tations of the data and struggled in the discussion to find a biologic basis other than that individuals living in desert climates may become dehydrated. No study has shown increased blood viscosity in the low water drinkers or reduced blood viscosity in the high water drinkers. In fact, the relationship between blood viscosity and stroke is likely due to underlying issues of hematocrit and fibrinogen levels, but when one has the opportunity to speak to the press, caution may fly out the window, and claims that are not justified by the data arise. Although authors are entitled to their theory about the implications of their work, they are not entitled to conclusions beyond the data they have or justified in making lifestyle recommendations just because the "cameras are rolling."

Drinking large amounts of water cannot be recommended as a prevention of stroke, unless you also deal with the well-defined risk factors such as smoking, hypertension, high blood lipids, diabetes, and obesity. Drinking a few extra glasses of water can be harmful if it substitutes for really effective, established measures. Unfortunately, the combination of a microphone and/or a reporter and a notepad along with an investigator who has toiled in a laboratory for many years without public recognition can lead to "irrational exuberance."

Finally, if you publish an article that reaches the popular media, you are likely to encounter the celebrity expert injected into the discussion. One journalist wrote in regard to our editorial, "Whether the average human *needs* that much (water), many diet advisers—from the late Robert Atkins to Oprah Winfrey—firmly believe that drinking extra water helps people feel fuller and makes the body retain less fluid, even though some concede the benefit may be as much behavioral as metabolic." There is absolutely no rational basis for drinking more water to promote water excretion above that consumed. Dealing with Oprah Winfrey's opinions is more than most scientists can handle.

If you try to be cautious and highly circumscribed in discussing your results or hypotheses, then you will likely become enmeshed in a discussion that goes well beyond "the data," and if you happen to land on Australian talk radio, then be prepared for difficulty in understanding the dialect, particularly at 11:30 p.m.

Whether the public is well served by the interaction of the media and health information is quite unclear. The need for objective health information has been attempted by many groups, public agencies, and for-profit enterprises, but as long as the medical reporter is involved without a rigorous review of his or her pronouncements by health professionals with expertise in the specific topics under discussion, one is likely to see ongoing frustration and confusion about the validity of the information. Moreover, the media would be well served to rely on clinicians who understand the nature of research data and the limitations of both observational and experimental research studies. One encounters this kind of insight in major television network reporting, but the local evening news or the local newspaper is unlikely to have such resources. They would be better off concentrating on the weather.

DISCLOSURES

None.

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How Many Different Roads May a Cell Walk down in Order to Become a Fibroblast?

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Renal interstitial fibroblasts are an essential component of the kidney interstitium and presumably the main effector of renal fibrogenesis, a process responsible for pernicious interstitial deposition of matrix and eventual loss of organ function. The origin of these matrix-producing cells has been a matter of debate for a long time. As early as 1867, fibroblasts (they were called contractile cellular elements at the time) were thought to be descendents of migrating leukocytes.[1] This theory was widely accepted until 1970, when Ross *et al.* [2] proved in a very elegant set of experiments using parabiotic rats that fibroblasts are mostly of local origin. These fibroblasts were subsequently classified as type I (of three types) interstitial cells by Bohman[3] and were thought to be a relatively homogeneous cell population.

Today, we know that fibroblasts can be much more heterogeneous than previously thought.[4] Some preexisting, resident fibroblasts convert to myofibroblasts during fibrogenesis, the term myofibroblast implying the *de novo* expression of α-smooth muscle actin (α-SMA), whose expression is otherwise typically or physiologically confined to vascular smooth muscle cells. Immu-

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nohistochemical analyses of normal human kidneys (unlike rodent kidneys) suggest a small population of interstitial cells also express α-SMA constitutively.[5] In various forms of renal disease, the number of α-SMA–positive cells increases and correlates with declining renal function and outcome; however, *de novo* expression of α-SMA is not the only change during the transition from fibroblasts to myofibroblasts. Okada *et al.*[6] observed that not all fibroblasts *de novo* express α-SMA. Fibroblast-specific protein (FSP1) is another marker for fibroblasts,[7] and its expression correlated with outcome in a number of clinical studies and is thus of prognostic value.[8]

In recent years, it also has become clear that not all activated fibroblasts derive from resident interstitial fibroblasts. A number of groups have demonstrated a tubular origin for fibroblasts,[7,9] the most conclusive evidence coming from a study by Iwano *et al.* using lineage-tagged proximal tubular epithelial cells in a model of unilateral ureteral obstruction. That study demonstrated that up to 36% of all matrix-producing cells within the tubulointerstitial space may be of tubular epithelial origin, up to 12% of bone marrow origin, and the rest presumably of residential origin.[10] The contribution of local epithelial-to-mesenchymal (EMT) transition to the formation of fibroblasts may be smaller in other models[11]; however, that is a matter of continued debate.

Regarding the potential bone marrow origin of fibroblasts, Roufosse *et al.*[12] used a transgenic mouse expressing both luciferase and β-galactosidase reporter molecules under control of the promoter for the α2 chain of type I collagen and identified a mean of 8.6% of α-SMA–positive cells being of bone marrow origin in renal fibrosis; however, these cells were negative for collagen and thus do not seem to participate in matrix synthesis. In analogy to an important source of fibroblasts in tumors,[13] Wiggins *et al.*[14] a number of years ago also proposed periadventitial cells as yet another possible source of activated fibroblasts; however, these cells at the time were not clearly characterized in the kidney.

In this issue of *JASN*, Zeisberg *et al.*[15] implicate endothelial cells as an alternative fibroblast precursors and add yet another way for the generation of fibroblasts to enter the fibrosis puzzle. Using three different murine models of fibrosis, the group found 30 to 50% of interstitial cells coexpress the endothelial marker CD31 with fibroblast/myofibroblast markers FSP1 and α-SMA. Interestingly, the level of endothelial-to-mesenchymal transition varied according to the model used. The unilateral ureteral obstruction model displayed a somewhat lower percentage of fibroblasts deriving from endothelial cells compared with the streptozotocin diabetes and Alport models, despite similar degrees of fibrosis, although the kidneys in the last two models had longer exposure to persistent injury.

To confirm these histochemical observations, the group also used endothelial lineage tracing by controlling the expression of yellow fluorescence protein with the Tie2 promoter. This promoter is endothelial cell specific and independent of any subsequent phenotypic changes. A significant number of interstitial FSP1 and/or α-SMA–positive cells coexpressed yellow fluorescence protein, confirming their endothelial origin, although we are not told the exact percentage of coexpressing cells. This current study in kidney builds on previous work by the same group showing endothelial-to-mesenchymal transition in cardiac fibrosis[16] and in the generation of carcinoma-associated fibroblasts.[17] In the latter study, endothelial-to-mesenchymal transition resulted in approximately 30% of FSP1 and approximately 12% of α-SMA–positive fibroblasts having an endothelial provenance.

What are the mechanisms of endothelial-to-mesenchymal transition? Similar, to EMT, TGF-β1 is implicated as a key inducer of the process. The transcription factor, Snail, again very comparable to what has been described previously in EMT, is required for TGF-β induction, at least in embryonic stem cell–derived endothelial cells.[18]

What are the consequences of the findings by Zeisberg *et al.*[15]? Is the fibrosis puzzle becoming more and more complicated? Not necessarily. We have learned in recent years that cellular plasticity is much higher than previously thought, be it for epithelial or, as now shown, for endothelial cells; in fact, traditional teaching is that endothelia-lining blood vessels and lymphatics are a specialized form of epithelia. Apparently, cells may walk down a number of different roads to become a fibroblast or myofibroblast. Zeisberg *et al.* have taught us that endothelial cells should not be overlooked in renal fibrogenesis. Moreover, blocking just one pathway of fibroblast activation will probably not suffice to halt progression of chronic renal failure. Many new inhibitors of vasculogenesis are available, and it will be interesting to see whether these inhibitors also inhibit endothelial-to-mesenchymal transition and thus delay or even stop renal fibrogenesis.

DISCLOSURES

None.

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See related article, "Fibroblasts in Kidney Fibrosis Emerge *via* Endothelial-to-Mesenchymal Transition," on pages 2282–2287.

Occult Hepatitis C Virus Infection in Hemodialysis

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Nosocomial transmission in dialysis units maintains a higher prevalence of hepatitis C virus (HCV) infection in patients on maintenance dialysis than in the general population.[1,2] HCV infection has a detrimental effect on survival in patients on maintenance dialysis[3] and after renal transplantation. In a recent meta-analysis of observational studies,[3] incorporating 11,589 unique patients on maintenance dialysis, the summary estimate for adjusted relative risk for all-cause mortality was 1.34 (95% confidence interval 1.13 to 1.59). The excess risk for death in HCV-positive patients was partially attributed to chronic liver disease with its attendant complications, particularly hepatocellular carcinoma and liver cirrhosis.

Routine serologic testing for anti-HCV antibody (twice a year) and periodic testing for alanine aminotransferase and γ-glutamyl transpeptidase were suggested for detection of transmission of HCV within hemodialysis (HD) units.[4] In the presence of elevated levels of liver enzymes, dialysis patients are usually tested for the major hepatitis viruses (hepatitis B virus [HBV] and HCV) with the differential diagnosis in this population including drugs hepatotoxicity, steatohepatitis, iron overload from repeated blood transfusions with ineffective erythropoiesis, and congestive heart failure. Three percent of patients on maintenance dialysis have elevated liver enzymes with unclear cause.[5]

A newly described entity that needs to be considered in this circumstance is so-called "occult HCV infection," which refers to detection of HCV viremia (HCV RNA) in hepatocytes or peripheral blood mononuclear cells in the absence in serum of conventional serologic or virologic evidence of infection. Support for existence of this entity comes from the observation that HCV, although a hepatotropic virus, also can replicate at extrahepatic sites, including peripheral blood mononuclear cells.[6] One report[7] described occult HCV infection in patients with intact renal function and chronic liver disease of unknown cause, 57% of whom had HCV RNA in their liver.

Information about occult HCV infection in patients on maintenance dialysis is limited.[8–10] Barril *et al.*[9] in this issue of *JASN* detected genomic HCV RNA in the PBMC from 45% (49 of 109) of long-term HD patients who had unexplained abnormalities in liver chemistries and were repeatedly anti-HCV antibody and serum HCV RNA negative. Antigenomic HCV RNA was found in 26 (53%) of 49 patients detected by strand-specific real-time PCR. These patients were followed up for a mean of 23.8 ± 24.5 mo; mortality was significantly and independently associated with age and occult HCV infection (odds ratio 3.84; 95% confidence interval 1.29 to 11.43; $P = 0.015$), according to their logistic regression model.

This is the first description of the epidemiology and potential significance of occult HCV infection in patients on maintenance HD; however, there are some caveats, including the relatively small number of patients studied and the seemingly striking association between occult HCV and mortality in these dialysis patients. This link between occult HCV and mortality (odds ratio 3.84) was much stronger

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