Comprehending Kidney Disease

A simple theory may explain a complex syndrome

By ROBERT POLLIE

For many people whose kidneys are damaged by disease or physiologic disorder, the prognosis is grim: a long deterioration of kidney performance ending in complete renal failure, at which point either dialysis or kidney transplantation is required to sustain life. Even if the illness that caused the initial injury abates short of total kidney destruction, the steady deterioration of the kidneys may well continue.

Why so many kinds of kidney injury should evoke the same pattern of nearly inexorable decline — known clinically as "progressive renal disease" — has been a mystery for decades. Now, a team of medical researchers has produced what is in effect a "unified field theory" of chronic renal failure, incorporating diverse experimental and clinical evidence. Barry M. Brenner, Timothy W. Meyer and Thomas H. Hostetter, all of Harvard Medical School and Brigham and Women's Hospital in Boston, summarized their theory in the Sept. 9 NEW ENGLAND JOURNAL OF MEDICINE.

The new theory proposes that all forms of progressive renal disease, whatever their initial causes, share a single major mode of injury: the chronic increase of blood pressure in the kidney's glomerular capillaries. The glomeruli are the tiny cup-shaped membranes through which fluid from the bloodstream filters into the urinary tract. When blood pressure in the glomerular capillaries is elevated, the membranes are forced to filter larger volumes of fluid. According to the theory, this increased filtration rate in turn leads to a disabling sclerosis, or hardening, of the glomeruli. And as more glomeruli are disabled, the theory asserts, a greater burden of blood flow (and with it, pressure) is shifted to the units still functioning, and they, too, succumb to sclerosis.

Such a cycle of destruction could be set in motion by any trauma that inactivates enough glomeruli to cause a harmful elevation of blood pressure in those that survive. Hence, the theory might account for the wide range of maladies — from streptococcal infection to systemic lupus erythematosus — that can precipitate progressive renal disease.

While the majority of these maladies may act indirectly to raise intrarenal blood pressure by causing initial kidney destruction, other factors may work directly to dilate glomerular blood vessels and thus increase blood flow. One of the theory's most striking contentions is that a normal component of the human diet — protein — does exactly this. Animal studies conducted by several groups indicate that high-protein diets can lead to sustained increases in intrarenal blood pressure.

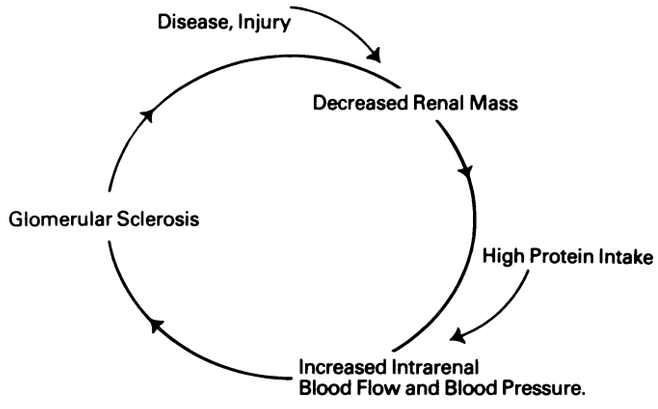
This hypothesis, if confirmed, could have a widespread impact on current medical practice. Brenner and other researchers have found that reducing protein intake can slow the progression of renal disease and prolong life in rats with injured kidneys. And four teams of medical researchers in Europe are currently testing this treatment in human patients. The researchers reported on their work at a meeting of the Third International Congress on Nutrition and Metabolism in Renal Disease held in September in Marseilles, France, and so far the results are encouraging: instituting protein restriction early in renal disease appears to slow the advance of kidney deterioration. Remarks Brenner, "The hope here is that we have a form of prevention, so kidney disease doesn't get to the point where you require dialysis."

Also of clinical significance is the idea that loss of kidney mass may bring about the destruction of remaining tissue. This suggestion has already prompted some doctors to reexamine the long-standing belief that donating a kidney for transplant does not lead to chronic impairment of renal function (SN: 9/25/82, p. 197).

Brenner and colleagues have gone so far as to suggest that the diet of present-day humans is poorly matched to the needs of our kidneys, which evolved in carnivores with lower-protein diets and less-frequent meals. Such a "fundamental mismatch between the evolutionary design characteristics of the human kidney and the functional burden imposed by modern *ad libitum* eating habits" could explain the fact that some glomerular sclerosis is observed even in healthy humans as they age, the scientists speculate. "We walk around with a form of intrarenal hypertension, and we lose a large population of our glomeruli," Brenner says. "We survive because we have some to spare." But this protein-induced loss could contribute to renal deterioration in cases where the amount of working kidney tissue has already been reduced (by disease, surgical removal, birth defects, etc.), Brenner contends.

While the new theory rests on a large body of data from many studies, some of its principal arguments are still hypothetical. The exact relationship between the loss of kidney tissue and the increase of blood pressure in remaining tissue, for instance, is not well understood. And scientists are uncertain about the link between intrarenal blood pressure and glomerular sclerosis. "It's a major theory — an important new approach," comments Nancy Cummings of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, "but many of the ideas still need to be tested." She adds that "much of the theory is based on work that was done with animals, not humans."

Whatever its uncertainties, the theory has attracted a great deal of attention in the medical community. In the week following publication of the NEW ENGLAND JOURNAL OF MEDICINE article, Brenner was deluged with letters and phone calls from physicians — "most of them enthusiastic about the work," he reports. □



Proposed scheme for the initiation and progression of renal disease.

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