Snakebite Nephrotoxicity in Asia

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Summary: Snakebites have the highest incidence in Asia and represent an important health problem. Clinical renal manifestations include proteinuria, hematuria, pigmenturia, and renal failure. Nephropathy usually is caused by bites by snakes with hemotoxic or myotoxic venoms. These snakes are Russell's viper, saw-scaled viper, hump-nosed pit viper, green pit viper, and sea-snake. Renal pathologic changes include tubular necrosis, cortical necrosis, interstitial nephritis, glomerulonephritis, and vasculitis. Hemodynamic alterations caused by vasoactive mediators and cytokines and direct nephrotoxicity account significantly for the development of nephropathy. Hemorrhage, hypotension, disseminated intravascular coagulation, intravascular hemolysis, and rhabdomyolysis enhance renal ischemia leading to renal failure. Enzymatic activities of snake venoms account for direct nephrotoxicity. Immunologic mechanism plays a minor role.

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Bites by snakes still represent an important health problem in the tropical world. The true incidence of snakebites is difficult to assess and often is underreported. There are approximately 5.4 million victims per year, with 4 million in Asia, 1 million in Africa, 300,000 in central and South America, and 100,000 in the other continents.[1] Among the estimated 125,345 deaths in 1998, 100,000 were in Asia, 20,000 were in Africa, 5,000 were in central and South America, and 345 were in the other areas. In Asia, deaths by snakebites per year have been estimated to be around 20 in Thailand, 200 in Nepal, 250 in the Philippines, 1,000 in Sri Lanka, and 20,000 each in India and Pakistan.[2]

Among 2,700 species of snakes, 500 are venomous. Venomous snakes belong to 4 families, including Atractaspidae, Colubridae, Elapidae, and Viperidae. Snakes in the Atractaspidae family are not present in Asia. Common poisonous snakes in Asia include the cobra (Naja), king cobra (*Ophiophagus Hannah*), krait (Bungarus), and sea-snake (Hydrophinae) in the Elapidae family, Asian red-necked keelback (*Rhabdophis subminiatus*) in the Colubridae family, Russell's viper (*Daboia russellii*), green pit viper (Cryptelytrops, Trimeresurus, and Protobothrops), Malaysian pit viper (*Calloselasma rhodostoma*), saw-scaled viper (*Echis carinatus*), and hump-nosed pit viper (*Hypnale hypnale*) in the Viperidae family.[3–6]

The kidney, a highly vascularized organ with excretory function, is prone to venom toxicity as an innocent bystander. Renal involvement is therefore common and has been a subject of interest among nephrologists in the tropics, especially in Asia and South America. In Asia, most studies come from India, Thailand, Myanmar, Sri Lanka, Japan, and Taiwan. There is a broad spectrum of renal involvement[7–10] and this subject certainly deserves review.

CLINICAL RENAL MANIFESTATION

Renal involvement has been observed in victims of bites from snakes belonging to 3 families including Elapidae, Viperidae, and Colubridae. In Asia, snakes that cause nephropathy are the saw-scaled viper, Russell's viper, green pit viper, hump-nosed pit viper, and sea-snake. The distribution of nephrotoxic snakes in Asian

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Table 1. Distribution of Nephrotoxic Snakes in Asian Countries

	Cam	Chi	India	Indo	Japan	Laos	Mal	Mya	Nepal	Pak	Phi	Sri	Tai	Thai	Viet
Saw-scaled viper (*Echis carinatus*)			+*							+*		+*			
Russell's viper (*Daboia russellii*)	+	+	+*	+				+*	+	+		+*	+	+*	
Green pit viper (*Cryptelytrops, Trimeresurus, Protobothrops*)	+	+	+	+	+*	+	+	+	+		+	+	+*	+*	+
Hump-nosed pit viper (*Hypnale hypnale*)			+*									+*			
Sea-snake (*Hydrophinae*)	+	+	+	+	+		+*	+		+	+	+	+	+*	+

Abbreviations: Cam, Cambodia; Chi, China; Indo, Indonesia; Mal, Malaysia; Mya, Myanmar; Pak, Pakistan; Phi, Philippines; Sri, Sri Lanka; Tai, Taiwan; Thai, Thailand; Viet, Vietnam.
*Represents published report.

countries from available reports is shown in Table 1. Russell's viper, saw-scaled viper, green pit viper, and hump-nosed pit viper are hemotoxic snakes. Sea-snake and Russell's viper in some geographic areas are myotoxic. The red-necked keelback snake is hemotoxic and its venom activates factors II[11] and X.[12] This snake venom is potentially nephrotoxic, but the presence of posterior fangs makes envenoming human beings uncommon, and so this snake was not included in Table 1. Tubular necrosis has been observed in animals envenomated by *Rhabdophis tigrinus tigrinus*, a related species.[13] Renal manifestations vary from urinary sediment changes with mild proteinuria to renal failure.

PROTEINURIA

In the animal model proteinuria can occur after intrarenal injection of cobra venom in rats.[14] Proteinuria after snakebites varies in incidence depending on the kind of snakes. In a series of 400 patients bitten by tropical snakes in Thailand, proteinuria at the magnitude of less than 500 mg/24 h was noted in 4% and completely resolved on recovery.[15] In a study of Russell's viper bites in Myanmar, proteinuria greater than 1 g/24 h was observed in 50% of patients.[16] This magnitude of proteinuria is unusual and would suggest the effect of the environment on the venom composition. Yet, the proteinuria disappeared when the patients recovered. Anecdotally, nephrotic syndrome has been reported in snakebites without substantiation of the cause-effect relationship.[17]

HEMATURIA

Because of coagulation defects and vascular injury, gross or microscopic hematuria is a common finding in patients bitten by hemotoxic snakes, either viperids or crotalids. In our study the incidence was 35% among 400 patients.[15] Nephritic syndrome with decreased renal function secondary to diffuse proliferative and crescentic glomerulonephritis also has been described.[18–20] Crescentic glomerulonephritis is associated with severe renal failure.[20]

PIGMENTURIA

Snake phospholipase A_2 (PLA_2) can cause hemolysis and rhabdomyolysis. Hemoglobinuria caused by intravascular hemolysis is common in viperid and crotalid snakebites. Hemolysis is preceded by swelling of red blood cell and is calcium-dependent.[21,22] Calcium chelation by citrate decreases red blood cell swelling and increases the threshold for intravascular hemolysis. Rhabdomyolysis in myotoxic snakebite results in myoglobinuria. Both hemoglobinuria and myoglobinuria contribute importantly to the development of acute kidney injury (AKI) after snakebite. Several Australian snakes are both myotoxic and hemotoxic. In Asia, Russell's viper venom in certain geographic areas can cause both intravascular hemolysis and

rhabdomyolysis. Bites by sea-snakes are a common cause of rhabdomyolysis and myoglobinuria.

AKI

Snakebite-related AKI commonly occurs in myotoxic or hemotoxic snakebite accidents. The kidney is an innocent bystander. In tropical Asia, bites by Russell's viper and saw-scaled viper are the common causes. The other snakes reported to cause AKI include sea-snakes, green pit vipers, and hump-nosed pit vipers. AKI in snakebite constitutes 1.2% of total AKIs in Thailand, 3% in India, and as high as 70% in Myanmar.[23] Children are more prone to develop renal failure than adults. Table 1 lists the snakes with myotoxicity and hemotoxicity that can cause AKI. The incidence of AKI caused by these snakes varies from 5% to 29%, depending on the species of snake and the severity of envenoming.[3,24,25] The onset of renal failure varies from a few hours to as late as 96 hours after the bite. In a series of 123 patients bitten by Russell's viper, renal angle tenderness was noted in 39% and hypotension was noted in 35%.[24] Renal failure need not be associated with hypotension. Transient hypertension has been observed. In viper bites renal failure may accompany intravascular hemolysis or intravascular coagulation with hemoglobinuria and hematuria. Hemolytic uremic syndrome has been described after hemotoxic snakebites. In bites from sea-snakes renal failure is associated with rhabdomyolysis manifested by muscular pain, weakness, paralysis, and myoglobinuria. The serum creatine phosphokinase level is increased. In both events hyperkalemia can be alarming. Renal failure can be catabolic, with rapid increases in blood urea nitrogen and serum creatinine levels and hyperuricemia. Nonoliguric renal failure is not uncommon in Russell's viper bites. The course of renal failure ranges from 2 to 3 weeks. Acute glomerulonephritis in viper bites can cause mild renal failure. Prolonged renal failure with oligo-anuria suggests cortical necrosis or acute tubular necrosis associated with either interstitial nephritis or extracapillary glomerulonephritis. Clinical recovery usually is complete except for those with cortical necrosis. Mortality rates from snakebite AKI ranges from 1% to 20%.[3,24,25] Elderly patients and those with cortical necrosis or severe hemorrhagic complications have a bad prognosis.[23]

MANAGEMENT

Monospecific antivenom administration is the treatment of choice for snakebites. However, this does not guarantee prevention of AKI. Plasmapheresis and blood exchange have been used in snake envenomation where antivenom was unavailable.[26,27] These procedures should be performed early before the venom fixes to the tissue, and thus are not practical. Early and frequent peritoneal dialyses or hemodialyses are life-saving for AKI. Muscular symptoms caused by bites from sea-snakes are improved by hemodialysis.[28] Dialysis corrects hyperkalemia and removes some postsynaptic sea-snake neurotoxin, which has low molecular weight. Prevention of renal failure should be aimed considering pathogenetic factors involved. Prompt treatment with specific antivenom undoubtedly is required. Maintenance of good urine flow is important. Alkalization of urine by sodium bicarbonate helps in the prevention of AKI in the patient who has myoglobinuria or hemoglobinuria provided that this is performed early when dark urine is observed or when the snake is known to be myotoxic or hemotoxic. In animal studies, alkalization of urine before envenomation prevented pathologic changes and impairment of renal function.[29,30] In established AKI, the administration of sodium bicarbonate and mannitol can be dangerous and should be avoided because of fluid overload and hyperosmolality. In the animal model of Russell's viper envenomation, dopamine and furosemide attenuated renal dysfunction at the early stage.[31] In malaria and leptospirosis, dopamine and furosemide given at the pre–renal failure stage induced diuresis and prevented renal failure.[32,33] Clinical data in the snakebite model are not available. Interestingly, hypocalcemia induced by parathyroidectomy in a canine before Russell's viper venom administration attenuated the decrease in glomerular filtration and renal blood flow.[34] The role of hypocalcemia in the development of AKI in snakebite requires further study.

Table 2. Asian Snakes Causing Nephropathy

Snake	Clinical Toxicity	Mechanism of Action	Nephropathy
Russell's viper (*Daboia russellii*)	Coagulopathy Thrombocytopenia Hemolysis Occasional rhabdomyolysis	Factors X and V activation PLA_2	Tubular necrosis Cortical necrosis Interstitial nephritis Glomerulonephritis Mesangiolysis Vasculitis
Saw-scaled viper (*Echis carinatus*)	Coagulopathy Thrombocytopenia Hemolysis	Factor X and prothrombin activation	Tubular necrosis Cortical necrosis Glomerulonephritis
Hump-nosed pit viper (*Hypnale hypnale*)	Coagulopathy Thrombocytopenia Hemolysis	Procoagulant action Fibrinolysis	Tubular necrosis Cortical necrosis
Green pit viper (*Cryptelytrops*, *Trimeresurus*, *Protobothrops*)	Coagulopathy Thrombocytopenia	Thrombin-like action Fibrinolysis	Mesangiolysis Glomerulonephritis
Sea-snake (*Hydrophinae*)	Rhabdomyolysis	PLA_2	Tubular necrosis

RENAL PATHOLOGY

The renal pathology varies in severity from patient to patient and all renal structures can be involved. However, tubular changes are the most prominent finding observed in the patient presenting with AKI. Table 2 shows renal pathologic changes in Asian snake bites.

GLOMERULAR CHANGES

Glomerular involvement in snakebites often is overlooked. The most common histopathologic lesions are focal and segmental mesangial proliferation. In the mild forms, the lesions are minimal, and the glomeruli may appear normal or show minimal increases in the amount of extracellular matrix or the degree of cellularity. In addition, these changes may affect only a small number of glomeruli or a small portion of individual glomeruli. In some cases, polymorphonuclear cells as well as mononuclear cells may be found in the mesangial spaces or the capillary lumina, usually in the severe case during acute episodes. Localized crescents also may be found near the foci of mesangial proliferation. Areas of necrosis and thrombosis, if present, are rare and limited. Large crescents with foci of necrosis have been described during episodes of AKI; however, the lesion is a rare finding and has been observed in the puff adder bite[19] and Russell's viper bite.[20]

Mesangial changes are reliably reproducible in the murine injected with Habu snake (*Trimeresurus flavoviridis*) venom.[35] Glomeruli of rabbits appear to be more sensitive and to recover slower than those of rats. Injection of Habu venom into rats produced rapid mesangiolysis,[36,37] a process of an attenuation or dissolution of the mesangial matrix and degeneration of mesangial cells. Segmental glomerular microaneurysm is recognized on the first day after the injection. It is a large vascular space, filled with cells and thrombin, arising by merging of the dilated mesangium and several adjoining capillaries that have lost their attachment to the mesangium. Because the mesangial cell lines are adjacent to the glomerular endothelial cell, the injury of endothelium is an inevitable effect. In fact, injury of both tissues usually occurs together. The high proteolytic activity of Habu venom appears to be responsible for most of the damage of the glomerular mesangium whereas most of the endothelial lesions are believed to be secondary to the extensive disruption of the glomerular architecture. Hypercellularity of mesangial cells appears later as a healing reaction. In addition, endothelial proliferation also observed during the resolution

phase apparently originates from the vascular pole. Extracellular matrix glycoprotein tenascin C expression, platelet-derived growth factor, and vascular endothelium growth factor are significant in the healing process of glomerulonephritis.[38,39] It is uncertain whether glomerular mesangiolysis exists in human beings; however, ballooning of the glomerular capillaries, an indirect evidence of mesangiolysis, has been shown after the Russell's viper or green pit viper bites.[40]

The immunofluorescence findings are quite variable. Deposition of IgM and C_3 in the glomeruli may be intense, negligible, or absent, depending on the time that renal biopsy is performed. IgM and C_3 deposition may be absent when renal biopsy is performed early after the bite. In most cases in which renal biopsy was performed late in the course of the disease, the deposition appears fine and granular and is located commonly in the mesangial areas and sometimes along the capillary loops.[5] IgM deposits are more prominent in Russell's viper bite than in cobra bite and green pit viper bite. Deposition of C_3 is more intense in cobra bites. Fibrin deposition in the peripheral capillary loops and the Bowman's space is observed in hematotoxic snake victims.

The electron microscopic findings are parallel with the light microscopic changes. However, in the case with minor changes, morphologic changes are better observed by an electron microscopic study. Slightly mesangial abnormalities were detected in cases with a deposition of an electron-dense material in the mesangium and the subendothelial in some capillary loops. Two patterns of podocytic changes have been described in the snakebite victim. The first pattern shows patchy effacement with hypertrophic mitochondria, swollen endoplasmic reticulum, and thin filamentous structures. The other pattern reveals neither organelles nor microvilli on the plasma membrane resembling an apoptotic cell.[5]

TUBULOINTERSTITIAL CHANGES

Tubulointerstitial changes are the most common prominent finding observed in renal failure victims after a bite by either hematotoxic or myotoxic snakes.[3,5,41] There is a wide range in the severity of renal tubular pathology. A renal biopsy study of patients with nonoliguric renal failure has shown relatively inconspicuous changes, although tubular degeneration and necrosis also have been reported. Biopsy specimens obtained after recovery show regenerating tubules lined by flattened epithelium with deeply stained nuclei. Mitotic figures, if present, are most pronounced in the macula densa. In the severe case, interstitial edema and cellular infiltration are observed in the area where there is tubulorrhexis. The infiltrates consist of lymphocytes, plasma cells, and mononuclear phagocytic cells. Casts, often seen in the collecting tubules and the loops of Henle, are granular pigmented. Some stain positively for hemoglobin and hemosiderin, especially in the victim of hemotoxic snakebite. In myotoxic snakebite the tubules contain myoglobin casts. The tubules are lined by necrotic or flattened epithelial cells. These pathologic findings correspond well to the clinical picture of severe snakebite complicated by disseminated intravascular coagulation. Mild tubular degeneration is present in green pit viper bite and has been observed occasionally in cobra bite.

Acute diffuse interstitial nephritis has been observed in Russell's viper bite.[7,8,42,43] There is diffuse and intense interstitial infiltration with mononuclear cells out of proportion to tubular degeneration. Immunofluorescence study shows no deposition of immunoglobulins and complement.

VASCULAR CHANGES

There are few data on vascular changes in snakebite. Segmental necrotizing arteritis of the interlobular arteries has been described in Russell's viper bite.[5,44] The lesion could have been missed if the renal biopsy was superficial and occasionally contains an area of tissue infarction. Segmental thrombophlebitis of the arcuate vein and its tributaries has been reported in both Russell's viper bite and green pit viper bite.[5,44] Deposition of C_3 without immunoglobulins in the wall of necrotizing arteries is seen. Deposition of C_3 in the wall of afferent and efferent arterioles without any vascular change has been shown in both viper bite and cobra bite patients.

RENAL INFARCTION AND CORTICAL NECROSIS

In an animal model, Raab and Kaiser[45] showed renal infarction after crotalid snake venom administration. In human beings, hemorrhagic infarct has been observed in patients bitten by rattlesnake and Russell's viper. Fibrin platelet thrombi appear in interlobular arteries within or near the infarction areas. Hemoglobin casts are seen in necrotic tubules.

Cortical necrosis has been observed after the bite of Russell's viper, saw-scaled viper, and hump-nosed pit viper.[10,46–48] The lesion is associated with disseminated intravascular coagulation. There is necrosis of all elements of the kidney with thrombi in the renal vascular bed. In patients who recover there is residual impairment of renal function, and calcification of the renal cortex may be seen.[46,48]

PATHOGENESIS

Nephropathy in snakebite is the result of several mechanisms including the inflammatory process, direct nephrotoxicity, and immunologic reaction. A number of cytokines and mediators are released after snake envenomation.[49–52] Among various venom enzymes, PLA_2 and metalloprotease are of pathogenetic importance. PLA_2 can stimulate hypothalamus-pituitary and immune axes causing the release of adrenocorticotrophic hormone, corticosteroids, and arginine vasopressin, and elicits an acute phase response.[53] Histamine, kinins, eicosanoids, platelet-activating factor, endothelin, and catecholamines also are incriminated in the inflammatory process. Cleavage of glutathione-S-transferase–tumor necrosis factor α (TNFα) fusion protein by metalloprotease generates active TNFα.[54] Sarafotoxin, which is present in the venom of burrowing or mole vipers in the Atractaspidae family, can cause direct vasoconstriction similar to endothelin. The snake is not present in Asia. Thamaree et al,[51,52] studying vasoactive mediators in Russell's viper envenomation, showed an increase of plasma levels of norepinephrine, epinephrine, thromboxane B_2, 6 keto prostaglandin F-α, dopamine, and endothelin (Fig. 1). Vasoactive mediators are generated by the host in response to the venom. Macrophages exposed to Russell's viper venom released TNFα and interleukin-1 (IL-1) similar to what happens after endotoxin exposure.[55] Mice inoculated by the *Bothrops* venom showed increased serum levels of TNFα, IL-1, IL-6, IL-10, interferon-γ, and nitric oxide.[56,57] The response to snake venom is therefore similar to that of sepsis.

HEMODYNAMIC CHANGES

Because of vasoactive mediator release after envenomation, hemodynamic changes are ob-

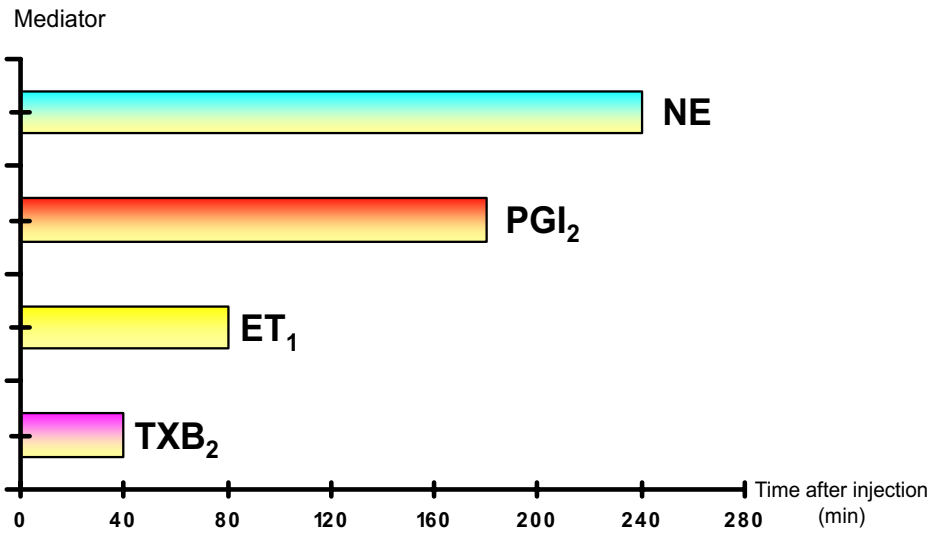

Figure 1. Maximal mediator response to Russell's viper venom injection in dogs. TXB_2, thromboxane B_2; ET_1, endothelin 1; PGI_2, prostaglandin I_2; NE, norepinephrine. Data from Thamaree et al.[51]

served. In Russell's viper envenomation, initially the cardiac output (CO) is decreased with increased systemic and renal vascular resistance. The renal blood flow (RBF) and glomerular filtration rate (GFR) are decreased.[58] Thromboxane A_2 results in pulmonary artery constriction and decreases CO owing to decreased blood return to the heart. At the later stages, CO was increased; systemic vascular resistance is decreased by the effects of nitric oxide and prostaglandin I_2, resulting in hypotension. Renal vascular resistance (RVR) is increased by vasoconstrictive mediators and perhaps down-regulation of nitric oxide synthase, as occurs in sepsis. RBF and GFR are decreased markedly. Hemodynamic alteration is thus similar to that of sepsis. Cobra venom injection only decreases GFR and RBF for a short period of time without development of renal failure. In a study of sea-snake venom, canines envenomated by *Lapemis hardwicke* showed increased RVR and decreased RBF and GFR without any change in CO and systemic vascular resistance.[30] The administration of sodium bicarbonate before venom injection prevents increased RVR and renal failure. Increased RVR and decreased RBF and GRF are attributed to myoglobin obstruction of renal tubules.

A number of studies of renal hemodynamics after the injection of viperid and crotalid venoms by isolated renal perfusion technique have shown decreased RBF and GFR with increased RVR.[59–61] Interestingly, *Bothrops mooojeni* venom caused decreased RVR, increased RBF, and unchanged GFR.[62] It is possible that the venom has an angiotensin-converting enzyme inhibitor or natriuretic peptide. This is a good side of snake venom that can be clinically advantageous.

Although decreased renal hemodynamics plays the basic role in the pathogenesis of renal failure, other factors also contribute importantly. Associated factors including hemorrhage, intravascular hemolysis, disseminated intravascular coagulation, rhabdomyolysis, complement activation, and free radicals should be taken into consideration. There is good correlation between impairment of renal function and hemotoxic and myotoxic actions of snake venom.[63] In this respect, renal failure is therefore common in myotoxic and hemotoxic snakebites. Elapid bites, manifested by neuromuscular symptoms without muscle injury, do not cause renal failure.

DIRECT NEPHROTOXICITY

Direct nephrotoxicity of snake venom is less recognized. Many clinical clues and evidences from the isolated kidney profusion technique together with in vitro studies support an existence of such a role of snake venom. Renal failure has been documented in patients a few hours after a snakebite without hypotension, hemorrhage, intravascular hemolysis, or rhabdomyolysis. In addition, many pathologic changes, including mesangiolysis,[36,37] glomerulonephritis,[18,20] and vasculitis,[5,40] occur without immunologic clues, indicating the direct effect of venom toward glomerular and vascular structures. Moreover, glomerular mesangium is suddenly disrupted after injection of Habu venom. Habu venom seems to have a direct effect on the mesangial cells and vascular endothelial cells because continuous incubation of the cells with the venom results in decreasing cell viability and an increasing number of apoptotic cells. However, a smaller dose with a shorter period of incubation creates the opposite effect by stimulating mesangial cell proliferation via protein kinase C activation. Russell's viper venom also causes nuclear pyknosis and cellular detachment from the substrate surface in cultures of proximal and distal/collecting tubular cells.[64] Mesangial cells are disintegrated. However, in our opinion, these effects only happen at a high dose of envenomization. In addition to the morphologic effect, Russell's viper venom decreases the potential difference across the proximal tubular membrane and decreases tubular reabsorption of sodium even at the low dosage.[34,59] The membrane depolarizing effect is caused perhaps by decreasing oxygen use by the mitochondria and by inhibitions of renal sodium-potassium adenosine triphosphatase.[34] In the Madin-Darby canine kidney cell culture, *Bothrops moojeni* crude venom decreases transepithelial electrical resistance across the cellular monolayers, decreases neutral red uptake of vero cells, causes disarray of the cytoskeleton, and impairs cell-to-matrix

adhesion.[65,66] In fact, the venom exerts diverse biological effects on the cells, ranging from cell activation and proliferation to lethal toxic injuries.

Snakes venoms are a rich source of enzymes such as phospholipases, endopeptidases, and L-amino acid oxidases that can directly cause cellular injury. Metalloprotease can cause proteolysis of the extracellular matrix and disrupts cell-matrix and cellular adhesion. The enzymes are present in the venoms of snakes in the *Viperinae* and *Crotalinae* subfamilies,[67] and bind with various degrees of specificity to integrin expressed on cells.[68–70] The integrity of cellular junctions is disrupted as a result of disruption of the actin cytoskeleton, resulting in a loss of cell polarity. Integrins, which are critical for cellular adhesion, redistribute away from the basal cell surface, contributing to the loss of adhesion to the basement membrane. Metalloproteases can induce apoptosis of vascular endothelial cells.[71] PLA_2 is present in several poisonous snakes including crotalids, viperids, elapids, and hydrophids. The enzymes are toxic and induce a wide spectrum of pharmacologic effects. PLA_2 can cause membrane injury and tubular necrosis. The enzyme interacts with the biological membranes via a distinct molecular region. This active region is likely to be formed by a combination of basic hydrophobic amino acid residues near the C-terminal of the protein. The high-affinity interaction of PLA_2 with its target protein probably is the result of the interaction of charges, hydrophobicity, and van de Waals contact surfaces between the toxin and the binding site as the surface of the cell membrane.[72,73] These events lead to membrane destabilization, loss of permeability, and cellular necrosis.

IMMUNOLOGIC MECHANISM

In acute animal experiments with venoms and in human beings glomerulonephritis has been shown without immunologic evidence.[18,20,35] However, in a number of patients bitten by snakes, immune complex glomerulonephritis has been observed later in the course of snakebite recovery in renal biopsy specimens regardless of antivenom administration.[5,18] There is deposition of C_3 and IgM in the glomerular mesangium.[18] The evidence suggests an immune complex glomerulonephritis. The rote of implanted venom antigen, followed by deposit of IgM later acquired, has been suggested. Alternatively, immune complex deposition could be caused by a concealed infection in the snakebite that results in immune complex glomerulonephritis with predominant deposition of IgM and C_3 in the mesangial areas. At present, the evidence is in favor of glomerulonephritis directly induced by the snake venom. The immunologic mechanism is rather weak and perhaps plays a minor role in the pathogenesis of glomerulonephritis in snakebite.

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