E Pluribus Unum: The Riddle of Focal Segmental Glomerulosclerosis

By Alain Meyrier

A recent consensus conference proposed a new classification for focal segmental glomerulosclerosis (FSGS). Five patterns have been defined: FSGS not otherwise specified, perihilar variant, cellular variant, tip variant, and collapsing variant. In light of the multiplicity of classification schemes in use, the promise of a rational and uniform scheme for FSGS pathology is most welcome. This approach has worked extremely well for the classification of lupus nephritis. It does not necessarily mean, however, that this new classification scheme will help to select treatment protocols according to histopathologic subsets of FSGS. In fact, one renal biopsy examination may show multiple variants and this classification, despite many merits, still lumps categories that should be split and splits categories that should be lumped together. It has become clear that despite its histologic diversity FSGS begins as a podocyte disease that progresses from a cellular to a scar lesion. Recent years have brought about astonishing insight into the complex molecular array of proteins forming the slit diaphragm between podocyte foot processes, a narrow space essential for restricting glomerular permeability to albumin. Concentrating on the podocyte rather than on the glomerular tuft is helpful for abolishing the classic distinction between primary versus secondary forms of FSGS, a distinction that crumbles away with each new evidence of genetic, ischemic, or viral etiologies of FSGS, despite similar lesions. In fact, recent studies focusing on the podocyte changes that occur in various subsets of FSGS have unraveled the striking phenomena of podocyte dedifferentiation and transdifferentiation along with differential expression of cyclin-dependent kinase inhibitors. Interestingly, the latter showed that expression of cyclin-dependent kinase inhibitors p21 and proliferation marker Ki-67 are the same in cellular FSGS, collapsing glomerulopathy, and human immunodeficiency virus–associated FSGS. Taken together these findings lead to a reassuring unitary interpretation of the pluralistic appearance of FSGS by histopathology. Clearly, further studies of the podocyte will lead to improved understanding of FSGS and to improved classification schemes that are grounded in molecular understanding of glomerular injury and that will guide the clinician in the choice of treatment and prognosis.

IN 1735, LINNAEUS (1707-1778) published “Systema Naturae,” a survey of all world plants and animals that provided for the first time a standardized nomenclature for plant and animal species.1 Flowering plants were identified by the number and arrangement of their floral elements, stamens, and pistils, as well as by their stems, leaves, fruit, and seeds. Confronted with the same endeavor of classification, renal pathologists over the past century have evolved increasingly sophisticated and thoughtful classification schemes for the diseased glomerulus. One of the most difficult classification problems has been focal segmental glomerulosclerosis (FSGS). As indicated by its name, the recognition and classification of FSGS depends on the appearance of the flowers (glomerular tufts) composing the bouquet (the renal biopsy sample). The glomerular capillary tuft emerges from the vascular hilum (Latin, meaning "little thing, trifile") that was borrowed from botany in which it denotes the mark on a seed produced on separation from its funicle or placenta. Thus, the glomerular tuft is more a fruit than a flower.

How many apples do you have to examine to be able to make a firm statement that there are rotten apples in the barrel? It is perfectly possible that one apple would be sufficient. By contrast, it might be necessary to examine a good many apples if none showed evident spots—although the skilled pathologist will examine the leaves (tubules) for clues of chronic injury as well. Further, it has been shown by using serial sections to reconstruct the entire glomerular tuft that what appears to be focal glomerulosclerosis is distributed more widely among lobules and among glomeruli than shown by conventional microscopy.2,3 Thus, an adequate number of glomeruli, including juxtamedullary glomeruli, is critical to excluding a diagnosis of FSGS.
The human glomerulus is made of 5 to 7 lobules, each one vascularized by its own afferent arteriole. Considering that segmental scarring affects some lobules and spares others, and reason telling us that the same blood conveys the offending factor(s) to all of the lobules, one is at a loss to understand why FSGS is not distributed evenly within the whole tuft. One could hypothesize that the segmental character of lesions can be explained by a circulating factor with a stochastic response by podocytes, or alternatively by viral infection affecting progressively an increasing number of podocytes with passing time. Because collapsing variants of FSGS are not segmental and focal, but affect the whole tuft and usually most glomeruli, the offending process at work in collapsing glomerulopathy might be the same, although much more rapid than in segmental forms, and characterized by massive simultaneous insult to the whole of the podocyte framework.

A recent consensus meeting gathered renal pathology authorities to lay out a new classification of FSGS, as elegantly described by D’Agati in another article in this issue. Five main light microscopic patterns of FSGS have been defined, including FSGS not otherwise specified, perihilar variant, cellular variant, tip variant, and collapsing variant. Although the new classification system for FSGS clearly is needed and has considerable appeal, the daring renal clinician is tempted to raise the standard of revolt. I will lay out my arguments as to why this classification, despite many merits, still lumps categories that should be split and splits categories that should be lumped together. We need to remember that a classification scheme is a hypothesis, and that hypotheses are not right or wrong, but more or less useful. It this instance, use can be defined as useful for clinical management and useful for asking research questions. Therefore, I probe the use of the classification for idiopathic FSGS.

It has become clear that FSGS begins as a podocyte disease. The glomerular podocyte, a highly differentiated octopus-cell covering the outer aspect of the glomerular basement membrane, is essential to maintain the architecture and function of the tuft. The slit diaphragm of the podocyte, in which tentacles of 2 neighboring podocytes meet, plays a key role in barring the egress of plasma proteins from the capillary lumen. As recently as 1995, we knew only that the slit diaphragm included the zona occludens (tight junction) protein ZO-1. In the past few years, there has been an astonishing increase in the complexity of our understanding of the protein architecture of the slit diaphragm, which now are known to include nephrin, NEPH-1, P-cadherin, and FAT, and these proteins in turn interact with podocin, catenin, and CD2-associated protein. NPHS2 was identified as a gene whose mutations caused autosomal-recessive, steroid-resistant nephrotic syndrome. The gene product, podocin, associates with CD2AP and with nephrin itself. Acquired or inborn defects of one, and maybe any of these proteins, leads to massive albuminuria, flattening and fusion of the foot processes, and podocyte injury. Some of these hereditary conditions may be expressed late in life, leading to familial forms of FSGS that are no longer considered idiopathic (as the terra incognita of idiopathic FSGS gradually shrinks in the face of improved maps). Acquired conditions also lead to podocyte injury. These include mechanical distension, hyperfiltration, toxic substances such as heroin, circulating factors that induce relapse on a transplanted kidney, renal ischemia, nephrovasculopathies, viruses, as well as various other glomerulopathies.

This unity is reassuring intellectually, but a question remains: Should the various appearances of FSGS described by pathologists really lead the clinician to altering his therapeutic strategy as, for instance, in lupus nephritis? One problem with the classification of idiopathic FSGS into 5 variants is that one renal biopsy examination may show multiple variants. Indeed, in the situation of a transplant nephrectomy in which hundreds of glomeruli are available, nearly all variants can be seen, including cellular, collapsing, and perihilar sclerosis. Thus, we need to think very carefully about whether each variant possibly can have a precise and distinct pathogenesis and implied prognosis. This problem is compounded when a diagnosis is made on the basis of a single glomerulus from a sample of 4, 8, or 12 glomeruli in a typical renal biopsy sample. This conservatism might lead us to lump together all the variants of idiopathic FSGS, thus making from many entities, one entity (E pluribus unum).

The consensus conference on the classification of FSGS, whose approach is outlined in another article in this issue, considered that the prognosis of FSGS not otherwise specified does not depend
on the number of glomeruli involved or the extent of the lesions. This is not the clinician’s experience who usually bases prognosis on the extent of lesions shown by the pathologist. However, this might also indicate that owing to the focal nature of FSGS the biopsy sample may be misleading when it concerns a zonal part of the kidney that is more damaged than other, relatively preserved areas. By contrast, the amount of daily protein excretion is of paramount importance to predict a rapid course to end-stage renal failure, but in the worst cases of nephrotic syndrome relapsing on a renal transplant, massive proteinuria precedes the first light microscopic lesions by weeks if not months.

Another problem with the classification of FSGS is the apparent nonspecificity of the histologic damage patterns. It is notable that none of histologic variants of idiopathic FSGS are restricted to idiopathic FSGS, but rather appear to be nonspecific manifestations of glomerular injury that can be seen in secondary FSGS or indeed in other glomerular diseases. One can cite several examples. The perihilar variant is the classic lesion of hypertensive nephrosclerosis, especially in hypertensive patients of African descent. The cellular and collapsing variants have been associated with glomerular ischemia in renal allografts. Nadasdy et al studied 3 cases of collapsing glomerular changes in renal allografts that showed a zonal distribution of lesions associated with obliterator vascular changes. They suggested that the morphologic pattern of collapsing glomerulopathy in renal allografts may not represent the same disease process as collapsing glomerulopathy in native kidneys.

Tip lesion is seen in minimal change nephropathy, including autopsy samples in which over 400 glomeruli were examined and other segmental sclerosis was excluded to confirm the diagnosis of minimal change nephropathy. I would be tempted to consider that this one-leaf clover will not keep its individuality among the various subsets of FSGS.

One of the most useful aspects of the proposed FSGS classification is the attention that it gives to the cellular and collapsing variants. Recent work has made these intriguing FSGS variants for what they may teach us about pathogenesis of FSGS. I will propose that it may be more useful, for research and clinical care, to combine the cellular and collapsing variants. The cellular variant was first observed in 1970 by Churg et al in children, then by Velosa et al in 1975, and, finally, by Schwartz and Lewis in 1985, who gave it its name. The current definition requires the presence of at least one glomerulus with segmental endocapillary hypercellularity involving at least 25% of the tuft and causing occlusion of the capillary lumina, and the collapsing variant requires at least one glomerulus displaying capillary loop collapse. Thus, the distinction between cellular and collapsing FSGS rests not with cellular changes but with the feature of capillary collapse. Because the pathogenesis and importance of capillary collapse are unknown, it is not clear that this feature is sufficiently critical to create these subtypes. In both cellular and collapsing FSGS, the podocytes are (or can be) hyperplastic, swollen, and vacuolated. They undergo detachment from the glomerular basement membrane, manifest multinucleation, are shed into the urinary space, and pass down the renal tubule where these large, former visceral epithelial cells assume a round shape. Whereas podocytes generally are considered postmitotic cells incapable of dividing, it is very likely that in these forms of FSGS they do proliferate. Although the mechanism accounting for glomerular collapse is unknown, it is possible that it is caused by the pressure of crowding of Bowman’s space associated with proliferating podocytes, which can form an impressive pseudocrescent.

Recognition of the cellular and collapsing variants of FSGS has spurred a provocative line of investigation. Oriakwa et al published a remarkably prescient study, in which they used cultured rat glomeruli. Cells identified as being derived from podocytes were noted to change into macrophage-like cells as they migrated from the glomeruli. On further time in culture, podocytes lost the ultrastructural appearance of podocytes and certain immunohistochemical podocyte markers, and acquired morphologic and functional characteristics of macrophages. Oda et al were intrigued by the appearance of the large round cells that migrated from Bowman’s space into the tubular lumens in collapsing FSGS, and identified them as macrophage-like cells. Bariety et al examined renal biopsy specimens from patients with collapsing glomerulopathy and found that as podocytes were shed into Bowman’s space they underwent phenotypic transformation. Podocytes still attached to the
glomerular basement membrane and possessing a normal morphology expressed podocalyxin, complement receptor 1, and vimentin. Hyperplastic podocytes with a cobblestone-like alignment or those that were detached from the tuft had lost normal podocyte epitopes and acquired a macrophage-associated phenotype. This was followed by an elegant analysis by Barisoni et al35 who coined the term dysregulated podocyte, which well encapsulates the phenomena of dedifferentiation and transdifferentiation. Recently, Shankland et al36 studied cell cycle derangement associated with dysregulated podocytes (Table 1).36 Their findings were identical in cellular FSGS, collapsing FSGS, and human immunodeficiency virus–associated FSGS, suggesting a similar phenotype among these diseases.

FSGS recurring after renal transplantation adds further information relevant to our consideration of the relevance of histologic subtypes. Recurrent FSGS may exhibit multiple variants of FSGS, including cellular, collapsing, and the scar variants.23 These biopsy specimens are notable for the shedding of large round cells into Bowman’s space and their presence within the tubular lumens. Some podocytes, identified by specific markers (podocalyxin, synaptopodin, glomerular epithelial protein-1), detach from the tuft and drift free in the urinary spaces. Loss of podocalyxin, synaptopodin, glomerular epithelial protein-1, Wilms tumor-1 protein, and complement receptor 1 expression characterize the podocytes in the cellular variant and on the cobblestone-like epithelial cells that cover the scar lesions. In all 3 variants, podocytes express various cytokeratins not present on normal podocytes. Expression of macrophage epitopes, identified by specific monoclonal antibodies, is observed on numerous cells located at the periphery of the tuft or free in the urinary space. These cells express epitopes that indicate macrophage maturation, and express human leukocyte antigen–DR and CD16, which indicate macrophage cell activation. By confocal laser microscopy, cells in Bowman’s space and tubular lumens co-express podocalyxin and cytokeratin, podocalyxin and CD68, and CD68 and cytokeratin. Taken together, these observations strongly suggest that podocytes transdifferentiate into a cell type not typical of either adult or fetal podocytes. Another syndrome can occur after renal transplantation, de novo collapsing glomerulopathy, occurring in a patient without FSGS before transplant. Ischemia has been proposed as an etiology, owing to the zonal distribution of affected glomeruli and associated vascular changes.24–26 This association with ischemia is reminiscent of observations that FSGS may be associated with atherosclerotic renal artery stenosis16,18 or cholesterol crystal embolism.17

The issue of prognosis is critical to the clinician, and the prognostic use of the classification of idiopathic FSGS remains to be tested in a systematic way. Patients with collapsing FSGS often progress rapidly to renal failure, but in the report by Valeri et al37 3 patients enjoyed spontaneous remission, which is most unusual in any form of heavily nephrotic FSGS.38 In a series of 100 nephrotic FSGS patients, 43 with cellular FSGS and 57 with classic segmental scar, the cellular lesion was associated with a higher probability of end-stage renal disease. However, response to steroids was the only variable that predicted remission, and patients with both histologies were equally likely to enter remission.39

Recent publications suggest that viruses, including parvovirus B1921-22 and SV40,40 might initiate the chain of events leading to podocyte dysregulation and subsequent FSGS variants. Are there hopes that some day viral FSGS will be considered, similar to herpes zoster occurring decades after initial varicella infection, a resurgence of an infectious process amenable to remission with specific antiviral therapy?

In conclusion, I am confident that further studies of the podocyte will lead us to improved under-
standing of FSGS and ultimately to improved classification schemes that are grounded in molecular understanding of glomerular injury and that will guide the clinician in the choice of treatment and prognosis. For the moment, we must be cautious and consider whether the diagnosis of idiopathic FSGS (*E pluribus unum*) might be as far as the limitations of clinical science will allow.

Note. *E pluribus unum* (Latin meaning “Out of many, one”) is the motto of the United States of America and appears on its Great Seal. The motto was chosen by the Great Seal Committee in 1776, having been recommended by the French consultant and artist Pierre du Simitière.

REFERENCES

Macrophagic cells outgrowth from normal rat glomerular culture: Possible metaplastic change from podocytes. Lab Invest 75:719-732, 1996


