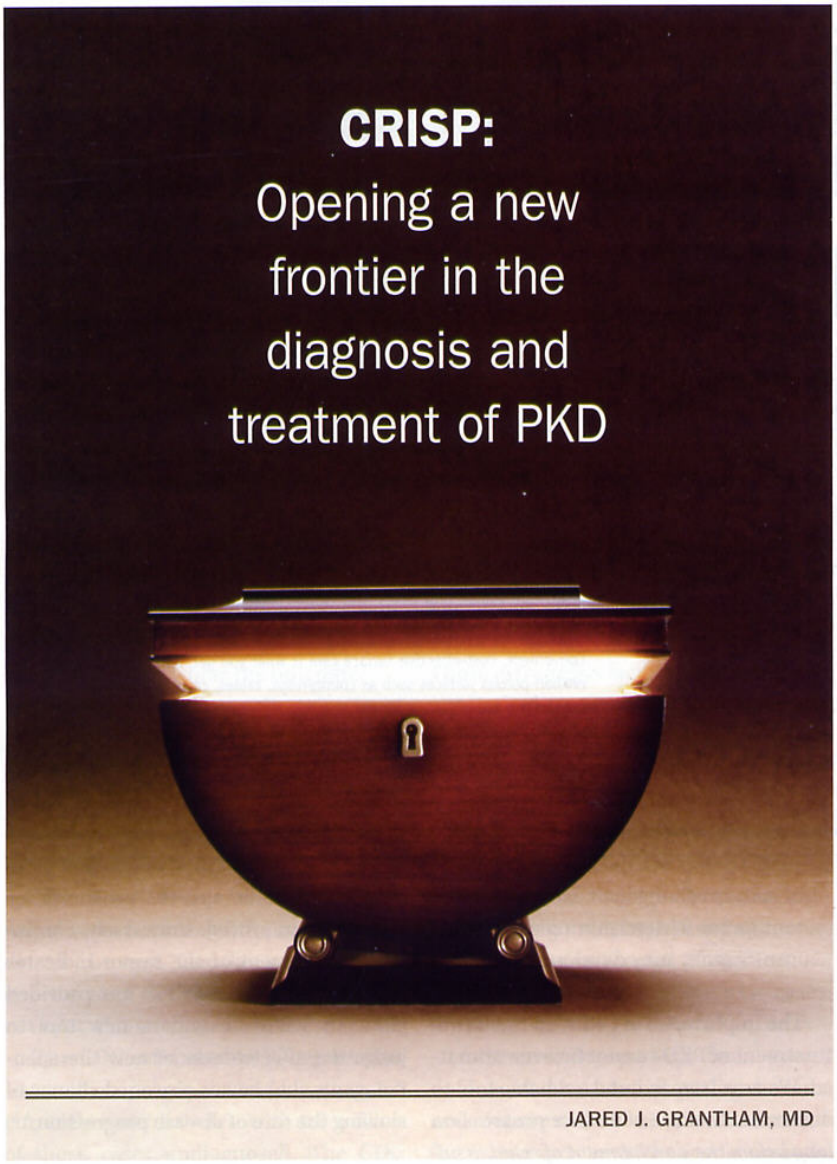
CRISP: Opening a new frontier in the diagnosis and treatment of PKD



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AUTOSOMAL DOMINANT POLYCYSTIC kidney disease (ADPKD) is characterized by the development within individual renal tubules of microscopic cysts that enlarge as the disease progresses. The cysts ordinarily develop in a tiny fraction of the kidney tubules and increase in some cases to fluid-filled masses as large as grapefruit. Consequently, the size of the kidney will be determined by the extra volume contributed by the cysts in addition to the volume contributed by the normal tissue.

Studies conducted over the last 20 years have provided circumstantial evidence to indicate that the disease progresses at an uncharacterized pace throughout the lifetime of the patient.[1] Moreover, at some point the cysts appear to trigger the development of renal insufficiency.

The Consortium for Renal Imaging Studies of Polycystic Kidney Disease (CRISP) is the first longitudinal study of individual patients with this condition supported by the National Institutes of Health. It was designed specifically to determine the extent to which renal enlargement is associated with the development of kidney failure. As reported in the May 18, 2006 edition of the *New England Journal of Medicine*,[2] 241 relatively healthy ADPKD patients with normal creatinine clearances were recruited and accurate measurements of total kidney volume and total cyst volume were made by magnetic resonance imaging annually for three years. Most of the patients remained in the study long enough to obtain useful data.

The accurate measurement of kidney and cyst volumes was important, because study designers hypothesized that the absolute volume of these parameters was a key factor in the development of renal failure. The results were striking in several respects.

- CRISP showed that patients with the largest kidneys upon entry to the study were the ones who had the fastest rates of renal enlargement over the course of the study. In other words, having large kidneys meant that the process had been going on at a relatively fast rate all of their lives.
- The initial size of the kidneys was found to predict the degree to which renal function would decline over the next three years. Designers had tailored the cohort, based on symptoms and signs,[3] such that about one-half to two-thirds would be expected to show evidence of a decline in GFR over the course of the study.
- The study proved that the net increase in overall kidney size was due to the net increase in cyst volume and not to unidentified factors.
- Repeated measurements in the same subjects proved that kidney enlargement is a continuous process. Until this, physicians were unsure of the growth rhythm of kidney enlargement.
- Curiously, in most of the patients, both kidneys increased in size at approximately the same rate. Scientist think this indicates that the rate of growth of individual cysts within a patient's kidneys may be coordinated, but just

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how remains to be determined.

- Finding that the absolute kidney volume ballooned by greater amounts each year has cued scientists to consider that cell growth, known to propel the increase of size in neoplasms, may also underlie the increase of total kidney size in ADPKD. That is not to suggest that ADPKD is a cancerous condition; rather cancer and ADPKD may share some of the same aberrant processes that contribute to increased cell growth.
- CRISP showed that individuals with the PKD2 genotype had smaller kidneys than those with the more common PKD1 genotype, and were less likely to demonstrate reductions in kidney function. Several previous studies had shown that patients with PKD1 genotype developed renal failure requiring dialysis approximately 15 years before those with the PKD2 genotype. The differences between PKD1 and PKD2 further support the hypothesis that the absolute amount of kidney volume increase is an important factor in determining when renal insufficiency may develop.

The importance of CRISP to the future treatment of PKD cannot be overestimated. We now have in hand a reliable tool to determine the rate of disease progression *long before the development of renal insufficiency.* Thus, nephrologists will soon be able to use a measurement of kidney volume to make an educated guess about how aggressive the ADPKD is in an individual patient. Moreover, this determination can be made in young patients long before symptoms appear or renal function is compromised. There is no other slowly progressive renal disorder where such an advantage for early therapy can be brought to bear.

It is now possible to determine if drugs or diets can slow the pace of this disease. Borrowing a strategy used by oncologists for many years, it is widely understood that if an x-ray shows that a tumor mass is smaller or fails to grow after radiation or chemotherapy, the prognosis for survival is improved. Conversely, continued enlargement of the tumor indicates a poorer prognosis. CRISP has provided clinician scientists with a new tool to judge the effectiveness of new therapeutic agents that have a reasoned chance of slowing the rate of disease progression.[4,5]

References

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