

Renal medicine

DISORDERS OF THE KIDNEY and related disturbances are being explored at the cellular and molecular level, and advances are moving apace.

Hypertension and the kidney. Kidney disease and high blood pressure are closely linked. Hypertension is multifactorial in origin and not previously considered a single gene disorder. However, although most people with high blood pressure do not have kidney disease, there have now been at least six single gene mutations linked to families with hypertension, all at sites of renal tubular proteins responsible for salt and water balance.¹ These genotype studies both lead us to novel causes of hypertension, and provide a potent source of likely targets for treating hypertension.

Delineation of the structures of salt transporters in the renal tubules, their alteration and genetic control has created an environment that suggests gene insertion and alteration may be possible and may be applicable to a variety of inherited renal transport disorders. Gene manipulation in such disorders as nephrogenic diabetes insipidus should not be far away. A wide range of genetic abnormalities have been identified in these rare familial salt-handling disorders, and they can be easily identified in babies within days of birth. Whether "salt-sensitive" hypertensive people who respond to salt restriction will be able to have their salt balance altered by genetic manipulation of the renal tubule remains unclear.

Patients with high blood pressure and proteinuria have a poor prognosis. Recent observations in such individuals have shown that the use of angiotensin-converting enzyme inhibitors and blocking agents not only controls blood pressure, but reduces proteinuria and improves prognosis by slowing the progression of the vascular dysfunction.² This is true in patients with diabetes and extends to patients with hypertension but no diabetes.

In acute (but reversible) toxæmia of pregnancy, studies are now unlocking the process that elevates blood pressure and damages the kidney (usually reversibly). Understanding this process, which involves vasoactive factors and the interleukins, will lead to a new approach to managing high blood pressure. The interrelationship between these vascular and immune reactive proteins has wider application in looking at the antecedents of "essential hypertension" and deciphering the reasons for end-organ (renal) damage.

Autosomal-dominant polycystic kidney disease (ADPKD). This disorder is responsible for 15%–20% of people on dialysis. Recent studies have recognised that people with ADPKD have normal kidneys at birth, and that the cysts develop later. ADPKD is being viewed as a neoplasm in disguise, so that expanding therapies for malignancy may affect the development of the cysts by reducing the rate of mutations. At the same time, recognition of the abnormal polycystins that may interfere with cell–cell interactions could provide a target for future interventions. Growth-factor tyrosine-kinase inhibitors are now entering trials in the management of malignancy that may be applicable in ADPKD.

Glomerulonephritis. There have been few developments in the understanding or management of



most causes of glomerulonephritis. Poststreptococcal glomerulonephritis persists only in disadvantaged communities with poor access to medical care. IgA nephropathy, probably the commonest cause of glomerulonephritis in our community, remains largely a mystery. There is increasing evidence that the IgA is abnormal in its chemical and spatial structure, and that its deposition triggers the inflammatory response.³ In the future, this may allow us to target the precipitant and prevent the disease.

Renal transplantation: allografts and xenografts. Organ replacement is the ideal management strategem for organ failure. Unfortunately, organ availability does not meet demand, and, even in successful transplants, chronic rejection remains a long term problem. The first issue has been approached by encouraging more family and unrelated "friends" to consider donations. The ethics of paying donors remain unresolved, especially in countries where payment provides a significant financial "win" for donors. It is illegal to pay for organs in Australia.

An alternative is xenografting, and an increasing understanding of the process of hyperacute rejection and the ability to manipulate the antigenicity of the donor tissue opens the way for "designer" organs.⁴ Xenografts may be possible in the next decade. Potential problems such as unknown infective agents, longevity of grafts related to the natural life of the animal donor, different physiological and pharmacological responses do not seem overwhelming in the short term — if organs can be manufactured for specific recipients then replacements may be possible with little problem.

Chronic rejection is also a major problem for successful allografts. Understanding the process of tolerance that occurs in some individuals should unlock this process and make possible treatments to facilitate tolerance. The two areas of xenografting and tolerance induction and maintenance will be closely linked and should see increased organ availability and longevity.

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