Drugs of abuse and renal disease

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The complications of drug abuse encompass a spectrum of glomerular, interstitial, and vascular diseases. They comprise the heroin-associated nephropathy seen in African-American intravenous drug addicts, which, however, has given way in the 1990s to HIV-associated nephropathy. Infections with methicillin-resistant *Staphylococcus aureus* may cause acute glomerulonephritis by releasing bacterial superantigens. Hepatitis C has supplanted hepatitis B and may give rise to membranoproliferative glomerulonephritis and cryoglobulinemia. Addicts who inject drugs subcutaneously ('skin popping') may develop amyloidosis. Cocaine causes rhabdomyolysis, severe hypertension, occasionally renal failure in the absence of rhabdomyolysis, and may hasten progression to uremia in patients with underlying renal insufficiency. 'Ecstasy', an amphetamine-like recreational drug, has caused acute renal failure, electrolyte disturbances, and malignant hypertension. In Belgium and some other European countries, women taking Chinese herbs in a slimming regimen have developed a severe and irreversible interstitial fibrosis that is assuming epidemic proportions.

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Abbreviations

FSGS focal segmental glomerulosclerosis
HAN heroin-associated nephropathy

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Introduction

The past 25 years have witnessed an explosive growth in illicit drug use in many parts of the world. Many of these drugs, in particular heroin and cocaine, cause a wide spectrum of renal complications, often chronic and irreversible but sometimes acute and remediable.

Glomerulopathies

Intravenous drugs have long been known to cause glomerular disease. Interestingly, proteinuria in morphine addicts was described as early as the 19th century. Intravenous heroin may have been first tried in Egypt and then disseminated elsewhere by sailors. Glomerular abnormalities were first described in proteinuric or nephrotic heroin addicts in the early 1970s and consisted of minimal glomerular changes [1], focal membranoproliferative glomerulonephritis [2], and increased periodic acid-shiff-positive material and focal thickening of the glomerular basement membrane [3]. Except for heroin-associated nephropathy (HAN) [4], it was difficult to establish a causal relationship between intravenous drug use and these abnormalities.

Heroin-associated nephropathy

HAN was consistently seen in male African-American intravenous drug addicts [4]. The patients presented with nephrotic syndrome and impaired renal function, and progressed to end-stage renal failure within 6–48 months [4,5]. They had focal segmental glomerulosclerosis (FSGS) with mesangial deposition of IgM and C3, widespread fusion of epithelial podocytes, and patchy tubular atrophy and interstitial fibrosis [4]. Over 95% of such patients seen in Brooklyn, New York, were male African-American intravenous drug addicts [5], and in the Buffalo area of New York State the annual incidence of focal sclerosis from 1974 to 1978 in the population aged 18–45 years was 611 per million among addicts versus only 15 per million in non-addicts, a ratio of 41 : 1, with blacks outnumbering whites by 7 to 1 [6]. At Cook County Hospital in Chicago we found that 36% of all cases of FSGS seen between 1977 and 1982 were in male African-American intravenous drug addicts; they were younger than the non-addicts, had more proteinuria, and often more tubulo-interstitial disease than non-addicts with idiopathic FSGS [7].

The pathogenesis of HAN has remained elusive. It was theorized [4–6,8] that it represented an immunological reaction to the injected substances or diluents, or to contaminating bacterial or viral antigens. Justifying this immunological hypothesis were the high IgM levels in the

sera of intravenous drug addicts, the presence of antibodies to self-antigens and of IgM and complement in the glomeruli, the occurrence of transverse myelitis in heroin addicts, and the increased binding of tritiated morphine by the gamma-globulin fraction in the sera of drug addicts. It seems that the intravenous route of drug abuse is necessary for the development of the immune reaction, as serum IgM levels decrease when heroin addicts switch to oral methadone, and levels are normal when heroin or cocaine are taken by the nasal route [4–6,8]. More recently it has been shown that morphine and cocaine enhance the accumulation of radiolabelled human IgG aggregates in the rat mesangium [9•], and that cocaine enhances rat mesangial cell proliferation, with transforming growth factor-β suppressing and IL-6 enhancing this effect [10•]. Host mechanisms, however, are very probably involved in the development of HAN. In this context, Haskell *et al.* [11] found a higher frequency of HLA-BW 53 in African-American addicts with HAN than in the general population of African-Americans.

Since 1989, as HIV-associated nephropathy has become so much more common [12], HAN has almost disappeared [13•]. This could be because of the increased purity of heroin [13•] or, more plausibly, because of the early death from AIDS of many drug addicts.

Glomerulonephritis associated with bacterial endocarditis

Diffuse as well as segmental proliferative glomerulonephritis may be seen in intravenous drug addicts with *Staphylococcus aureus* endocarditis [14]. Indeed, clinical evidence of glomerulonephritis has been reported in 40–78% of patients with methicillin-resistant *S. aureus* endocarditis. Circulating immune complexes and high rheumatoid factor levels are found in the serum, and 68% of patients have hypocomplementemia. The classical as well as the alternative complement pathways may be activated. *S. aureus* bacterial antigen has been identified in glomerular immune deposits. More recently Koyama *et al.* [15•], studying 10 non-addicts with glomerulonephritis and purpura associated with methicillin-resistant *S. aureus* infection, noted polyclonal increases in IgG, IgA, and immune complexes in the serum, an increase in DR^+CD4^+, DR^+CD8^+, and T cell receptor Vp^+ cells in the peripheral blood. IgG, IgA, and C3 deposits were found in the mesangium [15•]. Koyama *et al.* postulated that enterotoxin C and A, and toxic shock syndrome toxin, which are all produced by methicillin-resistant *S. aureus*, act as superantigens, causing the production of high levels of cytokines and polyclonal activation of IgG and IgA, with the formation of circulating immune complexes resulting in glomerulonephritis and vasculitis [15•].

The nephrotic syndrome is seen in 14% of cases of glomerulonephritis associated with endocarditis, but unlike the case in acute post-streptococcal glomerulonephritis, hypertension is rare [14]. The glomerulonephritis may be focal or diffuse, and epithelial crescents may be present. Morphologically it resembles post-streptococcal glomerulonephritis, exhibiting subepithelial electron-dense deposits as opposed to the subendothelial deposits seen in the indolent endocarditis of *Streptococcus viridans*. Interstitial lesions are common. Mesangial and peripheral IgG, IgA, IgM, and complement are seen on immunofluorescence microscopy [14]. The glomerular lesion usually clears with the resolution of endocarditis. A high serum creatinine at onset or persistent hypocomplementemia are associated with intractable and fatal endocarditis [14].

Glomerulonephritis associated with hepatitis B and C

Glomerulonephritis has also been reported in intravenous drug addicts with hepatitis B antigenemia. There is a focal increase in mesangial matrix, focal thickening of glomerular basal membrane and foot process fusion, endothelial cell inclusions of closely packed electron-dense virus-like particles, and mesangial as well as capillary loop deposits of IgG, IgM, and C3 [3]. Lately hepatitis C has supplanted hepatitis B, and recently membranoproliferative glomerulonephritis, vasculitis, and cryoglobulinemia were described in an intravenous drug addict whose serum had antibodies to hepatitis C [16•].

Necrotizing angiitis

Necrotizing angiitis resembling polyarteritis nodosa has been reported after intravenous methamphetamine use. The arcuate and interlobular renal arteries show aneurysms and sacculations, with thrombosis and infarction resulting in azotemia [17].

Amyloidosis

This is type AA, and is found in addicts who inject drugs subcutaneously (skin popping) and develop chronic skin abscesses [18]. In the 1980s investigators in New York City reported an increasing number of cases of glomerular amyloidosis in African-American intravenous drug addicts with nephrotic syndrome [19]. This entity, however, has not been common in our experience [7] or that of Friedman *et al.* [13•]. Rarely, resolution of the nephrotic syndrome and stabilization of renal function may be seen in addicts who abstain from drugs, although renal biopsy may not show much morphological resolution [20]. More recently clinical resolution of renal disease without perceptible morphological improvement occurred in an addict treated with colchicine, but it was not stated if the patient had also abstained from drugs [21].

Human immunodeficiency virus-associated nephropathy

Since the early 1990s this has largely supplanted heroin-associated nephropathy [12,13•]. Again, the lesion is one of FSGS [22], usually with prominent collapse of the glomerular tuft, earning it the unfortunate name of collapsing glomerulopathy. Other differences from heroin-associated nephropathy or idiopathic focal segmental

glomerulosclerosis are the abundance of tubulo-reticular structures in endothelial cells of the glomeruli and interstitial capillaries, microcystic dilations of the renal tubules, nuclear bodies in renal tubular cells, and tubular degeneration and simplification [22]. The kidneys are usually large and hyperechoic on ultrasound examination. Most patients are male African-American intravenous drug addicts. They present with nephrotic syndrome and azotemia, and progress within a few weeks or a few months to end-stage renal failure [23].

Chinese herbs nephropathy

This new disease is essentially a paucicellular interstitial fibrosis [24•] and the glomeruli are relatively spared. It affects mainly women undergoing a slimming regimen that includes the Chinese herbs *Stephania tetrandra* and *Magnolia officinalis* [25•]. Most reports have come from Belgium, where over 80 young women have developed end-stage renal disease. A few cases have occurred in France, England, and possibly Japan [26•]. The patients presented characteristically with renal insufficiency, disproportionately severe anemia, unremarkable urinary sediment, and mild proteinuria of predominantly tubular origin. Hypertension was absent in over half the patients and renal failure was relentlessly progressive. Some patients have also had extensive atypical cells in the transitional epithelium, extending from the papilla to the ureterovesical junction, evolving in a few cases into actual renal pelvic carcinomas [27]. Thus the clinical and pathological picture is reminiscent of Balkan endemic nephropathy, suggesting a common cause. Prime suspect is aristolochic acid, a mutagenic and nephrotoxic alkaloid found in the plant *Aristolochia* and possibly inadvertently included in the slimming formulations [24•–26•].

Vasoactive substances

Ecstasy

Ecstasy or 3,4-methylene-dioxymethamphetamine, a synthetic amphetamine derivative, was originally an appetite suppressant but was later used as a recreational drug, often at all night 'rave' parties, where the prolonged physical exertion of dancing may potentiate its effects. Serious medical effects from its use include seizures, hyperpyrexia, hepatic dysfunction, rhabdomyolysis, disseminated intravascular coagulation, and acute renal failure [28,29]. Patients have collapsed after dancing all night, or have become mute and catatonic with dilutional hyponatremia after drinking large quantities of water [30]. One patient developed acute urinary tract retention after taking 15 tablets in the previous 36 h, a complication also reported after intravenous amphetamine [31]. Another patient presented with accelerated hypertension (220/140 mmHg), with seizures, unconsciousness, and marked decerebrate posturing 2 days after taking ecstasy at a 'rave' party. He required ventilation and became dialysis dependent. Renal biopsy showed changes of malignant hypertensive nephrosclerosis with fibrinoid necrosis, thrombi occluding arterioles, glomerular infarctions, extensive tubular necrosis, and interstitial edema [32•].

Marijuana

Renal infarction after heavy smoking of marijuana, a vasodilator, appears to have been caused by hemodynamic factors [33].

Cocaine

As every inner city emergency room physician knows, cocaine causes chest pain, myocardial infarction, hypertensive crises, arrhythmias, strokes, and ischemia of other organs. A powerful activator of the sympathetic and dopaminergic systems, it reportedly precipitated severe scleroderma crisis with hypertension and renal failure in one patient [34], and acute renal failure without rhabdomyolysis, presumably from intense vasoconstriction and ischemia, in others [35]. Chronic cocaine use also exacerbates the hypertension of inner city African-American patients, who typically complain of headache, dizziness, and chest pain, and whose hypertension may be quite refractory to treatment. These patients often have hypertensive nephrosclerosis but sometimes a primary glomerular disease such as focal glomerulosclerosis, and progress to renal failure because of uncontrolled hypertension or intrarenal vasoconstriction. Most of these patients, reported from Chicago [36•] and Los Angeles [37], require maintenance dialysis and many continue to use cocaine even while on dialysis.

Cocaine appears to be particularly harmful in hypertensive African-Americans, who have greater vascular disease and renal vascular resistance compared with Caucasians and who on arteriography have comparatively more renal cortical ischemia, greater reduction in renal blood flow, and more nephrosclerosis. In this setting cocaine may well set up a vicious cycle of vasoconstriction, more hypertension, and further loss of renal function. It may also cause accelerated atherosclerosis, often with overlying thrombosis and marked narrowing of the interlobular and segmental intrarenal arteries by intimal fibrosis even in the absence of hypertension [38]. It is also noteworthy that in rats, repeated cocaine administration has resulted in damage to capillary walls and swelling of tubular epithelium, progressing to necrosis, hemorrhage, glomerular obsolescence, and interstitial lesions [39].

Acute myoglobinuric renal failure after rhabdomyolysis

Perhaps the best known effect of cocaine [40–42], this syndrome of non-traumatic rhabdomyolysis was described earlier in patients taking amphetamine, phencyclidine, and heroin, and continues to be frequently seen in nephrology services. As many as 33% of patients with acute rhabdomyolysis from cocaine will develop acute myoglobinuric renal failure, and over one-half of these will require

an average of three sessions of dialysis [40]. One-half of the patients who develop acute renal failure may also have disseminated intravascular coagulation, often a fatal complication. The etiology of the rhabdomyolysis is probably multifactorial, involving constriction of muscular arterioles, hypotension, and malignant hyperthermia. The acute renal failure is probably related to tubular injury and obstruction by myoglobulin, decreased glomerular filtration rate, and the compounding factors of hypotension, volume contraction, hyperthermia, disseminated intravascular coagulation, and possible renal vasoconstriction by cocaine [40].

Conclusion

Drug-induced renal disease clearly constitutes a major public health problem. This is especially so if one also considers the problems caused by antibiotics, analgesics, and non-steroidal anti-inflammatory drugs, and now by drugs taken for slimming. Heroin and cocaine remain the main offenders, but there are many others. Thus 'sniffers' of toluene or toluene-containing compounds (glue, lacquer thinners, spray paint, transmission fluid) may develop proximal or distal renal tubular acidosis, pyuria, hematuria, mild proteinuria, renal calculi, tubulo-interstitial fibrosis, or acute renal failure [43]. Abusers of trichloroethylene (solvent sniffers) also develop acute renal failure [43]. In the Far East Djenkol beans are eaten as a delicacy but may cause bilateral loin pain, gross hematuria, and oliguric acute renal failure, from acute tubular necrosis or perhaps from tubular obstruction by crystals [44]. In recent case reports people have developed renal failure after eating 'magic' mushrooms, for hallucinogenic purposes [45]; and a 'green water' syndrome of renal failure and hemolysis followed drinking a copper-containing water prescribed by Nigerian church leaders to purge their congregation of physical and spiritual impurities [46]. Now as ever, man's urge to take medicine is irrepressible and the potential for self damage is immeasurable.

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