Therapeutic Use of Growth Factors in Renal Failure

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ABSTRACT

Polypeptide growth factors regulate kidney development, growth, and function and participate in processes of repair after renal injury. The use of one or more growth factors as therapeutic agents has been proposed in the settings of acute and chronic renal failure. In animal models of acute renal injury, the administration of epidermal growth factor, insulin-like growth factor I (IGF-I), or hepatocyte growth factor accelerates the restoration of kidney function and the normalization of histology post-acute renal injury and reduces mortality. The mechanisms by which the growth factors act in acute renal failure include the stimulation of anabolism, the maintenance of glomerular filtration, and the enhancement of tubular regeneration. IGF-I has been safely administered to humans with chronic renal failure. The growth factor enhances GFR and RPF in these individuals. Further studies will be required to establish a role for IGF-I or other growth factors as therapeutic agents for acute renal failure in humans and to define the utility of IGF-I as a medical therapy for chronic renal insufficiency.

Key Words: Epidermal growth factor, growth hormone, hepatocyte growth factor, insulin-like growth factor I, transforming growth factor-α

The administration of erythropoetin to patients with chronic renal insufficiency to correct anemia reflects an accepted use of a growth factor in renal failure (1). Similarly, the administration of growth hormone (GH) to children with chronic renal insufficiency to stimulate skeletal growth (2) represents the therapeutic use of a growth factor in renal failure because GH acts through insulin-like growth factor I (IGF-I). Both erythropoetin and GH/IGF-I are used in this setting to correct abnormalities that accompany the uremic state, but neither acts to correct the uremia itself.

A number of other growth factors exert actions directly in the kidney. Many of these agents are produced in renal tissue and participate as autocrine or paracrine regulators of metabolic, transport, growth, and repair processes. Others act as endocrine agents and interact with the kidney from the circulation (3).

Modifications of renal metabolism, transport, and growth underlie the processes that result in the repair of damaged kidney tissue after acute injury and the adaptations in renal function that allow for the maintenance of homeostasis in the face of reduced functional renal mass. Because alterations of renal growth factor expression occur in parallel with these modifications, it is suggested that one or more growth factors are key effectors of the processes and adaptations (3–6). Therefore, the pharmacologic use of growth factors in the setting of acute renal injury to accelerate regeneration or in the setting of chronic renal failure to enhance kidney function represents, in theory, a logical extension of the roles that these agents play in physiologic or pathophysiologic states. Unlike the administration of erythropoetin to correct anemia or GH to enhance growth, the successful use of growth factors to accelerate regeneration or to enhance kidney function would address directly the cause of the kidney failure itself.

The purpose of this editorial review is threefold: (1) to consider the rationale for the use of three polypeptide growth factors—epidermal growth factor (EGF), IGF-I, and hepatocyte growth factor (HGF)—as therapeutic agents for acute renal failure and to examine the experimental evidence that they may be useful in this setting; (2) to review data supporting the utility of IGF-I as an agent to enhance kidney function in chronic renal insufficiency; and (3) to discuss briefly directions for future investigations relating to the therapeutic use of growth factors in renal failure. Experimental data that have been generated in ani-
mals and in humans supporting the utilities of growth factors will be summarized. These topics will be discussed within the context of the biochemistry and the cellular and molecular biology of the growth-promoting agents.

**GROWTH FACTOR BIOCHEMISTRY CELLULAR AND MOLECULAR BIOLOGY**

**IGF-I**

IGF-I is a single-chain proinsulin-like polypeptide that is 70 amino acids in length. It circulates in tight noncovalent association with specific carrier proteins. The functions of the carrier proteins are incompletely defined. However, in vitro, one or another carrier protein has been shown to function as both an agonist and an antagonist for the biologic activity of IGF-I. IGF-I is a GH-dependent growth factor. Its levels in the circulation are regulated by GH, and it is produced in several tissues in a GH-dependent manner. The growth-promoting and anabolic actions of GH are thought to be effected by IGF-I (7).

The collecting duct is a major source of IGF-I production within the adult kidney (8). Both GH (9) and EGF (10) enhance IGF-I production at this site. IGF-I is also produced by glomerular mesangial cells in culture (11,12) and by developing rat kidney. Its production by the metanephros is essential for growth and development in vitro (13).

Six IGF-binding proteins have been identified (14). Most are synthesized within the kidney (4). Receptors for IGF-I are present in the glomeruli (11,12,15) and on the basolateral membrane of the renal proximal tubular cell (16).

**EGF**

EGF is a 53-amino-acid peptide. In adult mammals, EGF levels are highest in the salivary gland and second highest in the kidney. In humans, EGF was first purified from urine. The high levels in urine (5 \( \times 10^{-10} \text{M} \)) compared with blood (\( <10^{-12} \text{M} \)) suggest that the kidney is the source of urinary EGF (17).

EGF precursor proteins contain hydrophobic membrane-spanning regions that anchor them to plasma membranes. The portions that contain mature EGF are located extracellularly (18). Newly synthesized EGF precursors appear to be resistant to cleavage until they reach the plasma membrane. The precursor is biologically active. Therefore, cleavage is not necessarily aimed at generating active hormone, but at switching between two active forms, one that is membrane bound and a second that is diffusible (18,19).

Whereas the submaxillary gland rapidly processes prepro-EGF to the 53-amino-acid form, the precursor accumulates in the kidney. The distal tubule and medullary thick ascending limb of Henle’s loop are the predominant sites of EGF production within the adult kidney (17). Glomeruli, proximal tubules, medullary interstitial cells, and collecting duct all have EGF receptors (20,21). These receptors are present in the basolateral membranes of the tubular epithelial cells (22,23).

The developing rat kidney produces transforming growth factor-\( \alpha \), (TGF-\( \alpha \)) a member of the EGF family of growth factors that acts via the EGF receptor (19). The growth and development of the metanephros in vitro is dependent on TGF-\( \alpha \) (24).

Studies characterizing the localization of immunostainable EGF within the adult kidney show it to be localized to the luminal membrane of distal tubular cells under most conditions. The positive immunostaining probably represents prepro-EGF (17). The peptide must bind to receptors present in the antiluminal membrane of sensitive renal cells to exert biologic activity. Recently, it has been shown that a redistribution of EGF immunoreactivity occurs in the distal tubule in one condition under which its synthesis is enhanced—compensatory renal hypertrophy—such that it is present at both luminal and antiluminal membranes. Such a redistribution of precursor peptide might permit the cleavage of mature EGF from the basolateral membranes and the release of mature peptide into the renal interstitium, where it could interact with basolateral membrane receptors (25).

**HGF**

HGF was first identified in the serum of partially hepatectomized rats and was purified to homogeneity from rat platelets (26). The peptide is a heterodimer consisting of a 68-kd \( \alpha \)-subunit and a 34-kd \( \beta \)-subunit. It has a 38% homology with plasminogen but does not appear to be related to any other growth factor (27,28). HGF is produced by cells of mesenchymal origin, and its mRNA has been localized within the kidney to interstitial cells and macrophages located between renal tubules (29). The HGF receptor, present in renal membranes, is the product of the c-met proto-oncogene (30).

**GROWTH FACTORS AND ACUTE RENAL FAILURE**

**Rationale for Use of Growth Factors in Acute Renal Failure**

Ischemic renal injury in rat results in damage to the most distal (S3) segment of the proximal tubule and, in some instances, the medullary thick ascending limbs of the loop of Henle (31,32). Recovery is dependent on the ability of the tubular cells to regenerate and reline the damaged areas along the nephron. The rationale for the use of EGF, IGF-I, or HGF as therapeutic agents in acute renal failure is pro-
vided by observations that: (1) EGF (20) and IGF-I (16) bind to specific receptors in the proximal tubule and regulate metabolic (22,33) and transport processes (34) at this site; (2) EGF (35), and HGF (36) are mitogens for proximal tubule in vitro, and expressions of EGF (25), IGF-I (37), HGF (29), and the HGF receptor (30) are enhanced in kidneys undergoing compensatory growth; (3) expressions of IGF-I (38), HGF (39), and the HGF receptor (30) in the kidney are increased after acute renal injury in rats; and (4) both IGF-I (13) and the EGF-like peptide TGF-α (24) are essential for the growth and development of the metanephric kidney in vitro, a process that may be recapitulated by tubular regeneration postinjury. In addition, levels of EGF mRNA in the kidney (Figure 1) and urinary EGF fall precipitously after the induction of acute ischemic injury (40). This may result in a relative deficiency state for EGF. Alternatively, decreased EGF expression may be required for regeneration to proceed normally.

Of interest, levels of mature EGF peptide in the kidney have been reported to be increased after acute ischemic renal injury in parallel with diminished levels of membrane-associated EGF precursor (41). In addition, EGF immunoreactivity is detected in the proximal tubules after nephrotoxin- or aminoglycoside-induced renal injury (42,43). These findings considered together suggest that the production of the EGF precursor falls in the kidney after acute renal injury, but that the breakdown of preexisting EGF membrane precursor to mature peptide is enhanced. The mature peptide may bind to receptors in the proximal tubule and act at this site after acute tubular injury.

Growth Factors Accelerate Recovery From Acute Renal Failure in Rats

**EGF in Acute Renal Failure.** Humes et al. first reported that the administration of EGF postinduction of ischemic renal injury in rats enhances renal tubular cell regeneration and accelerates the recovery of kidney function postinjury (44) (Figure 2). Similar findings were reported subsequently by Norman et al. (45) and by us (46). We showed that, in addition to accelerating the restoration of normal renal function and improving histology, EGF reduces mortality in rats with ischemic renal injury. Coimbra et al. demonstrated that EGF accelerates renal repair in mercuric chloride nephrotoxicity (47), and Morin and coworkers showed that EGF accelerates repair in a model of gentamicin nephrotoxicity in rats (48).

Because EGF increases DNA synthesis in tubular cells postischemic injury (44) and postischemic injuries (47,48), it is proposed that the growth factor acts to accelerate normal regenerative and repair processes, resulting in a more rapid relining of the injured renal tubular epithelium and a shortened time to recover renal excretory function.

**IGF-I in Acute Renal Failure.** We have shown that IGF-I administered post–acute ischemic injury to rats accelerates the recovery of normal renal function (Figure 3) and the regeneration of damaged proximal tubular epithelium (Figure 4) and reduces mortality compared with vehicle (46). Similar findings were reported by Ding et al. (49).

Several explanations for the effectiveness of IGF-I postischemic injury of rats have been proposed. First, IGF-I increases the GFR in normal rats (50) and in rats postischemic injury (4) (Figure 5). The enhance-
Use of Growth Factors in Renal Failure

Figure 3. Levels of serum creatinine in rats with ischemic acute renal failure treated with vehicle or IGF-I. Ischemic ATN was induced at time 0. IGF-I was administered beginning 30 min postischemia (arrow). Data are expressed ±SE. Significant differences between groups (t test) are indicated by asterisks. Reprinted with permission (46).

Figure 5. Clearance of creatinine ($C_{\text{creatinine}}$) in rats treated with vehicle (VEH) or IGF-I postischemic injury. Administration of vehicle or IGF-I was begun 30 min postischemia (arrow). Data are means ±SE. $P$ values (t test) are shown for comparisons between vehicle- and IGF-I-treated rats. NS, not significant. Reprinted with permission (4).

ment of glomerular filtration could alter the course of acute renal failure, possibly by limiting the extent of injury due to obstruction of tubules by cellular debris. Second, IGF-I is a renotropic agent for the proximal tubule (see above). It enhances DNA synthesis in the renal cortex postischemic injury (51), as reflected by the increased incorporation of the uridine analog 5-bromo-2'-deoxyuridine (BrdU) in the nuclei of tubular cells (Figure 6). Third, IGF-I is an anabolic agent (3,4,14). It reduces protein breakdown and exerts a generalized anabolic action that results in the attenuation of weight loss in the setting of the

Figure 4. Photomicrograph of histologic sections stained with hematoxylin and eosin originating from kidneys of rats administered vehicle (Veh) or IGF-I after ischemic renal injury. Kidneys were obtained 7 days postinjury. Reprinted with permission (46).

Figure 6. DNA synthesis is enhanced by treatment with IGF-I beginning 30 min after acute ischemic injury. DNA synthesis is reflected by the incorporation of BrdU in the nuclei of renal tubular cells in the cortices of nonischemic rats or rats with acute ischemic injury administered vehicle or IGF-I. Mitogenic indices reflect the number of tubular nuclei staining for BrdU divided by the total number of nuclei examined. Relatively few nuclei in tubules from nonischemic rats stain for BrdU, reflecting low mitotic activity. The mitogenic index is increased significantly in rats with kidneys rendered ischemic compared with nonischemic animals and in rats with ischemic injury treated with IGF-I compared with rats with ischemic injury treated with vehicle. Data are expressed as means ±SE. Reprinted with permission (51).
catabolism that accompanies acute ischemic injury (46) (Figure 7).

In a clinical setting such as postsurgery of humans, acute kidney failure resulting from renal ischemia is usually diagnosed within a time frame of 24 h postinsult (52). The studies described above report the salutary effects of EGF or IGF-I administered to rats between 30 min and 5 h after renal injury. Although the results of these studies establish the potential for the use of growth factors as therapeutic agents for acute renal failure in humans, a more clinically relevant model would be helpful to advance our understanding of their utilities. Accordingly, we performed studies to determine whether IGF-I administered to rats 24 h postischemia or before the induction of renal injury accelerates the recovery of renal function and the restoration of normal renal cortical morphology.

In fact, IGF-I hastens the recovery of renal function and the restoration of normal cortical morphology in rats when administered 24 h post–acute ischemic injury. Furthermore, it ameliorates the course of renal failure and hastens the restoration of normal histology when administered before the induction of injury (53).

By 24 h posts ischemic injury, the damage to the proximal tubules is well established (53). The effectiveness of IGF-I administered at this time undoubtedly reflects, at least in part, its action to accelerate the regeneration of the proximal tubule. Additional evidence that this is the case is provided by the finding that DNA synthesis in renal cortical epithelia is enhanced 1 day after the administration of IGF-I at 24 h posts ischemia, as reflected by the enhanced incorporation of BrdU in the nuclei of cortical epithelial cells (53).

To provide insight into the mechanism by which pretreatment with IGF-I accelerates recovery from acute ischemic renal injury, we compared histologies in sections of kidney cortices originating from rats pretreated with vehicle or IGF-I obtained 24 h or 7 days postinjury. Cortices from the kidneys of all rats obtained 24 h postinjury were indistinguishable in appearance from one another, whereas at 7 days postinjury, cortices from IGF-I-pretreated rats were markedly improved in histologic appearance (53). These observations suggest that the extent of renal injury is not different between vehicle and IGF-I-pretreated rats and that pretreatment with IGF-I augments the regeneration of the renal cortex. However, it is possible that subtle differences in cell structure and function 24 h postinjury would not be detected by a comparison of gross histology. Therefore, these findings do not exclude the possibility that pretreatment with IGF-I is cytoprotective.

Whatever the mechanism of its action may be, a potential for the clinical use of IGF-I, a growth factor that can be safely administered to humans (see below), as a therapeutic modality in established ATN is clearly established. Furthermore, the potential exists for the use of IGF-I as a prophylactic agent if it is administered before events that might result in acute renal injury, such as surgery.

**HGF in Acute Renal Failure.** The effects of HGF administration to rats posts ischemia were examined in the model of acute ischemic renal injury used in our other studies (51). Compared with rats administered vehicle, rats administered HGF had significantly lower serum creatinine and BUN levels over the course of 7 days postocclusion (Figure 8), enhanced inulin clearances measured on Day 2 postocclusion, reduced mortality, and much less injury evident by examination of kidney histologies 7 days postinjury (51). The weight loss that occurs posts ischemic injury was not ameliorated by the dose of

**Figure 8.** Levels of serum creatinine (A), BUN (B), and body weights (C) in rats measured over time. Shown are levels in vehicle- (○) and HGF-treated (■) rats. Data are expressed as means ±SE. Reprinted with permission (51).

![Figure 8](image-url)
HGF we used (Figure 8), in contrast to findings with IGF-I (Figure 7). Therefore, HGF was not anabolic in this setting.

To determine whether HGF accelerates the regeneration of cortical tubular cells posts ischemic injury, we measured the incorporation of BrdU injected in vehicle and HGF-treated rats into regenerating tubular epithelia and compared it with BrdU incorporation in the cortical tubular epithelia of noninjured animals. Kidneys originating in noninjured normal rats incorporated relatively little BrdU in cortical tubular epithelia. In contrast, vehicle and HGF-treated rats all incorporated more BrdU than did noninjured animals. BrdU incorporation was significantly greater in both vehicle and HGF-treated rats compared with noninjured animals and was significantly enhanced by HGF compared with vehicle (51). Similar to our findings in acute ischemic injury, HGF-enhanced DNA synthesis in renal tubules of mice with mercurochloride-induced renal injury was reported by Igawa et al. (39).

It is possible that EGF, IGF-I, and HGF exert their salutary actions postinjury via different mechanisms. For example, IGF-I is anabolic in this setting (Figure 7), whereas HGF is not (Figure 8). If the mechanisms of action are different, the use of multiple growth factors may prove to be more beneficial than the use of any one growth factor. It may also prove useful to use agents in combination with agents that by themselves have no effect on recovery posts ischemic injury, but that may potentiate one or more actions of a given growth factor. An example of such an agent may be GH, which by itself does not affect the recovery of rats posts ischemic injury, but which has been shown, when used in combination with IGF-I, to potentiate the anabolic actions of the growth factor (54).

GROWTH FACTORS AND CHRONIC RENAL FAILURE

Rationale for Use of Growth Factors in Chronic Renal Failure

Anabolic and Growth-Promoting Actions of Growth Factors. One rationale for the use of growth factors in end-stage chronic renal failure is to reverse the catabolic state that accompanies this condition. GH has been administered to adults with chronic renal failure on hemodialysis and was shown to reduce urea generation and improve the efficiency of dietary protein utilization in these individuals. GH administration resulted in increased circulating IGF-I and the actions of GH in this setting are thought to be mediated via IGF-I (55,56).

Chronic renal insufficiency in children is accompanied by growth retardation. As discussed above, the administration of GH to children in this setting stimulates skeletal growth via the stimulation of IGF-I production (2). Children with chronic renal failure are not GH deficient. Therefore, the growth-promoting effect of GH/IGF-I in this setting represents a pharmacologic action.

Actions of Growth Factors To Enhance Kidney Function. The potential for the use of IGF-I as a therapeutic agent to enhance kidney function in the setting of chronic renal failure is based on clinical and experimental observations relating to the actions of GH on the kidney. O'Shea and Laysh have provided an excellent historical perspective of many of the studies (57), and a complete summary of the experimental findings within a historical context will not be repeated in this editorial review. In short, conditions of GH deficiency in humans and in experimental animals are associated with a reduction of kidney size, GFR, and RPF, and states of GH excess are associated with an increase in kidney size and enhancement of GFR and RPF. Therefore, hypopsomatropism results in both renal hypertrophy and hyperfuntion. In hypopsomatropotropic humans, the GFR is increased out of proportion to the increase in kidney weight. Furthermore, the reduction in GFR and RPF that occurs after hypophysectomy in acromegalic humans occurs more rapidly than the decrease in kidney size and is excessive relative to the decrease in kidney size. These findings indicate that, although changes in renal function may be explainable, in part, by the alterations in kidney size, there are probably other factors involved.

The actions of GH to increase kidney size and enhance GFR and RPF are not mediated by GH directly, but rather through IGF-I. One mechanism by which IGF-I exerts these actions is via rapid alterations of glomerular hemodynamics. In rats, an infusion of IGF-I decreases renal glomerular afferent and efferent arteriolar resistances and increases the glomerular ultrafiltration coefficient (58).

Given their abilities to increase GFR, the potential use of either GH or IGF-I as therapeutic agents in the setting of chronic renal failure has been suggested (57). However, early investigations into their utility were disappointing. For example, Haffner et al. found that GH had no effect on GFR in seven patients with chronic renal insufficiency, even though it was anabolic and the identical dosage increased the GFR of individuals with normal renal function (56). The administration of GH to children with chronic renal insufficiency and growth failure has been found to have no significant effect on renal function, despite its beneficial action to enhance somatic growth (2). The administration of IGF-I to humans (59) or to rats (50) with normal renal function increases the GFR. However, the administration of IGF-I to rats that had undergone one-third and two-thirds nephrectomy (50) or one and one-half nephrectomy (60) did not...
increase GFR compared with the administration of vehicle, despite effects to enhance growth and nitrogen balance.

It was suggested, on the basis of the evidence detailed above, that the uremic state is one of relative renal resistance to the actions of GH and IGF-I. The observations that levels of circulating immunoactive GH are elevated in uremia, whereas those of immunoactive IGF-I are normal, and the observation that IGF-I bioactivity is reduced in uremia (61) lend some credence to this hypothesis.

**IGF-I Improves Renal Function in Humans With Chronic Renal Failure**

To address the question directly as to whether humans with reduced kidney function are responsive to the renal effects of IGF-I, we administered IGF-I to four individuals whose baseline inulin clearances were 22 to 55 mL/min per 1.73 m² and evaluated its effect on inulin and p-aminohippurate (PAH) clearances and on kidney size. We showed that IGF-I increases GFR and RPF in these patients with moderate degrees of renal insufficiency (62) (Figure 9).

Our findings illustrate differences between the rat model and actual human disease. The reasons for the difference in response between rats and humans are unknown. It is possible that the model of chronic renal failure that we used in rats is not applicable to human renal disease, at least not to all human disease. In the “remnant-kidney” model of chronic renal failure, adaptations occur rapidly after renal mass reduction such that GFR increases by approximately 50% by Day 3 in the absence of IGF-I (50). We postulated that an increase in IGF-I produced by the remnant kidney is responsible for this adaptation and that exogenously administered IGF-I has no effect in the face of such an increase. We (63) and others (64) have shown subsequently that the IGF-I content of remnant kidneys is elevated, rendering plausible our postulate.

We have administered IGF-I to patients with end-stage chronic renal failure (65). As illustrated in Figure 10, IGF-I administered for 4 days in this setting increases the GFR and RPF. In fact, baseline inulin and PAH clearances were 10.6 ± 2.5 and 58.7 ± 12.0 mL/min per 1.73 m², respectively, in the first four patients we studied. After 4 days of treatment, inulin and PAH clearances were increased by 32 and 28% above baseline, respectively. It is clear that renal functional reserve remains, even with a severe loss of renal function, and that the potential exists to increase the GFR by medical means.

Unfortunately, the changes in renal function illustrated in Figure 10 were not sustained when IGF-I was administered to patients with end-stage chronic renal failure for a longer period of time. In addition, the side effects of IGF-I necessitated that the growth factor be discontinued in several patients (65). These side effects included the development of Bell’s palsy, gingival hypertrophy, and possibly, pericarditis. Other side effects encountered, such as nasal congestion and jaw pain, were relatively minor and did not require that IGF-I administration be stopped. In view of these potentially serious side effects of IGF-I and the observation that the changes in kidney function induced by the growth factor may be transient, caution is clearly advised relating to its use in patients with chronic renal failure. On the other hand, addi-
hypertrophy. Such a dual mechanism of IGF-I action could explain the clinical observations that suggest a dual effect of GH (see above).

One additional risk that could accompany the therapeutic use of IGF-I in chronic renal failure is that of glomerulosclerosis resulting from the hyperfiltration induced by this agent. Evidence that growth-promoting agents may be glomerulosclerotic comes from studies of rodent models of hypersomatotropism and models in which a reduction of functional renal mass is effected in normal and GH-deficient rats. Hypersomatotropic rats (67) and mice transgenic for GH (68,69) develop glomerulosclerosis. In contrast, mice transgenic for IGF-I with levels of circulating IGF-I no different than those in mice transgenic for GH do not develop glomerulosclerosis (68,69). This finding is consistent with the glomerulosclerotic action of GH in rodents being mediated via a mechanism other than its action to increase the synthesis and release of IGF-I. Additional support for the safety of IGF-I administration in humans may be derived from the observation that, in contrast to the case in rodents, glomerulosclerosis does not occur in acromegaly (70) and chronic renal failure is not a complication of hypersomatotropism in humans. In fact, as discussed above, patients with long-standing acromegaly manifest marked renal hypertrophy and have supranormal GFR, suggesting that the hyperfiltration that accompanies long-standing elevations of circulating GH and IGF-I in humans does not reduce renal function (71).

SIGNIFICANCE AND CONCLUSIONS

Acute renal failure in humans is the most costly kidney-related disease requiring hospitalization. The incidence of this condition is increasing. Despite many advances, the mortality rate for patients with acute renal failure has not changed in the last 40 yr (6). Strategies for the treatment of acute renal failure in humans are directed toward supportive care to permit regeneration to occur and toward acceleration of the pace of regeneration by the maintenance of good nutritional status (5). There exists a need for new therapeutic approaches that can speed recovery and reduce mortality. The use of growth factors could represent one such approach.

On the basis of the fact that it can be safely administered to humans with chronic renal failure (62) and data generated in rat models of acute renal injury, IGF-I might prove to be useful as a therapeutic agent for established acute ischemic, toxic, or drug-induced renal failure or as a prophylactic agent in the setting of events such as surgery that could result in compromised RBF. In addition, it may prove to be beneficial to administer IGF-I before the injection of radiographic contrast media to prevent compromise of renal function or at the time of renal transplantation.
to ameliorate the acute renal failure that occurs in this setting.

We have shown that humans with reduced functional renal mass are not resistant to the actions of IGF-I to enhance GFR, establishing the potential for the use of IGF-I as a pharmacologic agent for chronic renal failure. There is no effective drug therapy to enhance renal function in chronic renal insufficiency. Although much work remains to be done, and clearly caution is advised, our observations in a small number of subjects with chronic renal failure establish the potential for the use of IGF-I as a therapeutic agent in this setting. The observations that kidney function remains elevated over years in acromegalic patients (70) and that persistent and progressive increases in creatinine clearance resulted from the administration of IGF-I to a Laron dwarf (65) suggest that sustained improvement in kidney function can be achieved through the pharmacologic use of IGF-I.

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