



Amanita Mushroom Poisoning

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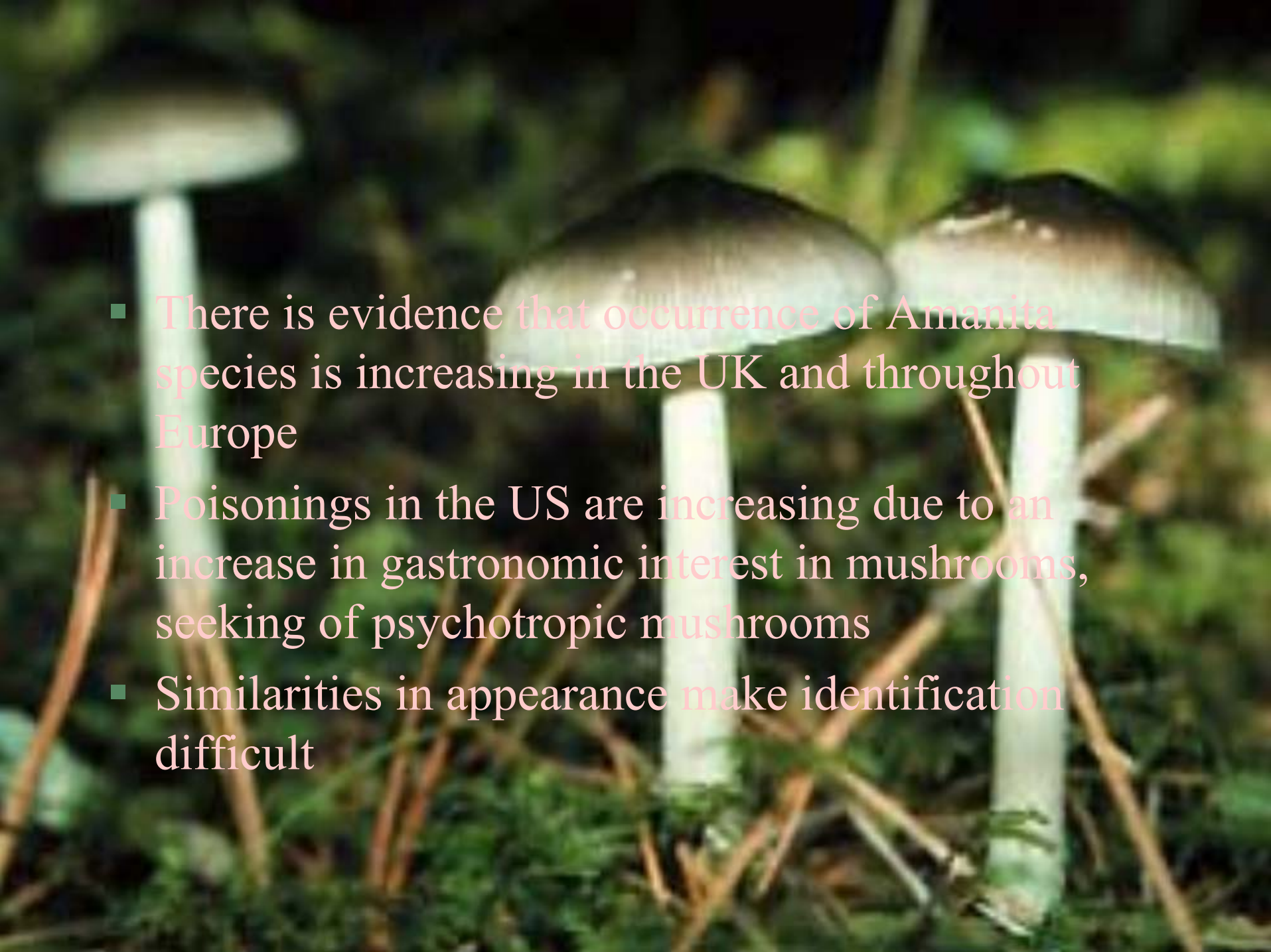
Historical

- Poisonous and hallucinogenic properties known since pre-history
- Amanita species (*A. muscaria*) used by eurasian peoples for shamanic rituals and rites
- *mycology* first became a refined science under the Greeks
- 1871- first documentation of mushroom-related death in US medical literature

The background of the slide is a photograph of a forest floor covered in dark, damp leaves and twigs. Two mushrooms are visible: a large, light-colored mushroom with a gilled cap on the left, and a smaller, round, light-colored mushroom on the right. The text is overlaid on this image.

Scope of problem internationally

- No adequate database exists to estimate worldwide exposures
- Mushroom foraging is more common in parts of Europe and Russia than in other parts of the world.
- From mid-July to September 1998, 9 people died and 180 were poisoned from mushrooms in Russia.
- In 1997, 34 people died of mushroom poisoning across Russia in July and August.
- It is thought that poisonings are vastly underreported worldwide

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- There is evidence that occurrence of *Amanita* species is increasing in the UK and throughout Europe
 - Poisonings in the US are increasing due to an increase in gastronomic interest in mushrooms, seeking of psychotropic mushrooms
 - Similarities in appearance make identification difficult

Mushroom poisoning in the US



- **In the US:** In 1996, 10,584 mushroom exposures were reported to the American Association of Poison Control Centers.
- Eighty-eight percent of reported mushroom exposures were unidentified.
- Only 54 were identified as amatoxin exposures; however, this number is undoubtedly an underestimation given the number of unknown mushroom exposures
- One author estimates incidence of mushroom exposures at 5 exposures per 100,000 population per year. (Chang, 2001)

The Culprit: Amanita

- Nearly all lethal mushroom poisoning worldwide caused by members of the genus **Amanita**
- Most common are *A. phalloides* (also known as the European death cap) , *A. virosa*, and *A. bisporigera*
- *Amanita* sp. Contain three classes of toxin: **amanitins, Virotoxins, and phalloidins**

- **Virotoxins and Phallotoxins** are present in smaller concentrations, are heat labile, and are generally of less concern from a toxicologic standpoint.
- **Amatoxins are the compounds of most concern**

(Chang 2001, Vetter 1998)

Mortality/Morbidity:

- “Ninety-five percent of all mushroom fatalities in North America are associated with cyclopeptide-containing species (amatoxins). Worldwide, most mushroom fatalities are ascribed to amatoxins. Amatoxins are associated with mortality rates ranging from 10-60%.”(Chang, 2001)

Amanita mushroom poisoning can be divided into three stages clinically:

- Latent period
- Gastrointestinal phase
- Clinically apparent hepatic and renal failure

(Chang, 2001)

Phase I: Latent period

- “Amatoxin poisoning has a characteristic latent period of 6-12 hours postingestion before onset of clinical symptoms (Chang, 2001)
- despite lack of symptoms, amatoxin is binding to RNA

(Chang 2001, Jaeger 1993)

Phase II: Gastrointestinal

- “After this asymptomatic period, abdominal cramping, vomiting, and profuse watery diarrhea (rice water, cholera-like) occur. Fluid losses may be severe enough to cause profound dehydration and even circulatory collapse”.

Phase III: Hepatic and Renal Failure

- “Although the patient appears to have improved clinically, ongoing liver damage is occurring as indicated by laboratory abnormalities (elevation of serum aminotransferases, prothrombin time). This stage may last as long as 2-3 days.”
- Hepatic and renal injury become clinically apparent and may progress to fulminant hepatic failure in the third phase. Death may occur in 3-7 days.

Other general clinical features:

- symptoms attributable to hepatic dysfunction, such as jaundice, lethargy, or bruising.
- Tachycardia
- hypotension
- poor turgor
- Neurologic (generally due to hepatic/hypoglycemia): confusion, lethargy, coma

Labs:

Liver function tests:

- Prothrombin time
- Aminotransferases
- Bilirubin
- alkaline phosphatase

(Chang, 2001, Olson 1982. Rosenthal 2001)

Labs:

- CBC
- Electrolytes, BUN, Creatinine
- Glucose (should be monitored closely with liver failure)
- urinalysis (for proteinuria and hematuria)
- Amylase/lipase (to detect pancreatitis)

Experimental labs:

Vetter describes several newer experimental techniques for quantification of Amanitins and other amanita toxins in biological samples (patient, mushroom samples, and animals)

- HPLC for use with serum, plasma and urine
- RIA (radioimmunoassay) for detection of immunoglobulins and labeled hapten
- limit of detection is 3 ng/ml

Treatment:

- **Gastric lavage-** within 1 hr of ingestion if possible. Efficacy uncertain
- **Administration of activated charcoal-** interrupts enterohepatic circulation
- **Aggressive IV rehydration, glucose repletion**

(Olson 1982, Chang 2001)

The following drugs are thought to reduce uptake of amanitins into hepatocytes:

- High dose Penicillin
- Silibinin (an extract from milk thistle, not available domestically)
- Vitamin K (for coagulation problems)

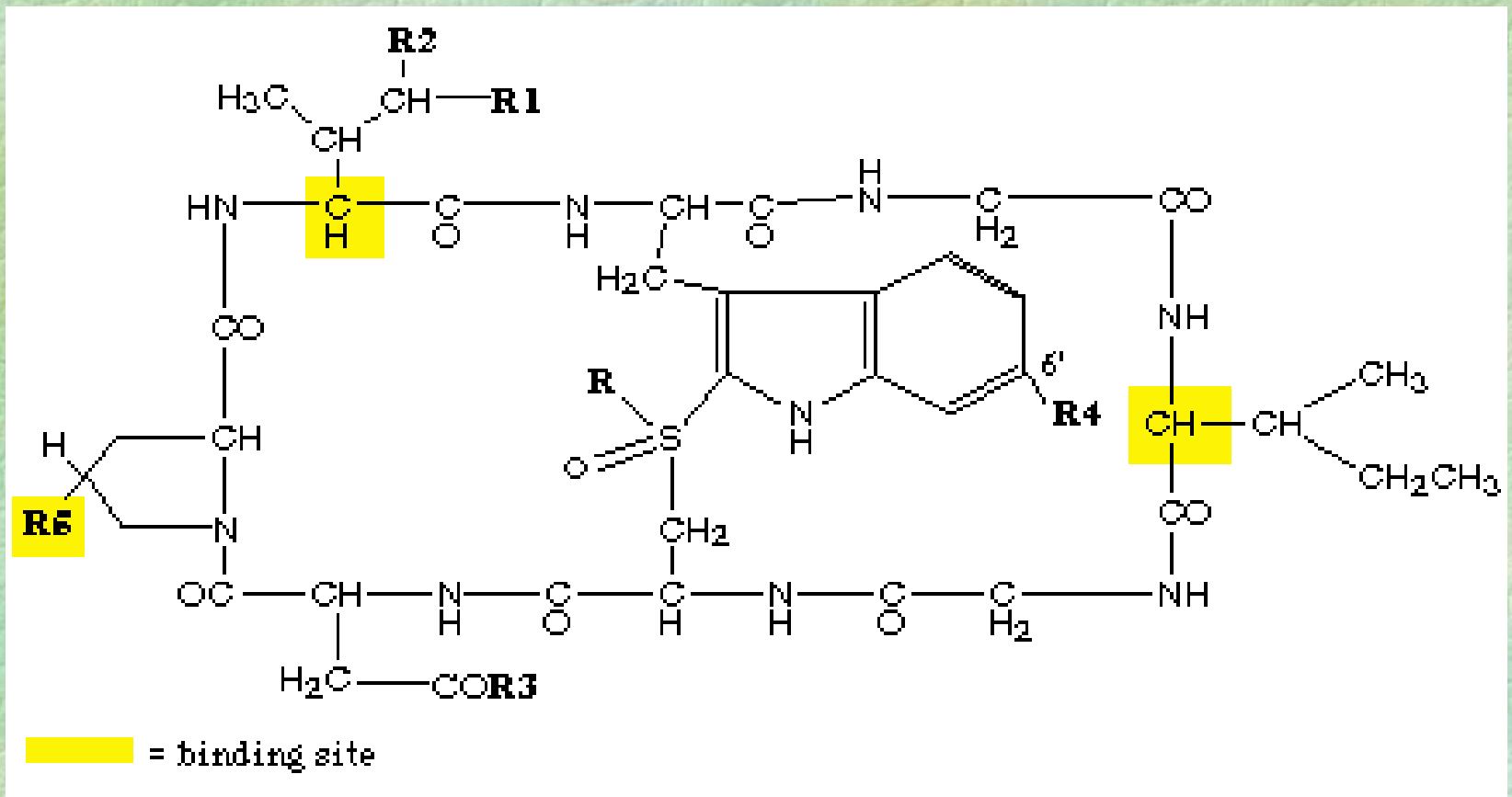
Animal studies support effectiveness, Human data is largely anecdotal

(Olson 1982, Chang 2001)

- “**Amatoxins** (cyclic octapeptides) represent 1 of 3 groups of cyclopeptides and are heat-stable, insoluble in water, and not destroyed by drying. At least 5 subtypes of amatoxins exist; alpha and beta amatoxins are the most significant subtypes”

(Navarro, 2001)

General structure of Amatoxin (weiland 1986)



Absorption

- amanitins are not hydrolyzed by enzymes found in the stomach or gut of mammals and seem to be readily absorbed by the intestine.
- The family is moderately lipid soluble, with different compounds affected by functional groups

Toxicokinetics

- concentrate in liver and kidney cells
- fragmentation of the nucleoli as early as 30 min. after administration.
- changes in the cytoplasm as early as 48 hrs after poisoning and rapidly leading to necrosis.
- Parenchymal cells of liver (and kidney) are targeted by low molecular amatoxins
- sinusoidal cells targeted by macromolecular protein conjugates

Toxicokinetics

- Lesions in the proximal tubes of the kidney are also commonly observed
- suggests that reabsorption of the toxin through the glomeruli is an important factor in the development of nephrosis

Toxicokinetics

- **Amatoxins primarily inhibit RNA polymerase II**
- Inhibition of RNA polymerase III is transient and can be recovered from, a few hours after toxin administration.
- RNA polymerase I is insensitive to the toxin.

(Navarro, 2001)

Toxicokinetics

- amatoxins stops the translocation of the enzyme along the DNA template after the formation of the first phosphodiester bond.
- Inhibitory binding constants vary among the natural toxins primarily by the side chain in position 3 and the structural features that interact between agents and receptor.
- binding involves hydrogen bonding and hydrophobic interactions.
- Hydrogen bonding seems to be an important part of the binding interaction since dissociation rates increase with their loss

Amatoxin binding to RNA polymerase II involves the binding at three sites

- hydroxylated L-isoleucine side chain in position 3
- isoleucine located in position 6
- *trans*-4-hydroxyl group at proline in position 2
- Binding occurs to the 140 KD subunit of RNA polymerase

(weiland 1986)

Excretion:

(from Vetter study, 1998)

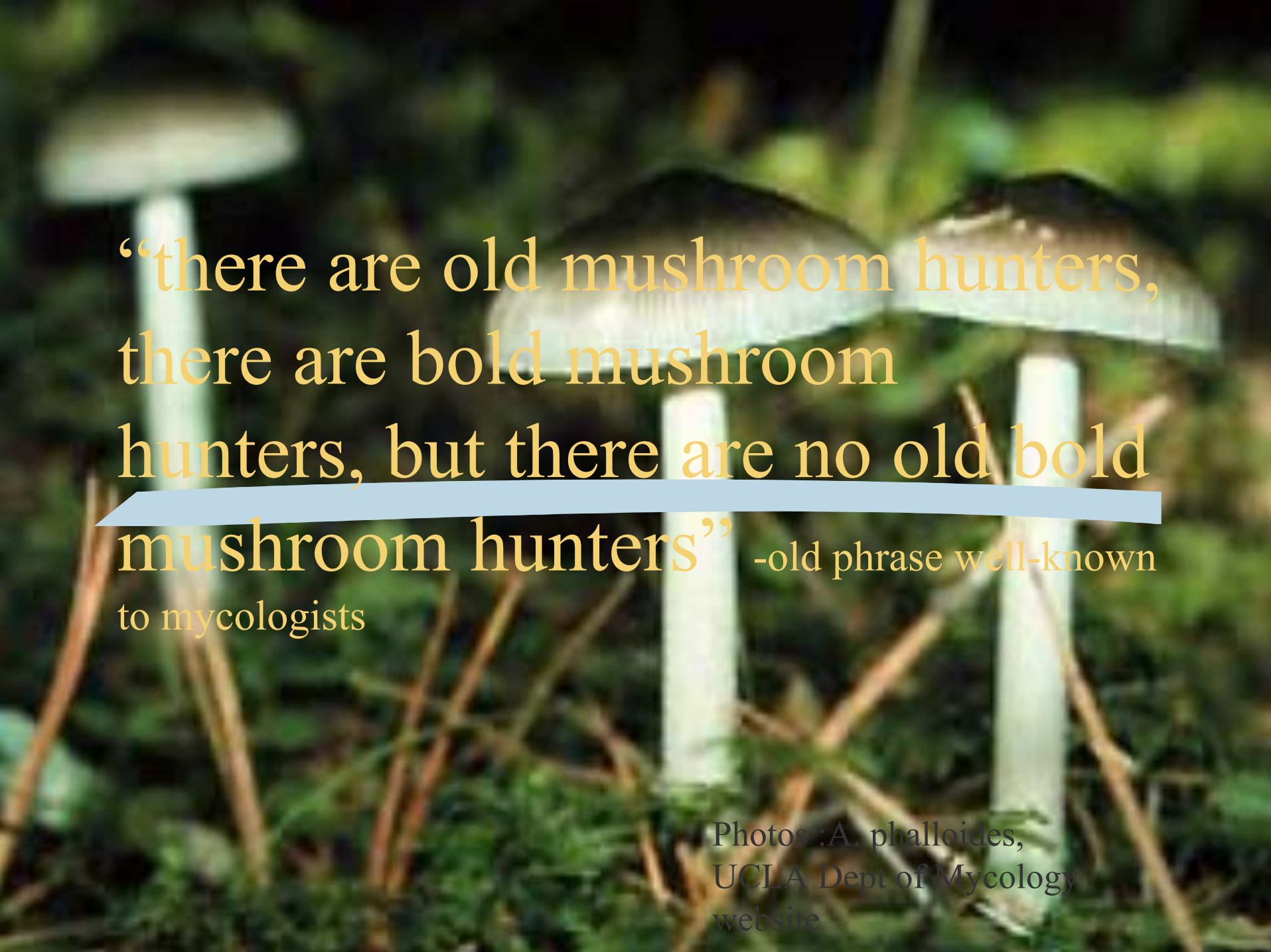
- Plasma concentrations for α -amatoxin ranged from 8-19 ng/ml, β -amatoxin 20-162 ng/ml after an average period of 37.9 hours after ingestion
- “32.8 ug excreted in urine”(volume not indicated)
- “8.4-152 ug excreted in faeces”
- detectable in plasma for up to 36 hours
- detectable in urine for up to 4 days

(Vetter, 1998)

Can amanitins be used in cancer therapy?

- injections of "very dilute" solutions of alpha-amanitin into skin tumors in mice produced an initial inflammatory response
- After this response, tumors necrotized, lesions healed
- Mechanism of inhibition of proteins synthesis makes it interesting in relation to cancer

(Navarro 2001)



“there are old mushroom hunters,
there are bold mushroom
hunters, but there are no old bold
mushroom hunters” -old phrase well-known
to mycologists

Photos :A. phalloides,
UCLA Dept of Mycology
website

Chang, Andrew, eMedicine Journal, May 31 2001, Volume 2, Number 5

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