility if the alterations in the regulation of growth and development can be reversed.

What direction should future investigation of congenital obstruction take? The true impact of putative mechanisms can only be confirmed by direct manipulation, either inhibition of the mechanism, or specific induction of the mechanistic pathway to produce the anticipated functional or developmental outcomes. Inhibition may be produced as simply as with surgical decompression, and the putative pathophysiologic pathways should be halted if they are of significant impact. Pharmacologic or genetic inhibition of mechanisms can provide mechanistic insights, as well as therapeutic potential. Translation to clinical practice will likely involve identification of biomarkers that predict functional and developmental alterations, either ongoing or potential [7]. The best markers will be those which are directly related to the pathophysiologically relevant mechanisms, and which are not diluted by the contralateral kidney. In all likelihood, these will be found in the urine, but serum markers should be considered as well. It is possible that the contralateral renal response may be an accurate biomarker of the condition of the obstructed kidney; markers of accelerated growth or compensatory mechanisms may prove to be useful. As with so many conditions being managed today, asymptomatic congenital obstruction can be easily diagnosed, but determination of the patient at real risk remains an obstinate challenge. Models of these processes that permit identification of patterns and mechanisms of effect, such as this mouse model, are the best tools for eventually permitting rational management decisions regarding risk.

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