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49. NEPHROTOXIC ACTION OF SNAKE VENOMS

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Experimental investigations have shown that animal venoms exert a nephrotoxic effect (1, 2). Thus, the clinical findings in subacute snake poisoning have been confirmed (3, 4, 5, 6).

The effects of snake venoms on the kidney reveal a most complex pattern. Several toxic components of the venom act either directly or indirectly on renal cells. Toxic degeneration of glomerular cells produces nephritis (7, 1, 8), toxic alteration of tubular cells evokes nephrosis (9, 10, 11, 1, 12, 13, 14, 15). Toxic lysis and degeneration of red blood cells or muscle cells (malayan sea snakes) provoke hemoglobinuric (4, 16) or myoglobinuric (14, 17) nephrosis. Toxic alteration of nerve cells cause an increased susceptibility of kidneys to all kinds of damages. Thus, an aggravation of the above-mentioned nephrotoxic effects of snake venom occurs (18, 19). In addition, enzymatic cellular lysis and thrombosis provoke renal infarct (7, 3, 6). Furthermore, the elicitation of anaphylactoid shock which is regularly found following snake poisoning (20, 21, 22, 23) causes renal hypoxia by collaps and vasoconstriction (see Table I).

TABLE I — EFFECTS OF SNAKE VENOMS ON THE KIDNEY

A. TOXIC EFFECTS

Renal glomerular cells	→	Nephritis
Renal tubular cells	→	Nephrosis
Red blood cells	→	Hemoglobinuric nephrosis
Muscle cells	→	Myoglobinuric nephrosis
Nerve cells	→	Increased renal susceptibility

B. ENZYMATIC EFFECTS

$$\left.\begin{array}{l}\text{Cellular lysis}\\ \text{Thrombosis}\end{array}\right\} \longrightarrow \text{renal infarct}$$

$$\left.\begin{array}{l}\text{Formation of anaphylatoxin}\\ \text{Mast cell degranulation}\end{array}\right\} \longrightarrow \left.\begin{array}{c}\text{anaphylactoid}\\ \text{shock}\end{array}\right\} \longrightarrow \begin{array}{c}\text{hypoxic}\\ \text{nephrosis}\end{array}$$

Following administration of snake venoms, three types of renal damage can occur: glomerular alterations (nephritis), tubular alterations (nephrosis), and renal infarct. The glomerular alterations consist in inflammatory and degenerative changes. The tubular alterations — which seem to be the most important in toxinologic respect — are produced by a direct toxic action ("intermediate nephron nephrosis"), by extrarenal cell degeneration (hemoglobinuric nephrosis), and by vascular hypoxia (Table II).

TABLE II — RENAL LESIONS FOLLOWING ADMINISTRATION OF SNAKE VENOM

1. GLOMERULAR ALTERATIONS (NEPHRITIS)
   a. Degenerative changes
   b. Inflammatory changes
2. TUBULAR ALTERATIONS (NEPHROSIS)
   a. direct toxic effects (intermediate nephron nephrosis)
   b. secondary effects by extrarenal cell degeneration (hemoglobinuric, myoglobinuric nephrosis)
   c. vascular hypoxia
3. RENAL INFARCT

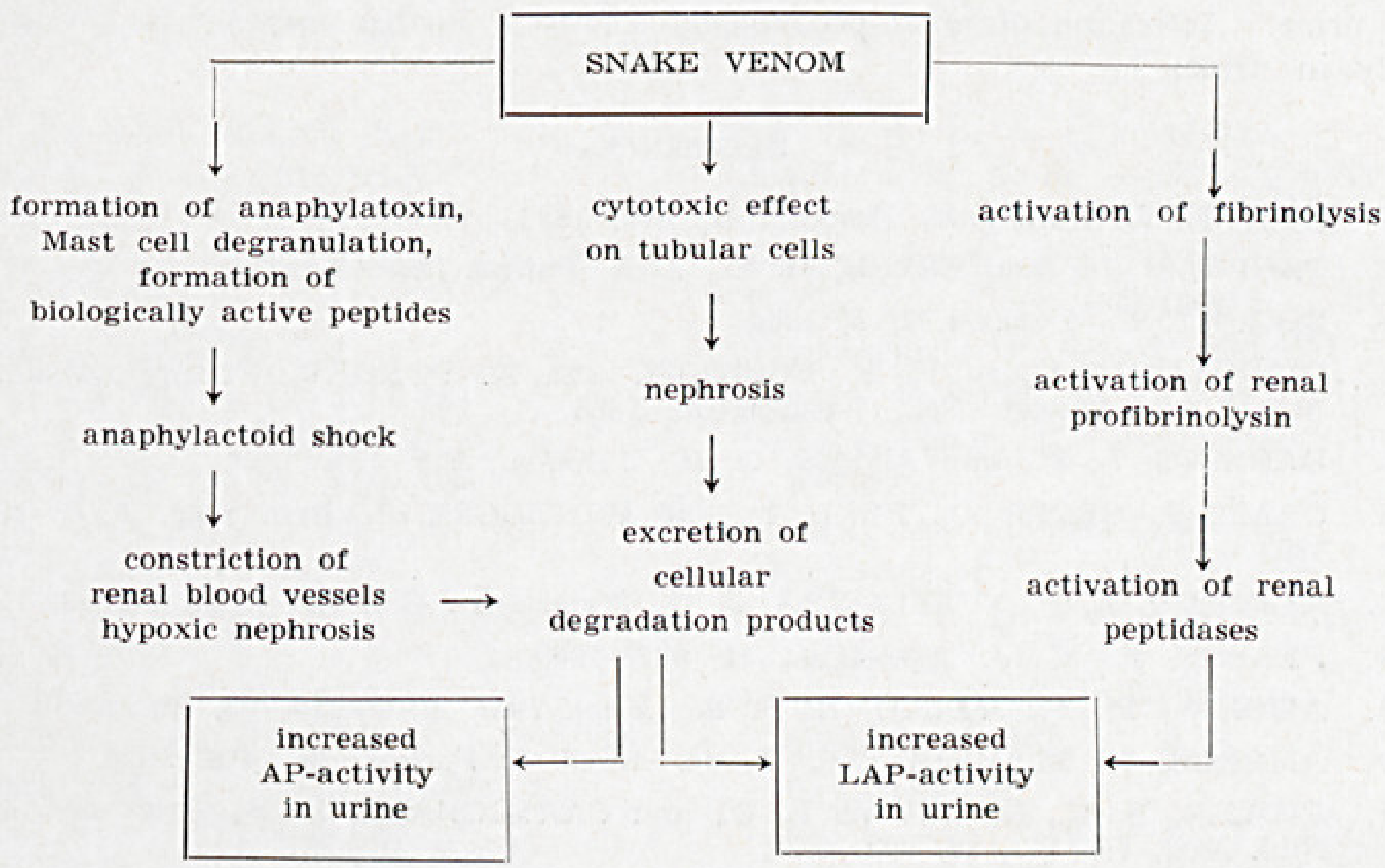
Until now, only pathologic and histologic examinations of kidneys in snake poisoning have been performed. In order to obtain information on the degree of renal damage *in vivo* and on the duration of nephrotoxic effect, biochemical investigations (24, 25, 26, 27, 15, 28) of renal function have been carried out following administration of snake venom.

After determination of normal alkaline phosphatase (AP) and "leucine aminopeptidase" (LAP) activities in 24-hours urine specimens (200 rats), 50 rats received a sublethal dosis of venom of *Agkistrodon piscivorus* LACEPEDE in saline (10 mg/kg subcutaneously). Daily determinations of enzymatic activities in urine were carried out for four days following administration of the snake venom. The enzymatic activities were calculated on 24-hours urine excretion.

As shown in Fig. 1, a significant increase in urinary AP- and LAP-activities occurs following injection of snake venom. On the second day, only a slight increase in urinary enzymatic activities is found. Beginning from the third day, normal activities were observed.

In 24-hours urine specimens following administration of snake venom, LAP-activity increases to the fivefold, AP-activity only to the twofold. AP-excretion depends upon renal tubular cells: following damage of these cells, an increase in urinary AP-activity occurs. The same statement applies for urinary LAP-activity: damage of tubular cells increases LAP-activity in urine. In addition, urinary LAP-activity is influenced by renal plasmine (see Table III). The activation of renal plasminogen provokes an activation of renal peptidases; this increases LAP-activity in urine.

TABLE III — MECHANISM OF INCREASE IN LAP- AND AP-ACTIVITY IN RAT URINE FOLLOWING ADMINISTRATION OF SNAKE VENOMS



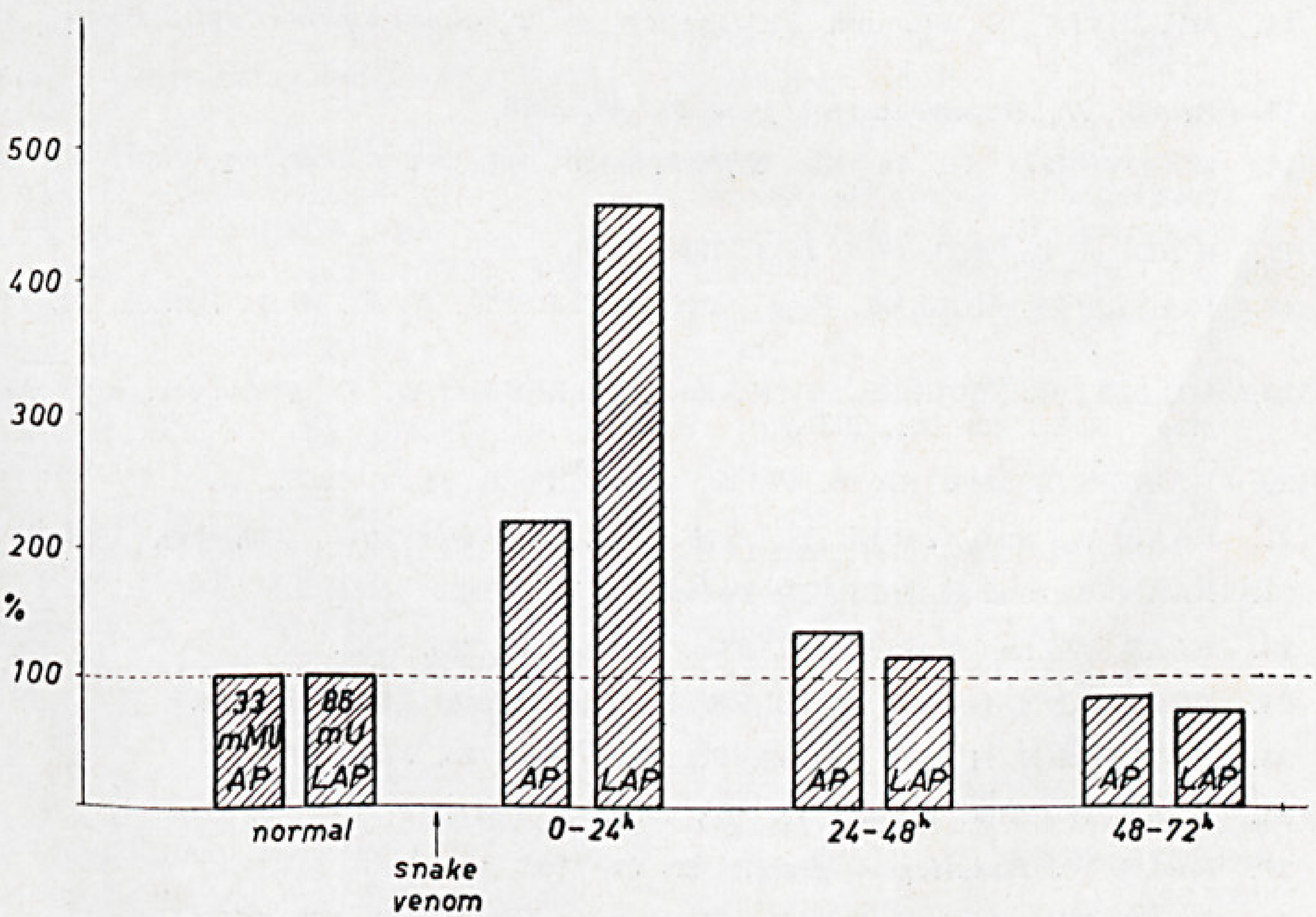


Fig. 1 — LAP- and AP-activities in rat urine (24 hours values) following injection of snake venom (*Agkistrodon piscivorus*). (Substrates: L-Leucyl-p-nitroanilide; Na-p-nitrophenylphosphate).

In anaphylactoid shock, an activation of fibrinolytic system occurs (23). In addition, certain snake venoms produce a direct activation of fibrinolytic system (29). Tubular damage by snake venom increases AP- and LAP-activities in urine. Activation of renal plasminogen causes a further increase in LAP-activity in urine.

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