OUR LOCAL MONSTER

Venom and Envenomation of the Gila Monster

ARIZONA
Poison and Drug Information Center

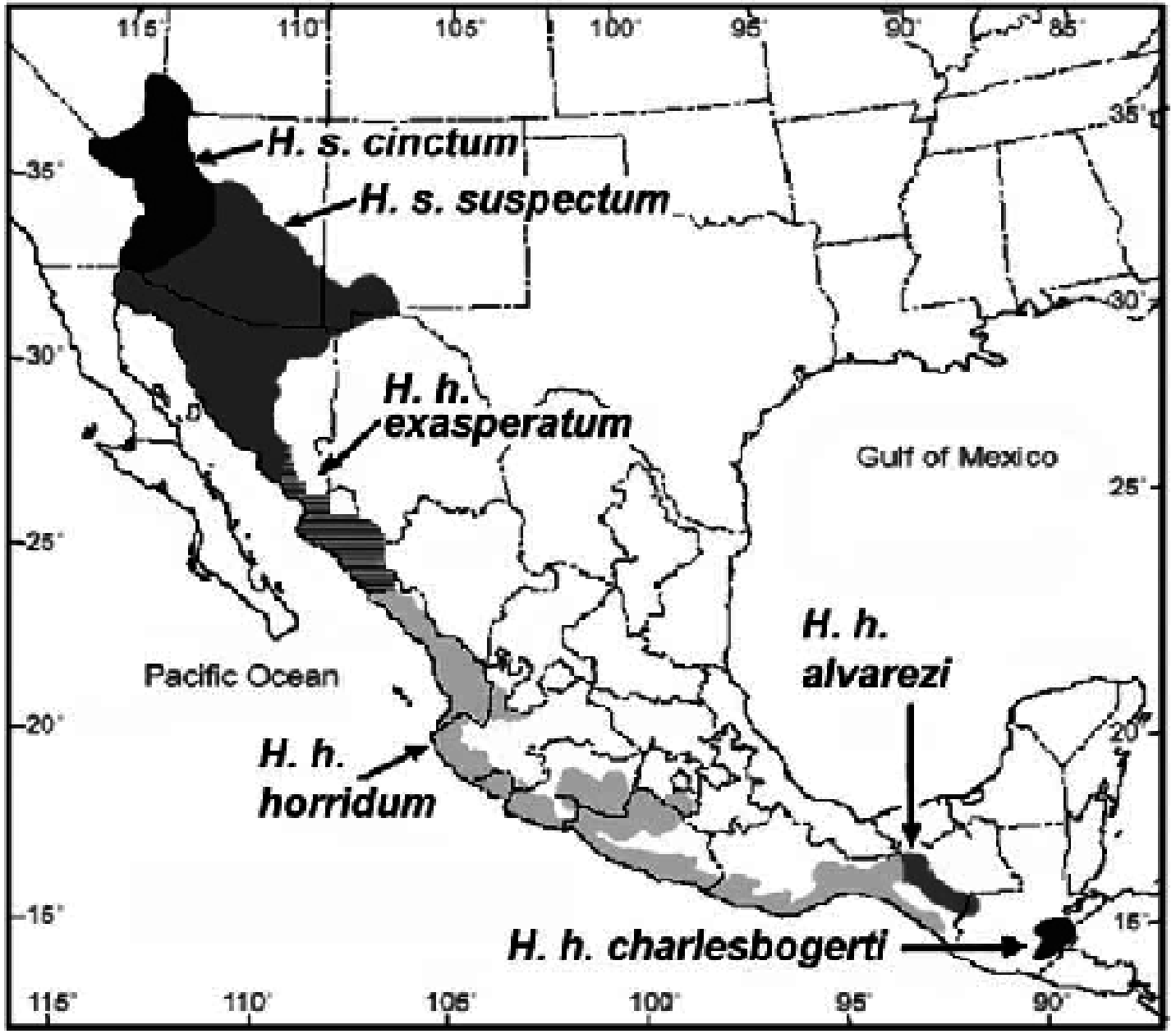
1-800-222-1222

ARIZONA GAME & FISH

Helodermatidae

- Greek word *helos* and *derma*
- Heloderma: Studded skin
  - Head of a nail or stud
- “Gila” monster
  - Gila River Basins
  - Arizona and New Mexico
- *Heloderma suspectum*
- *H exasperatum*
- *H horridum*
- *H alvarezi*
- *H charlebogerti*


H.s.suspectum
H.s.cinctum
H.h.exasperatum
H.h.horridum
H.h.alvarezi
H.h.charlesbogerti
Heloderma
sp. suspectum and horridum


H. s. cinctum
H. s. suspectum
H. h. exasperatum
H. h. horridum
H. h. alvarezi
H. h. charlesbogerti
Gulf of Mexico
Pacific Ocean
115°
110°
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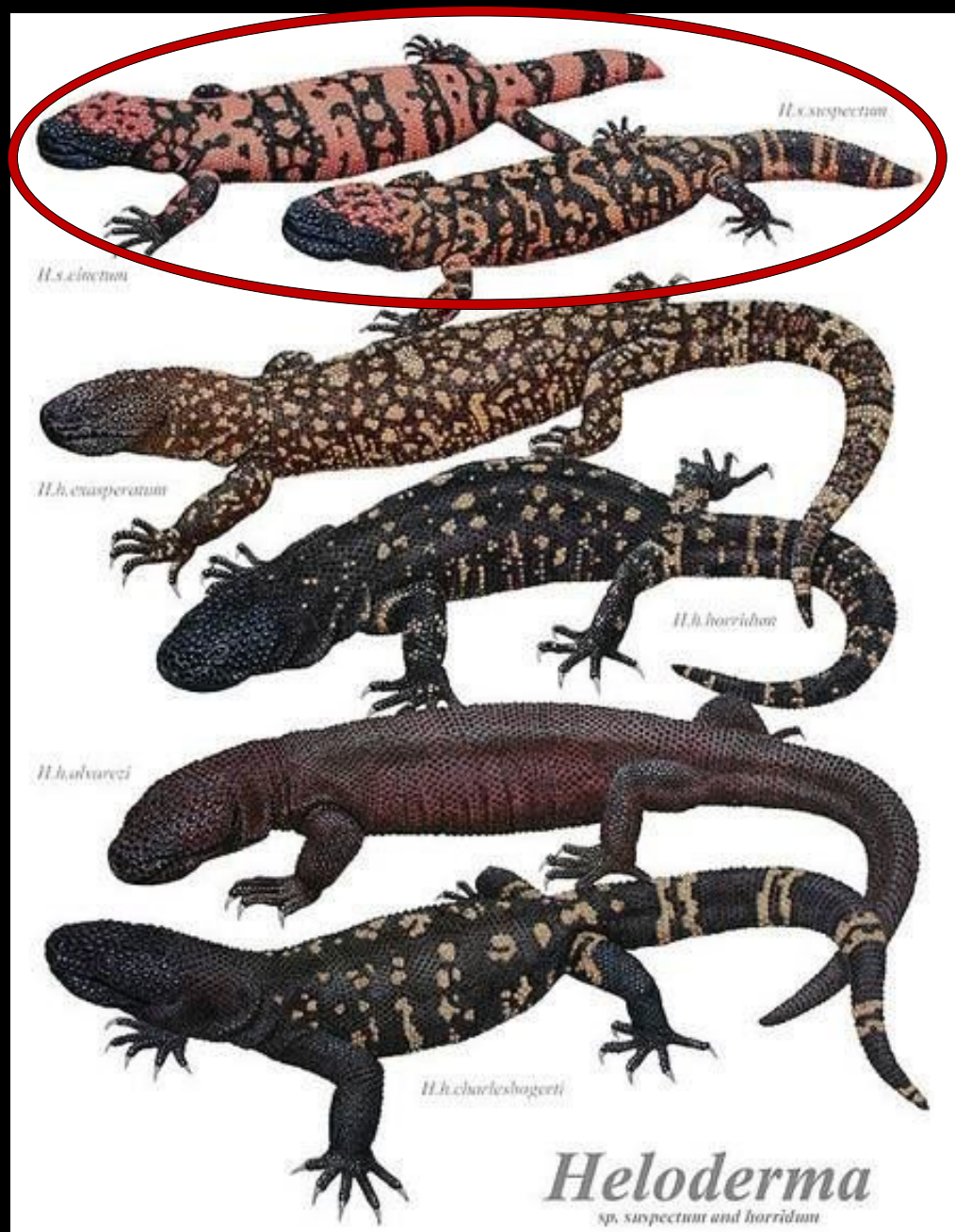
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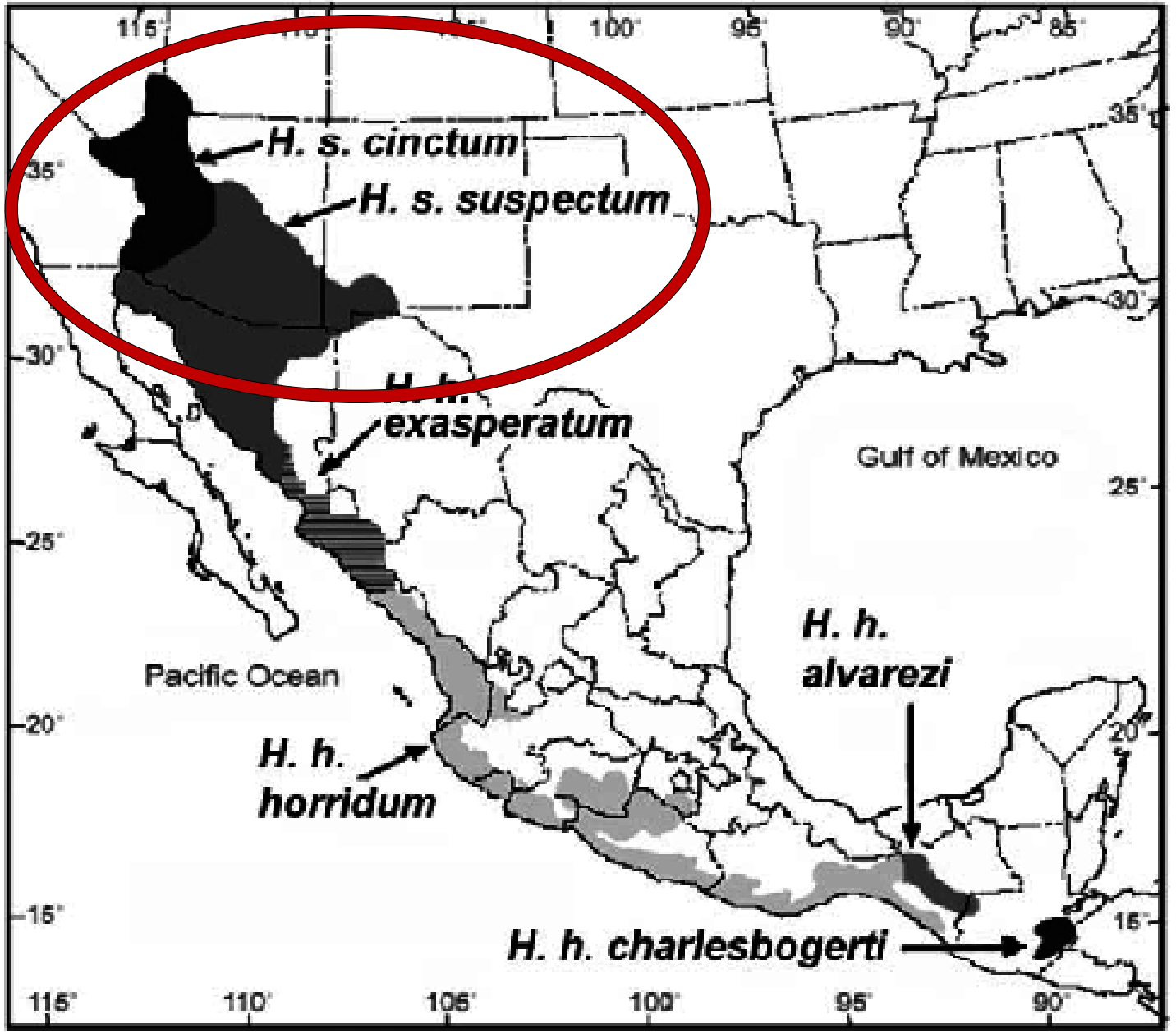
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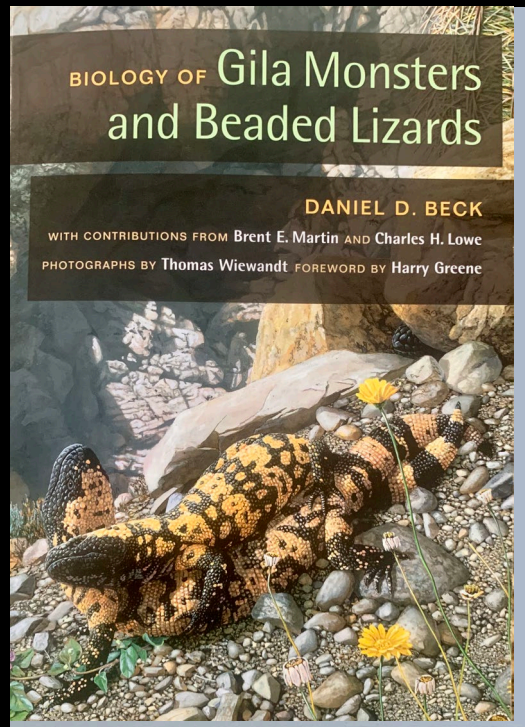
15°

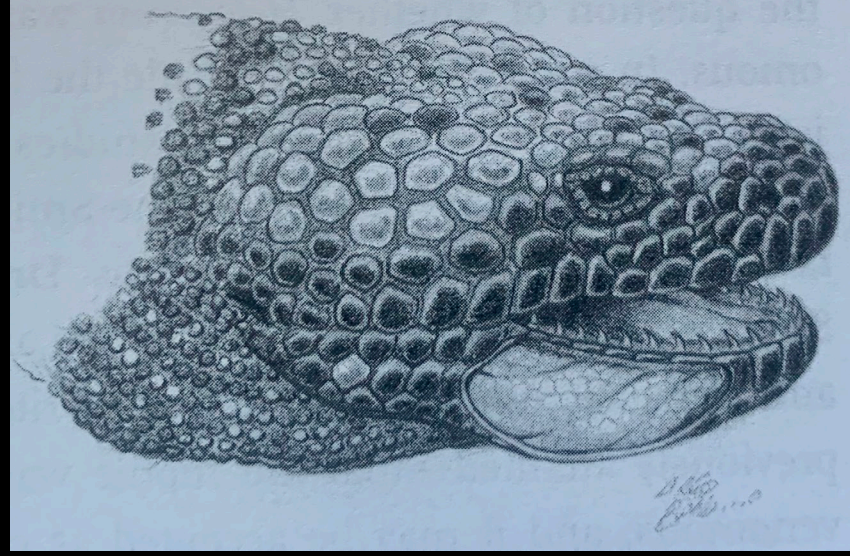
Historical background of the Helodermatida

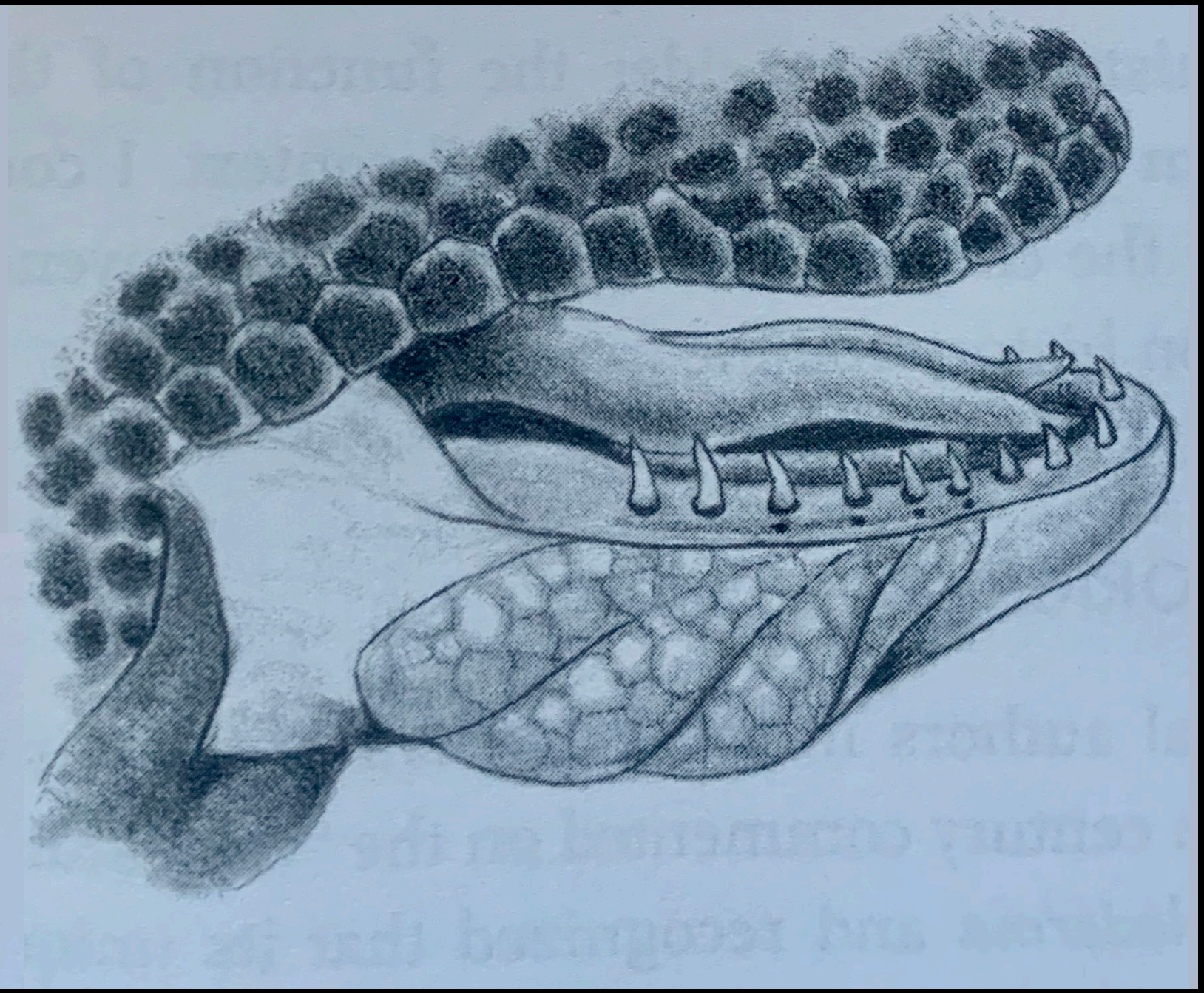
- 1577: (Hernandez) *Heloderma horridum* first described
- 1869: (E.D. Cope) “suspected” Gila monster was venomous: *Heloderma suspectum*
- 1907: (Goodfellow) “reptile was non-venomous” ”bite of the monster is innocuous”
- 1913: (Loeb et al): 244 page text/11 contributors: venom biochemistry, effects on physiological systems in different organisms.
- 1920: Scientific community agreed that helodermatid lizards are venomous and no longer “suspected”

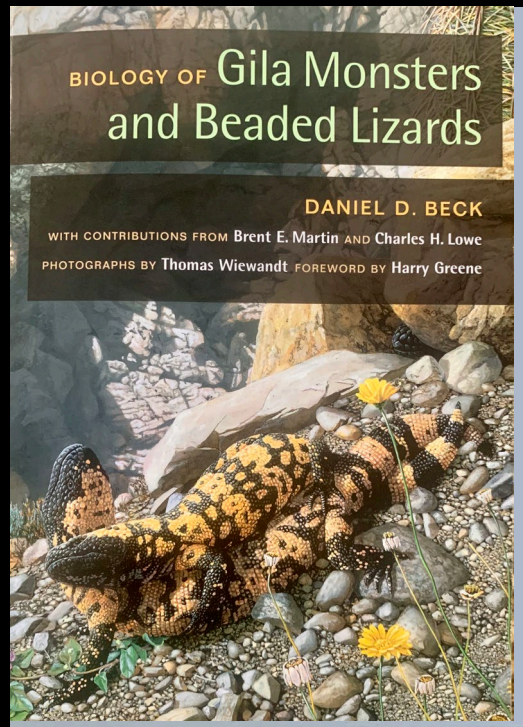
Venom delivery system

- Multilobed venom glands in lower jaw, venom drains through ducts associated with each lobe.
  - Somewhat simple when compared to snakes
  - Defense vs pray
- Venom gland is not surrounded by compressor musculature
  - Unlike venomous snakes
- Movement/pressure from the jaw while biting causes venom to excrete at base of grooved teeth ”venom conducting teeth” and capillary action carries venom into the wound.


BIOLOGY OF Gila Monsters and Beaded Lizards
DANIEL D. BECK
WITH CONTRIBUTIONS FROM Brent E. Martin AND Charles H. Lowe
PHOTOGRAPHS BY Thomas Wiewandt FOREWORD BY Harry Greene



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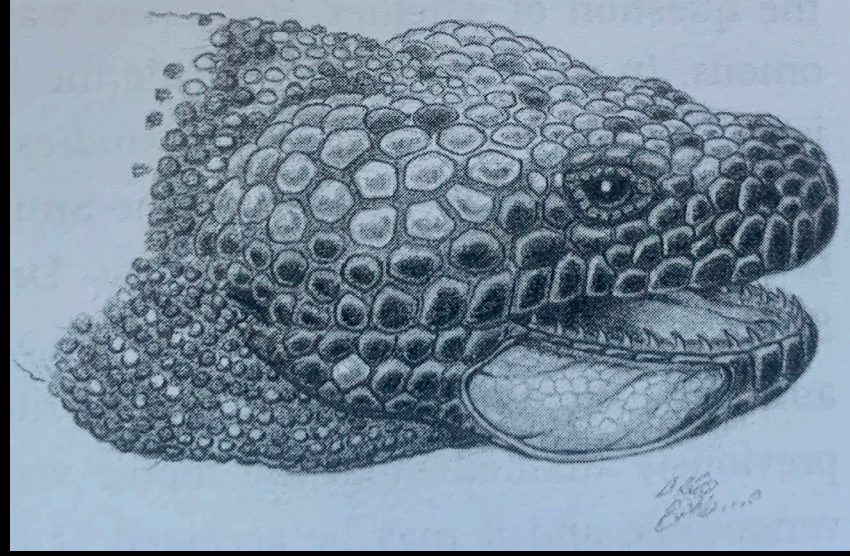

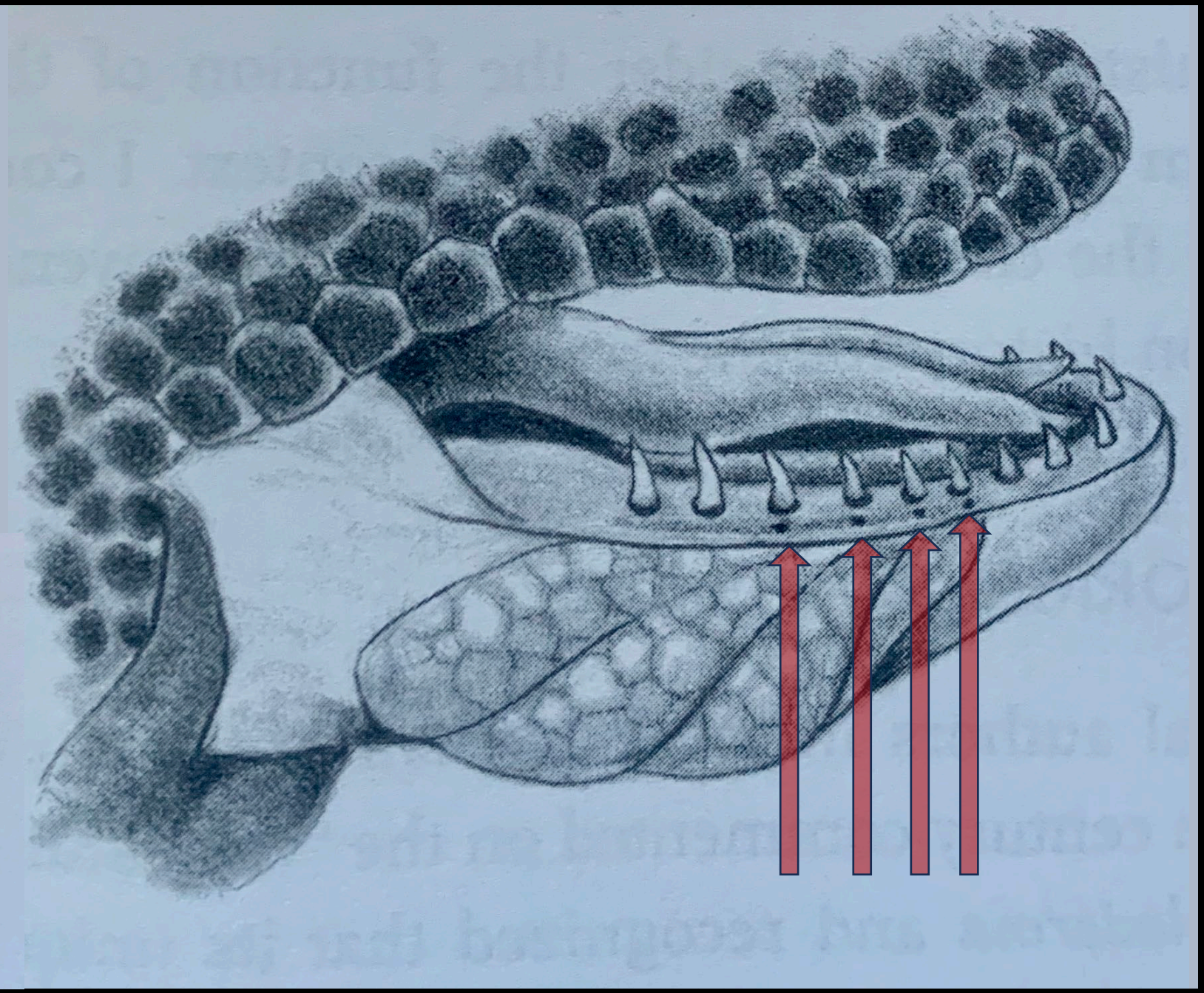

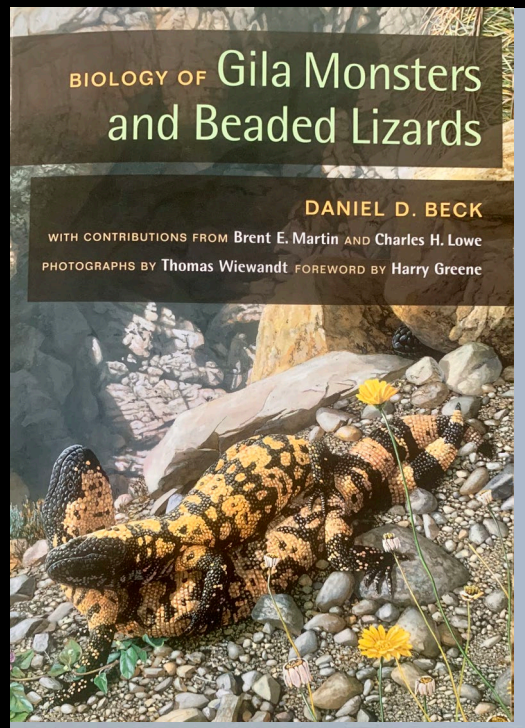
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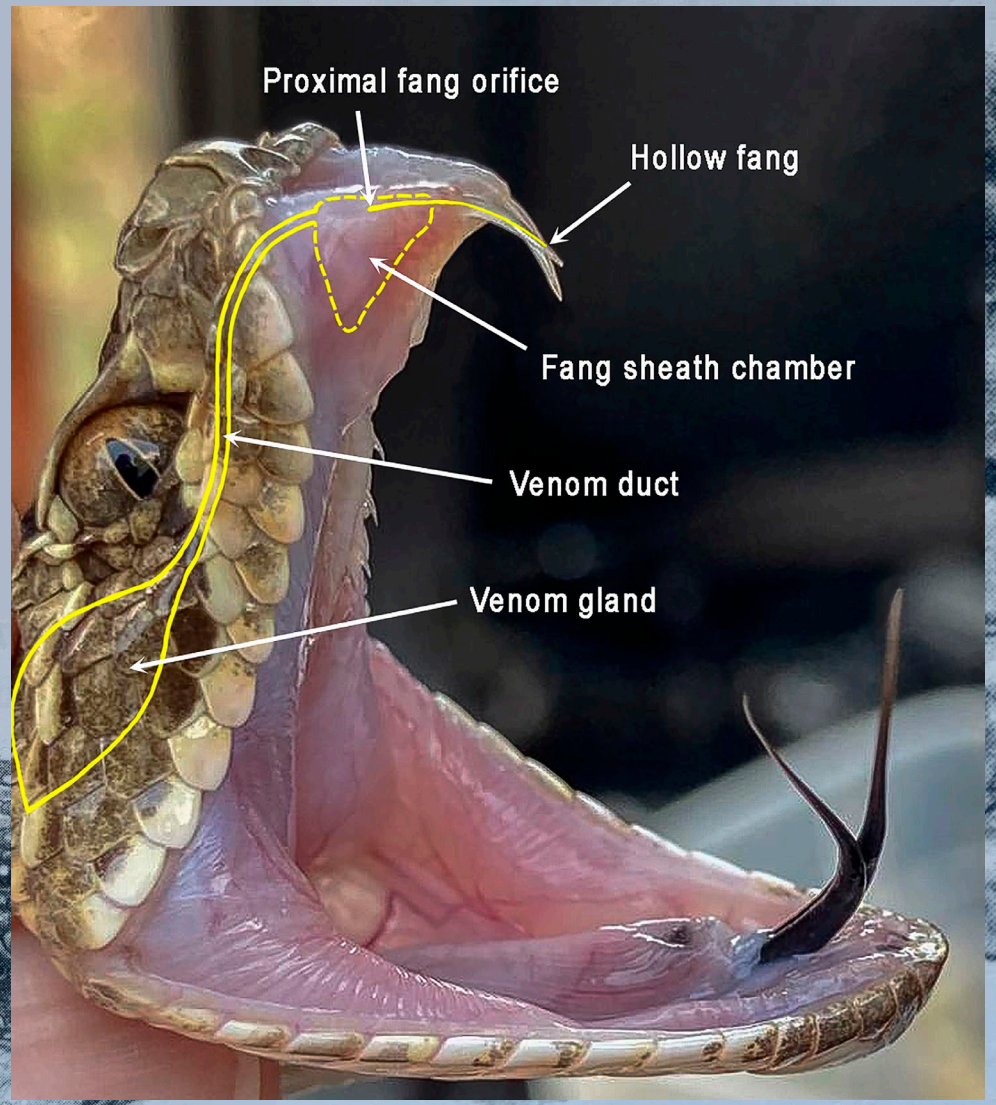
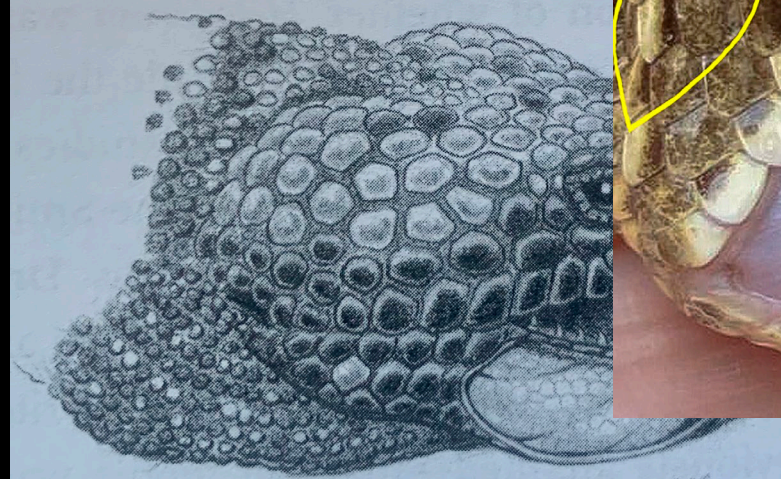
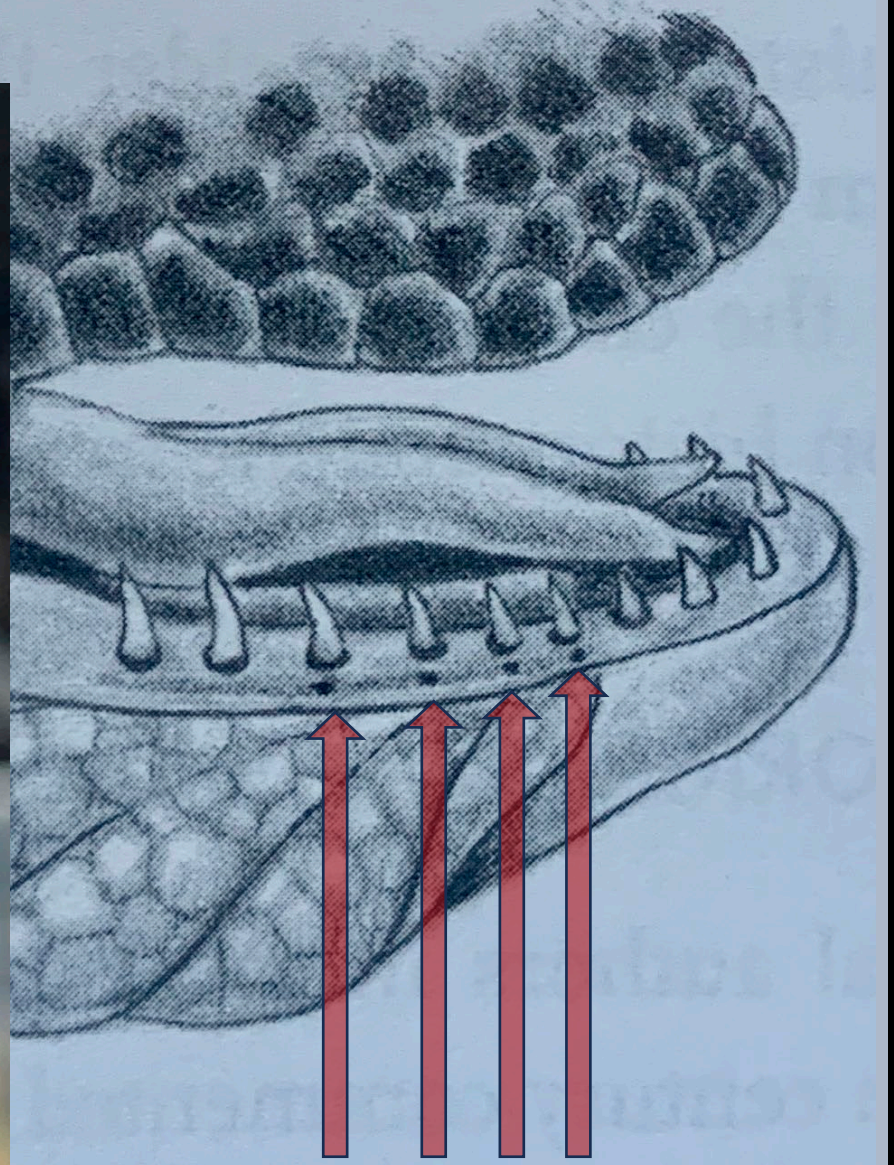
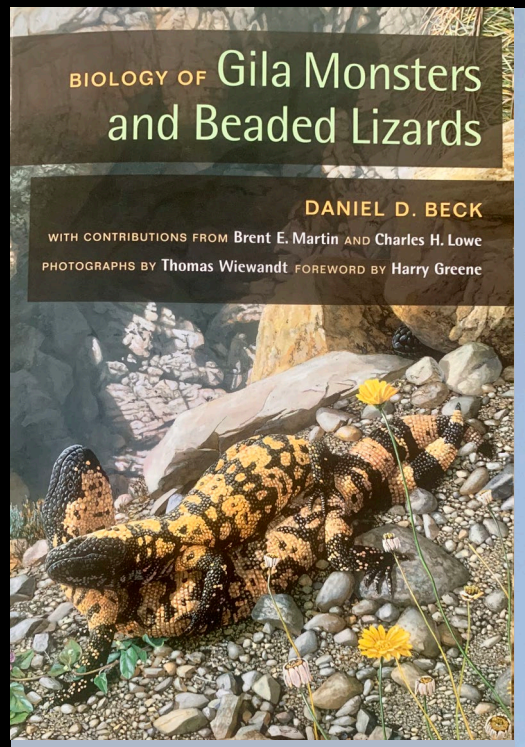

Proximal fang orifice
Hollow fang
Fang sheath chamber
Venom duct
Venom gland



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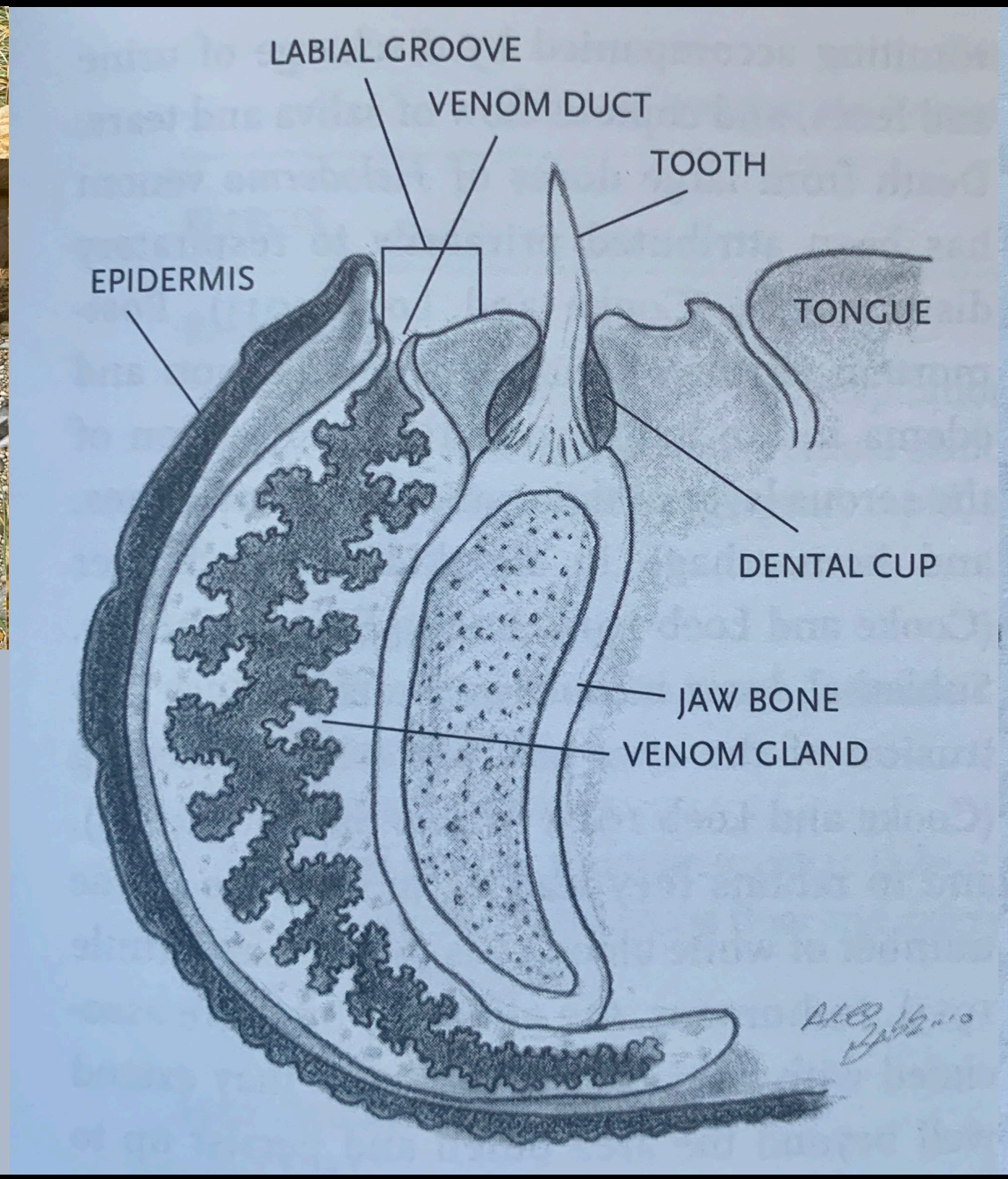
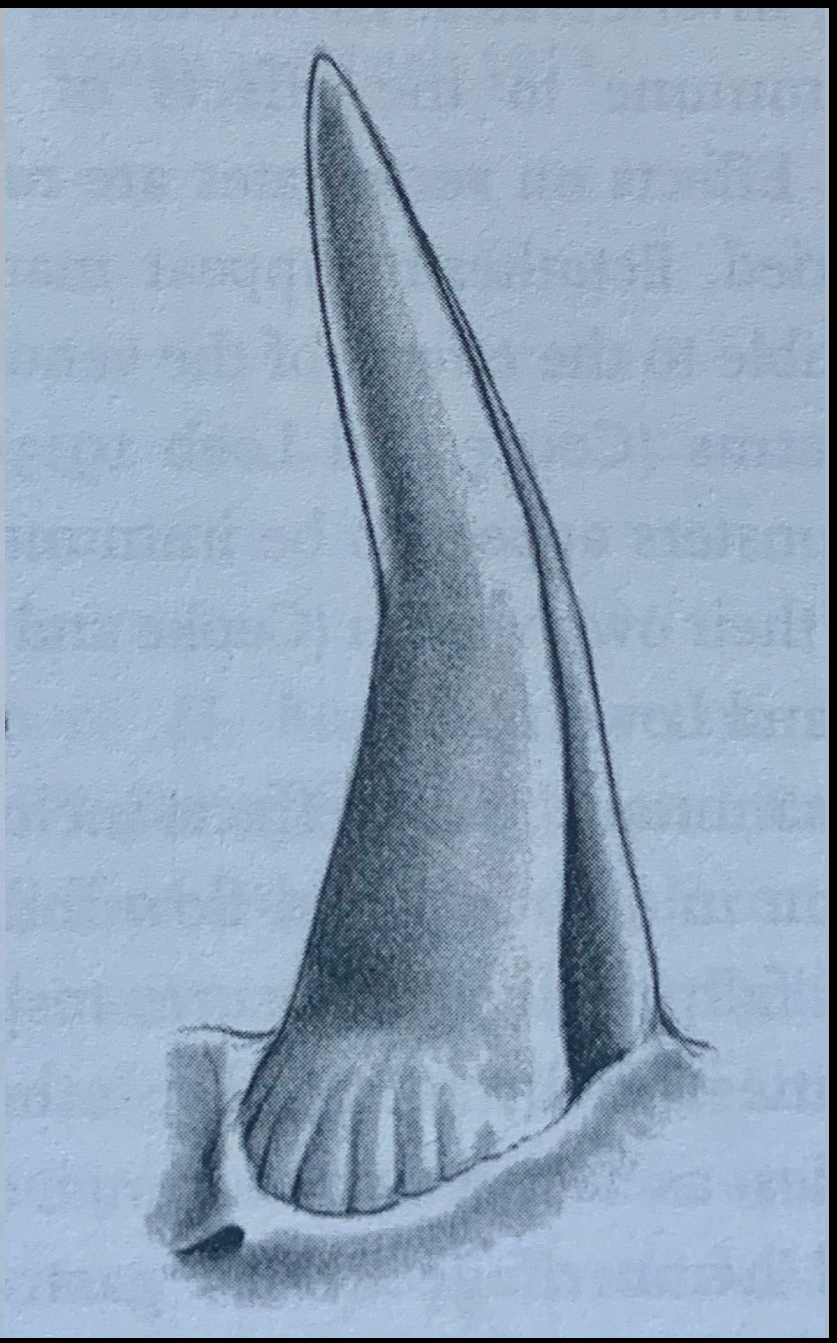

LABIAL GROOVE
VENOM DUCT
TOOTH
EPIDERMIS
TONGUE
DENTAL CUP
JAW BONE
VENOM GLAND



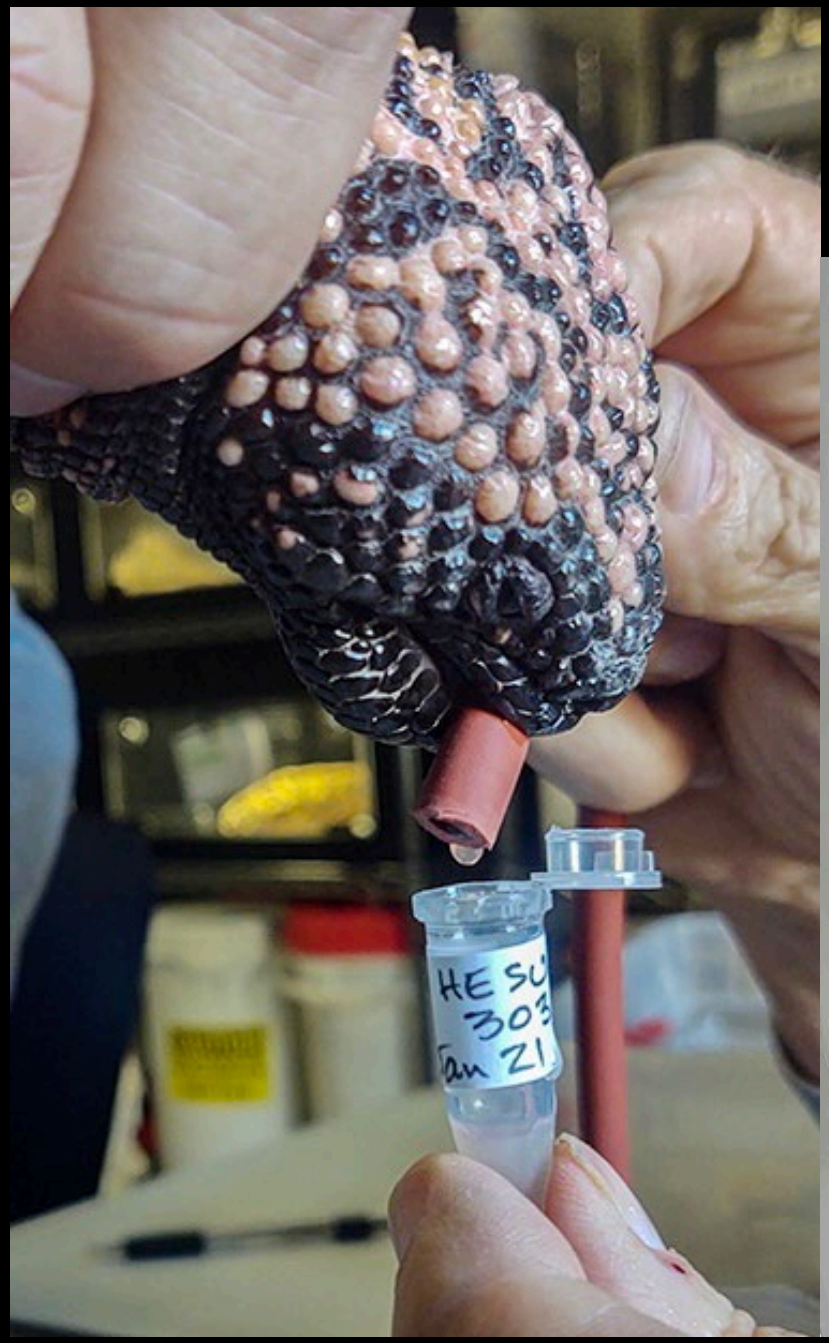
Helodermatida venom research

- 1897: (Santesson) Found two possible toxic compounds
- 1913: (Loeb et al): venom biochemistry, effects on physiological systems in different organisms
- 1960's: serotonin, amine oxidase, hyaluronidase, phospholipase A, kinin-releasing enzyme, kallikrein
- 1980's – 1990s: Enzymatic activity, bioactive venom components identified. The start of drug discovery
  - (Eng et al 1992) *H suspectum*; exendin-4 – most significant

Helodermatida venom research

- Some of the most comprehensive experiments: Loeb (1913)
  - Hundreds of species
    - Invertebrates are essentially immune (unlike some snakes)
    - Ectotherms are less susceptible than endotherms
    - Vertebrates can be severe and varied
- LD 50: varies
  - *H suspectum* 0.4 – 2.7 mg/kg; *H horridum* 1.4-2.7 mg/kg
  - When injected into mammals; LD 50 is comparable to *C atrox* – (Russel and Bogert 1981)
- Nonhuman mammals:
  - Respiratory, cardiovascular, hemorrhage, blood, smooth muscle, edema

Venom constituents



Hyaluronidase

Description/Action	Physiological effect
• Hydrolase enzyme • Cleaves hyaluronic acid	• “Spreading factor” • Facilitates diffusion of venom through connective tissues • Edema effects of bites

Serotonin

Description/Action	Physiological effect

• Neurotransmitter hormone	• Mediates local processes
	  • **Inflammation**
	  • Vasodilation
	  • Smooth muscle activity
	  • Aggregation of platelets

Phospholipase A2 (PLA2)

Description/Action	Physiological effect
• Hydrolase enzyme that act on fat molecules • Catalyze hydrolysis of phospholipid glycerol backbone	• Five types of PLA2 isolated • Effects of *Heloderma* PLA2 are unknown • Snakes • Presynaptic membrane toxins

Nerve Growth Factor

Description/Action	Physiological effect
• Induce nerve growth • Degranulate mast cells	• Unknown • Degranulation of mast cells; thought to contribute to inflammation

Helothermine

Description/Action

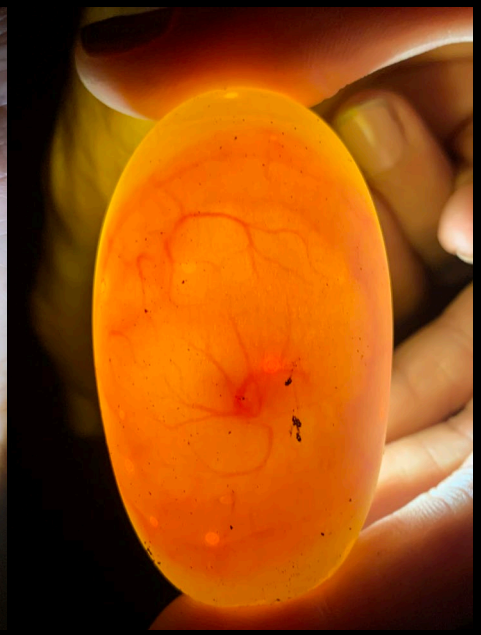
- Peptide
- Blocks ion channels in cell membranes
  - Ca++ cardiac, skeletal muscles
  - Ca++ cerebellar tissues
- No enzymatic activity

Physiological effect

- Mice
  - Lethargy
  - Partial paralysis of hind limbs
  - Lowering of body temperature
    - Hence the name of toxin


THIS SIDE UP
FRAGILE
HANDLE WITH CARE


THIS SIDE UP
FRAGILE
HANDLE WITH CARE



Kallikrein-like toxins SP

- Four types; three considered lethal toxins
- Cause pain
- Hypotensive hormones with powerful local physiological effects
- Cleave kinogens that release bradykinins
  - **PAIN**
  - Inflammation
  - Vasodilation of peripheral arterioles
  - Increase vascular permeability – edema
  - Stimulate adrenaline – increase heart rate

1 of 4 kallikrein-like toxin

Gilatoxin

Description/Action	Physiological effect

• Serine protease glycoprotein
• 1st lethal toxin isolated
  • Hendon and Tu 1981
• Kiniogen and angiotensin
	• Rats
	  • Hypotension
	• Contraction of uterus smooth muscle
	• LD50 decreases when administered in combination with other venom fractions
	  • Synergistic

2 of 4 kallikrein-like toxin

Horridum toxin

Description/Action	Physiological effect

• Glycoprotein similar to gilatoxin
• *H horridum*
• Lethal toxin
• Only hemorrhagic toxin isolated in helodermatid lizards
	• Rats
	  • Hypotension
	  • Hemorrhage in internal organs
	  • Hemorrhage in eyes leading to exophthalmia

3 of 4 kallikrein-like toxin

“Novel” lethal toxin

Description/Action	Physiological effect

• *H horridum*
• Lethal toxin
• Isolated in 1988 and still unnamed through 2005
• Lowest LD50
	• Mice
	  • Suppresses contraction of diaphragm
	  • No hemolytic, hemorrhagic, proteolytic, PLA2, or enzymatic activity

4 of 4 kallikrein-like toxin

Helodermatine

Description/Action	Physiological effect
• Serine protease glycoprotein • *H horridum* • Non lethal	• Rabbits • Dose dependent decrease in arterial blood pressure


304


305


306


307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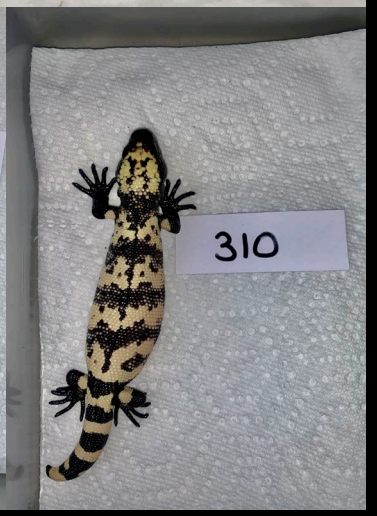

310

Bioactive peptides

- Five types
- 1980's research: helodermatid lizards caused secretory response from pancreatic acini
  - Similar structure and action to VIP
  - VIP powerful relaxant of smooth muscle, mediates secretion of water and electrolytes by small/large intestines
- 1990's research isolated exendins
  - Peptides from the exocrine glands of *Heloderma suspectum*
  - Endocrine actions
  - GLP-1 receptors
    - Insulin release and glucose metabolism

1 of 5 bioactive components

Helospectin I & II (exendin-1)

Description/Action	Physiological effect
• Peptides from exocrine gland having endocrine function	• Simulate amylase release from pancreas • VIP activity

2 of 5 bioactive components

Helodermin (exendin-2)

Description/Action	Physiological effect

• Peptide with stable structure
• *H suspectum*
	• VIP effects
	• Dogs
	  • Prolonged systemic hypotension
	• Rats
	  • Dose dependent hypotension
	  • Via K+ channels

3 of 5 bioactive components

Glucagon-like 3 (exendin-3)

Description/Action	Physiological effect
• Peptide • *H horridum*	• Amylase release from pancreas • Interacts with exendin receptor and mammalian VIP receptors

4 of 5 bioactive components

Exenatide (exendin-4)

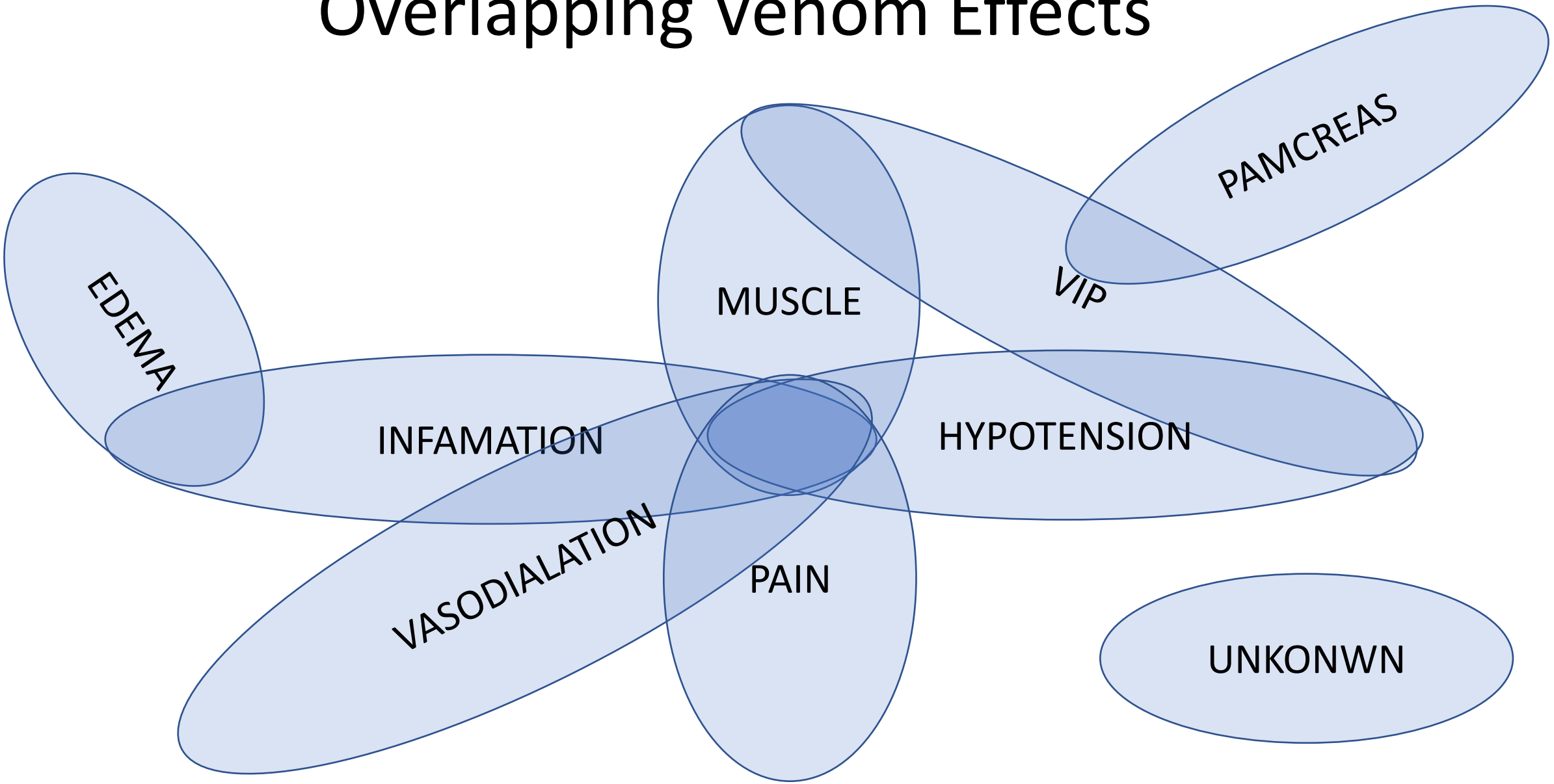
Description/Action	Physiological effect
• Peptide • *H suspectum* • GLP-1 in humans has short half life • Extendin-4 has long biological action	• Induces insulin release through activation of glucagon-like peptide-1 (GLP-1) receptor

5 of 5 bioactive components

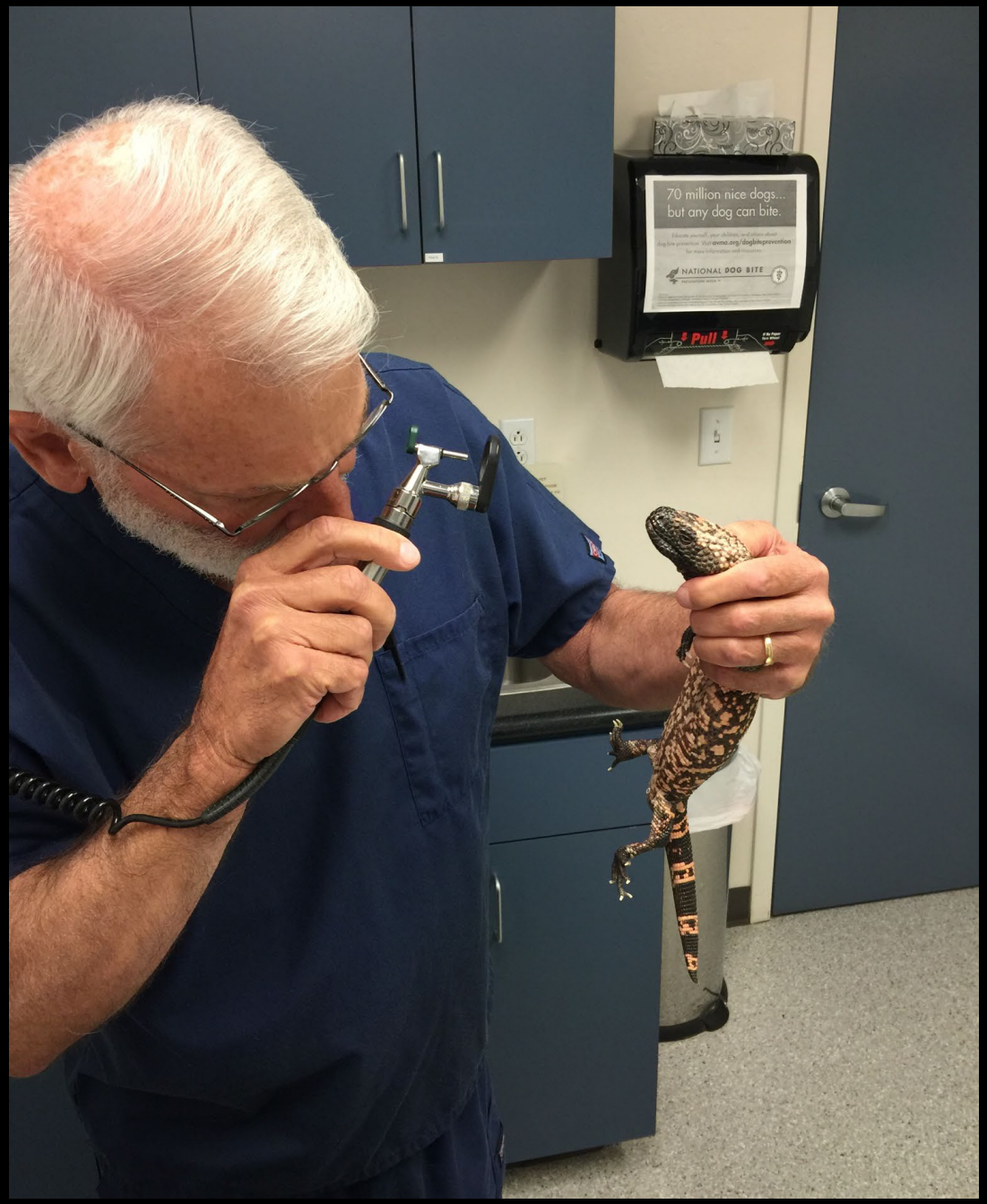
Gilatide

Description/Action	Physiological effect
• Fragment of exendin-4 peptide	• Acts on GLP-1 receptor • Rodents • Improves memory

Overlapping Venom Effects




LINCOLN
ELECTRIC


70 million nice dogs...
but any dog can bite.
NATIONAL DOG BITE
Pull

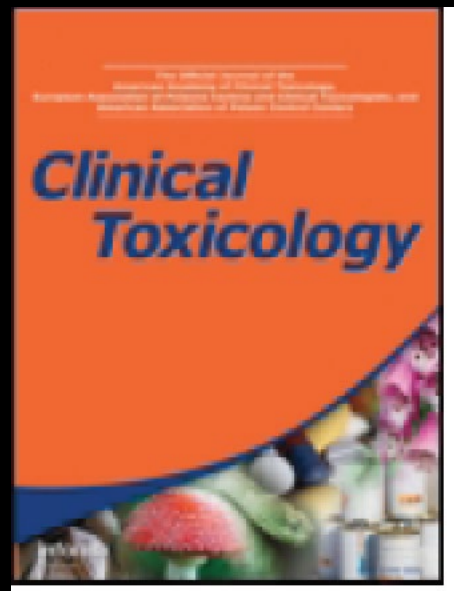
ENVENOMATION

- Most can be avoided
- No antivenom
- Symptomatic treatment

Can be significant

Envenomation

Let sleeping ~~dogs~~ Gilas lie



Clinical Toxicology, 53:1, 60-70

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Information Center

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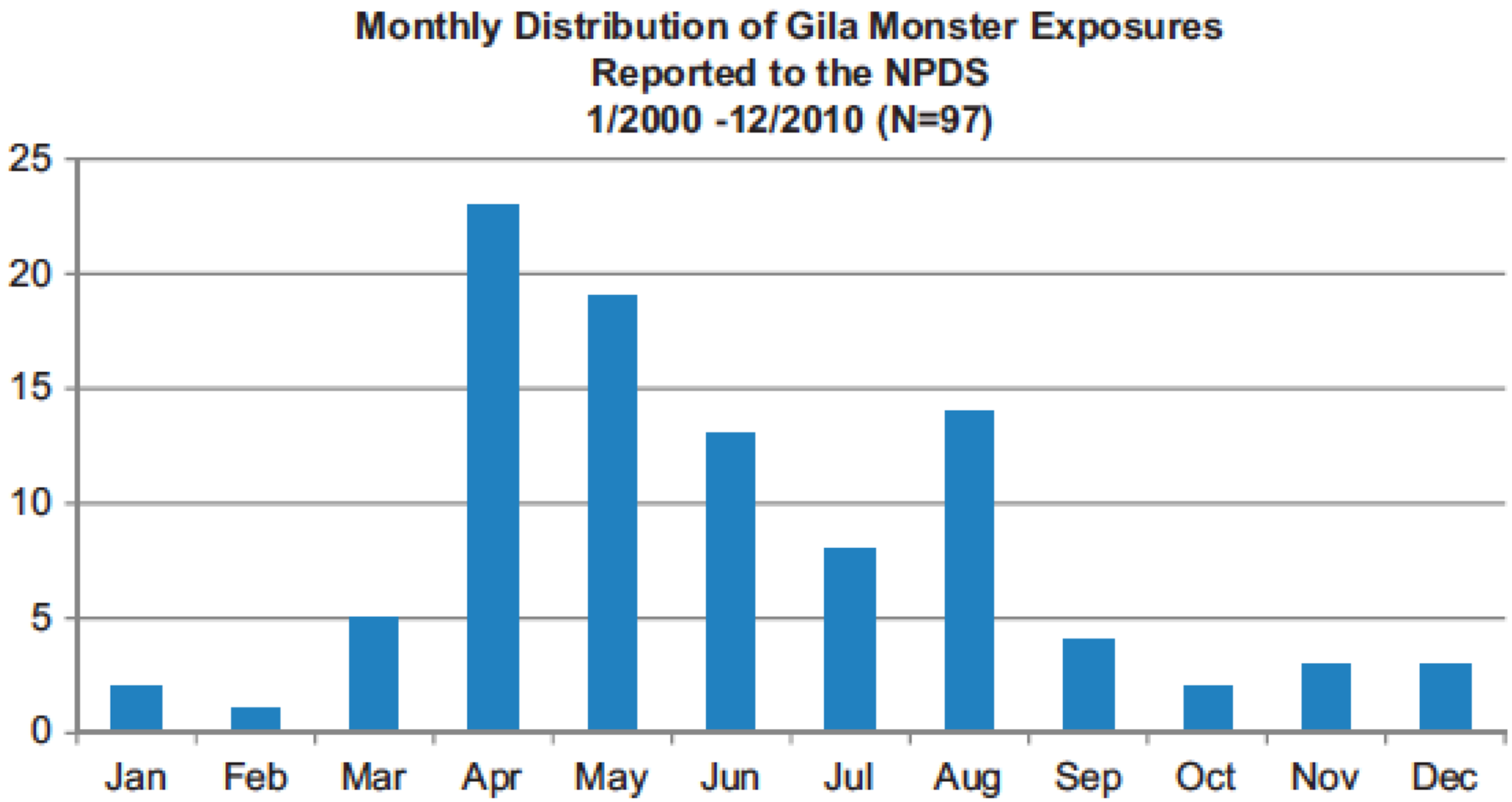
Gila monster (*Heloderma suspectum*) envenomation: Descriptive analysis of calls to United States Poison Centers with focus on Arizona cases

Robert French, Daniel Brooks, Anne-Michelle Ruha, Farshad Shirazi, Peter Chase, Keith Boesen & Frank Walter

Retrospective review of calls concerning Gila's between January 1, 2000 – October 31, 2011 using the American Association of Poison Control Centers National Poison Data System



The Arizona Poison and Drug Information Center
Tucson, Arizona

215 Reports
- 88 Information Only
- 79 Dogs
- 2 Cats
- 1 Cow

45 Human exposure records
- 1 Not a bite

44 Gila monster bite reports

Banner Good Samaritan Poison and Drug Information Center
Phoenix, Arizona

98 Reports
- 55 Information Only
- 11 Dogs
- 2 Cats

30 Human exposure records
- 1 Duplicate report
- 1 Not a bite
- 1 Not a Gila monster

27 Gila monster bite reports

Gila Monster Bite Reports to Arizona Poison and Drug Information Centers

71 Gila monster bite reports
1 Case was reported to both centers and was combined.

70 Unique Gila monster bite reports were included for this review.

Table 1. Anatomic sites of Arizona gila monster bites.

Site of bite	Number
Hand, Finger, or Thumb	46
Unknown or not documented	8
Foot or Heel	6
Arm	3
Neck	1
Neck and finger	1
Finger and forearm	1
Finger and thumb	1
Both thumbs	1
Upper extremity, not specified	1
Trunk	1
Total Arizona PCC cases	**70**

Now the who…any guesses?

- 70 bites – 58 had a Y chromosome
- 54 bites involved upper extremity
- 8 patients <18 yo
- 11 work related
- 28 evaluated at health care facility but not admitted
- 11 admitted to hospital
  - 5 to the ICU
  - 6 edema of airway structures
  - 3 required emergent airway management (1 cricothyrotomy)
  - No deaths

Effects of envenomation reported

Description from patient		Physiological effect recorded in EMR	
• **Pain** • Dizziness • Numbness • Tingling • Burning • Drowsy	• Abdominal cramps • Anxiety • Spasms • Nausea • Syncope • Dyspnea	• **Edema** • Puncture/Bleeding • Erythema • Ecchymosis • Lymphangitis • Tachycardia • Bradycardia • Diaphoresis	• Hypertension • Hypotension • Airway edema • Fasciculation • Vomiting • Incontinence fecal • Incontinence urine

Some of the interesting cases

- 36 yo M: hand: documented incident on video, bite lasted 42 seconds
  - Required intubation, pressors
- 26 yo M: neck and finger: placed Gila on shoulder, bit on neck, Gila fell to ground, he picked it up and placed in his hat, then bit through hat on finger
  - Tongue swollen, difficulty swallowing/breathing
- 46 yo M: neck: no description
  - Required intubation, pressors
- 29 yo M: arm: stated Gila was “moving towards girlfriend” so he placed his arm between them to protect her.
  - Diaphoretic, edema entire arm and airway, tachycardia

What about the ladies?

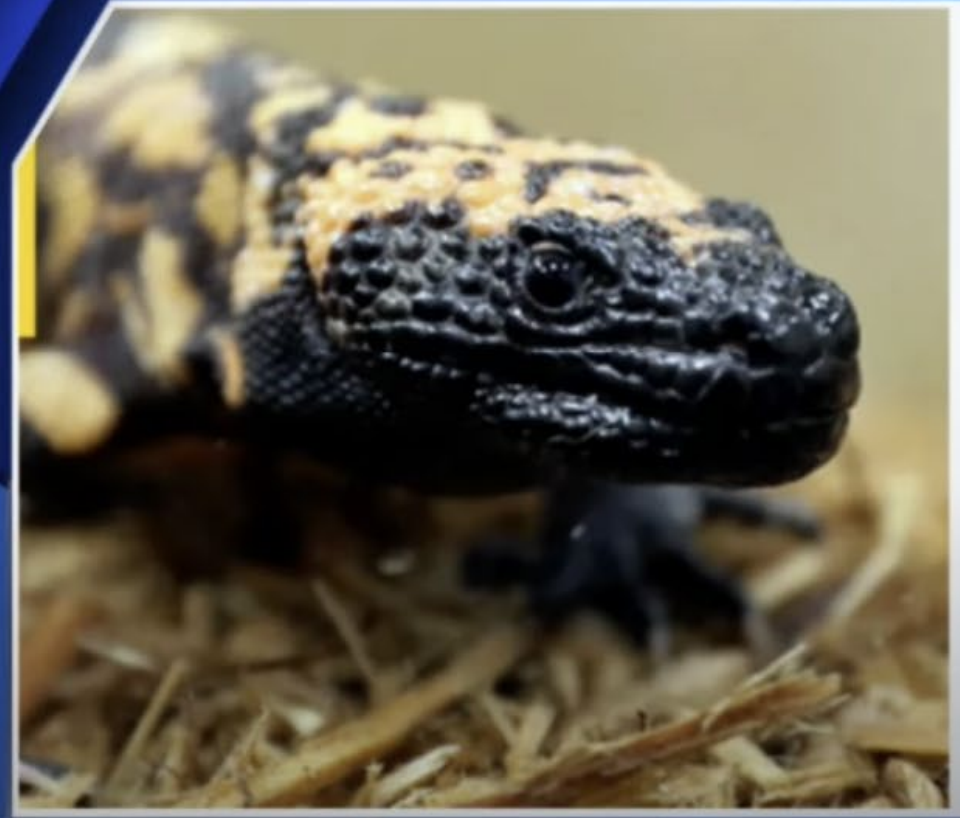
- 26 yo F: hand: researcher bitten through protective gear
- 45 yo F: hand: zoo employee performing procedure
- 49 yo F: finger: bitten while removing Gila from another individual
  - (PROBABLY SOMEONE WITH A Y CHROMASOME)

Conclusion

- Kallikrein-like toxins – hydrolize kininogen and produce bradykinin
  - Pain
  - Local edema – including airway structures
    - Can be delayed
  - Hypotension
- Arizona Gila bites: 15-16% admitted to hospital
  - 4% REQUIRED emergent airway managment
- Nationally Gila bites: 24% admitted to hospital
- Gila bites are uncommon
  - Managed by AZPDIC or in ED and not admitted to the hospital
  - Edema of airway is infrequent (8%) but potentially life threatening
  - Consider 12h observation

34 yr old man, died from complications from a bite from his pet Gila monster on February 16, 2024, less than four days after being bitten.

LAKEWOOD MAN DIES AFTER BITE FROM GILA MONSTER
AUTOPSY RELEASED



- LIZARD BIT HAND FOR 4 MINUTES
- WAITED 2 HOURS TO CALL 911
- COMPLICATIONS FROM THE GILA MONSTER VENOM

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Only in the “Old Pueblo”

Tucson Wall Art - Euclid and Grand