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Skin Toxicity

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TOXIC RESPONSES OF THE SKIN

- Skin is the body's first line of defense against external insults.
- The skin's large surface area (1.5–2 m^2) is exposed routinely to chemicals and may serve as a portal of entry for topical contactants.
- Based on frequency, severity, and the potential for prevention, the National Institute of Occupational Safety and Health in the US placed skin disease in the top ten leading work-related diseases.

SKIN AS A BARRIER

- The skin protects the body against external insults to maintain internal homeostasis.
- Its biological sophistication allows it to perform a plenty of functions above and beyond that of a suit of armor.
- Physiologically, the skin participates directly in thermal, electrolyte, hormonal, metabolic, and immune regulation, without which a human would perish.
- If an insult is severe, acute or chronic injury becomes readily manifest in various ways, depends on a variety of intrinsic and extrinsic factors including body site, duration of exposure, and other environmental conditions.

Percutaneous Absorption

- The skin was thought to provide an impervious barrier to exogenous substances.
- Gradually, the ability of substances to penetrate the skin became appreciated.
- The stratum corneum has been recognized as the primary barrier.
- Diseases (e.g., psoriasis) or other conditions (e.g., abrasion, wounding) in which this barrier is compromised can permit greatly increased uptake of poorly permeable substances, as does removal of the stratum corneum by tape stripping or organic solvents such as acetone.

- The viable layer of epidermis provides a much less effective barrier, because hydrophilic chemicals readily diffuse into the intercellular water, while hydrophobic chemicals can partition into cell membranes, and each can diffuse readily to the blood supply into the dermis.

- Two intrinsic factors contribute to the absorption rate of a given compound:

1. Its hydrophobicity, which affects its ability to partition into epidermal lipid.

- Its rate of diffusion through this barrier.

- This is particularly relevant for exposure to contaminated water, as occurs during bathing or swimming.

- Partitioning of a chemical into the skin is greatly affected by its solubility in or adhesion to the medium in which it is applied.

- Similarly, very hydrophobic compounds, once in the stratum corneum, may diffuse only very slowly into less hydrophobic regions below.

2. The second property is an inverse function of molecular weight (MW) or molecular volume. Thus, hydrophobic agents of low MW permeate the skin better than those of high MW.

- Diffusion through the epidermis is considerably faster at some anatomical sites than others.

- A list in order of decreasing permeability gives the following hierarchy: foot sole > palm > forehead > abdomen.

- Under ordinary conditions, absorption through the epidermal appendages is generally neglected, despite the ability of chemicals to bypass the stratum corneum by this route, because the combined appendageal surface area is such a small fraction of the total available for uptake.

- In some cases, the effects of appendages can even be dominant, such as benzo(a)pyrene penetrates the skin of haired mice several-fold faster than that of hairless strains.

Transdermal Drug Delivery

- The ability of the stratum corneum to serve as a store for exogenously applied chemicals is well illustrated by the recent development of methods for the delivery of pharmaceuticals.

- Application of drugs to the skin can produce systemic effects, a phenomenon observed unintentionally before the ability of the skin to serve as a delivery system was appreciated.

- For example, topical exposure of young girls to estrogens has led to reports of pseudoprecocious puberty, whereas in young or adult males, such exposure has produced gynecomastia.

- Specially designed patches are currently in use to deliver estradiol, testosterone, nitroglycerin, and nicotine for therapeutic purposes.

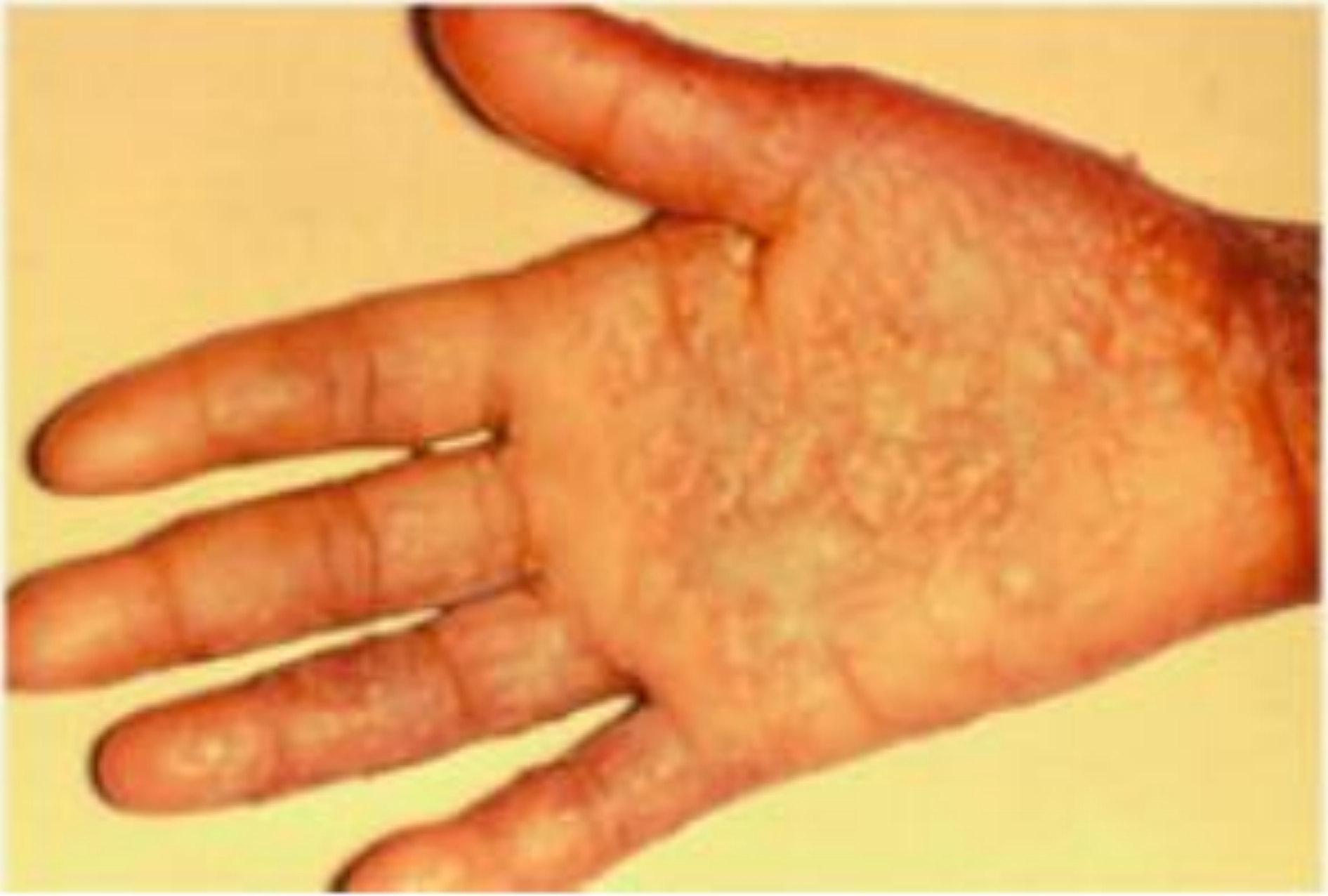
- The advantages of this approach over oral dosing include:
  - Providing a steady infusion for extended periods (typically 1–7 days), thereby avoiding large variations in plasma concentration.
  - Preventing exposure to the acidic pH of the stomach.
  - Avoiding biotransformation in the gastrointestinal tract or from first-pass removal by the liver.
- The contrast in plasma concentration kinetics between different methods of delivery is particularly evident for agents that are rapidly metabolized, such as nitroglycerin, which has a half-life of a few minutes.

Measurements of Penetration

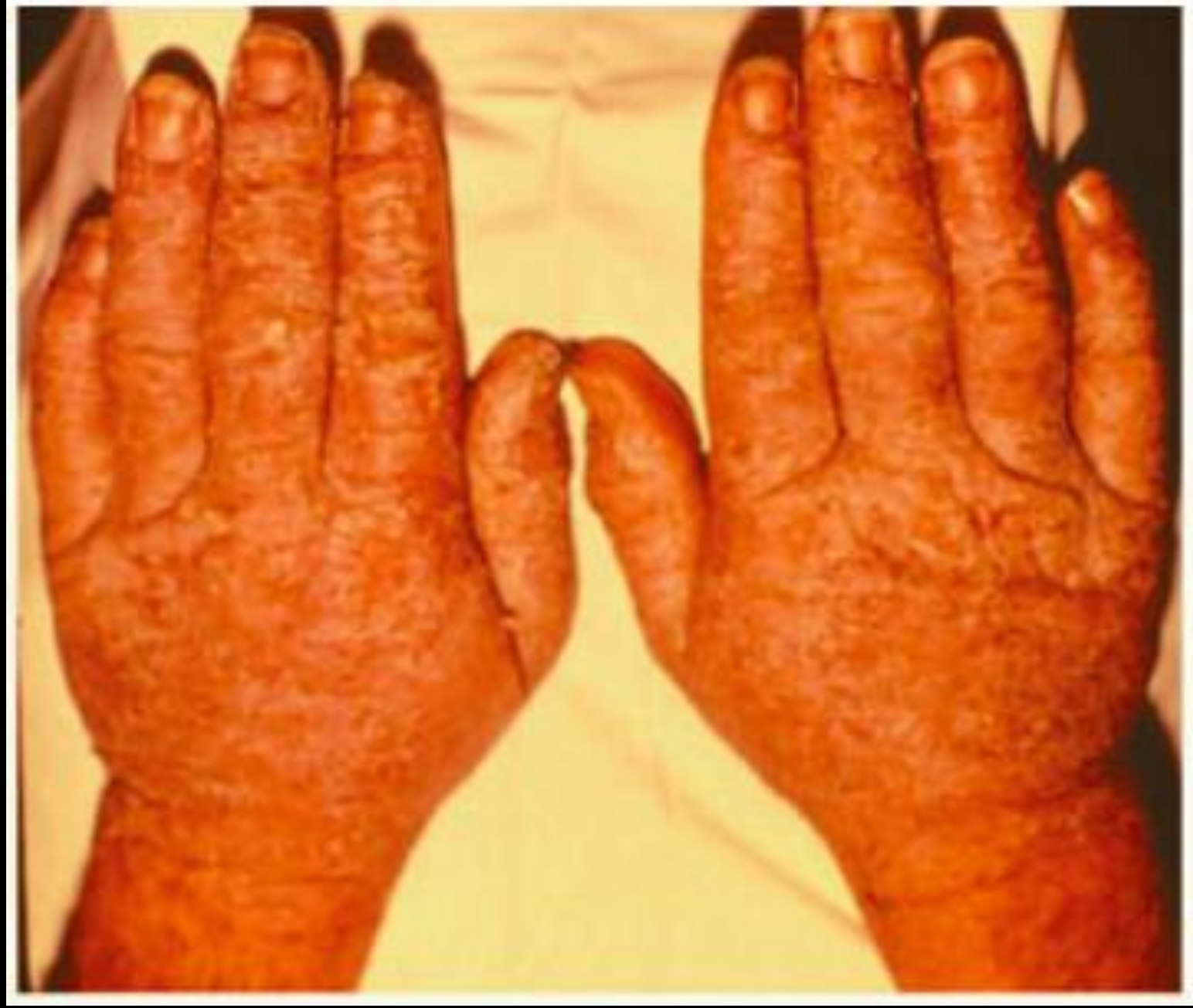
- The most useful subject for experimentation is human skin.
- For in vivo work, volunteers are dosed, plasma and/or urine concentrations are quantified at suitable intervals, and amounts excreted from the body are estimated.
- For in vitro work, excised split-thickness skin can be employed in special diffusion chambers, and the chemical is removed for quantification from the underside by a fluid into which it partitions.

Biotransformation

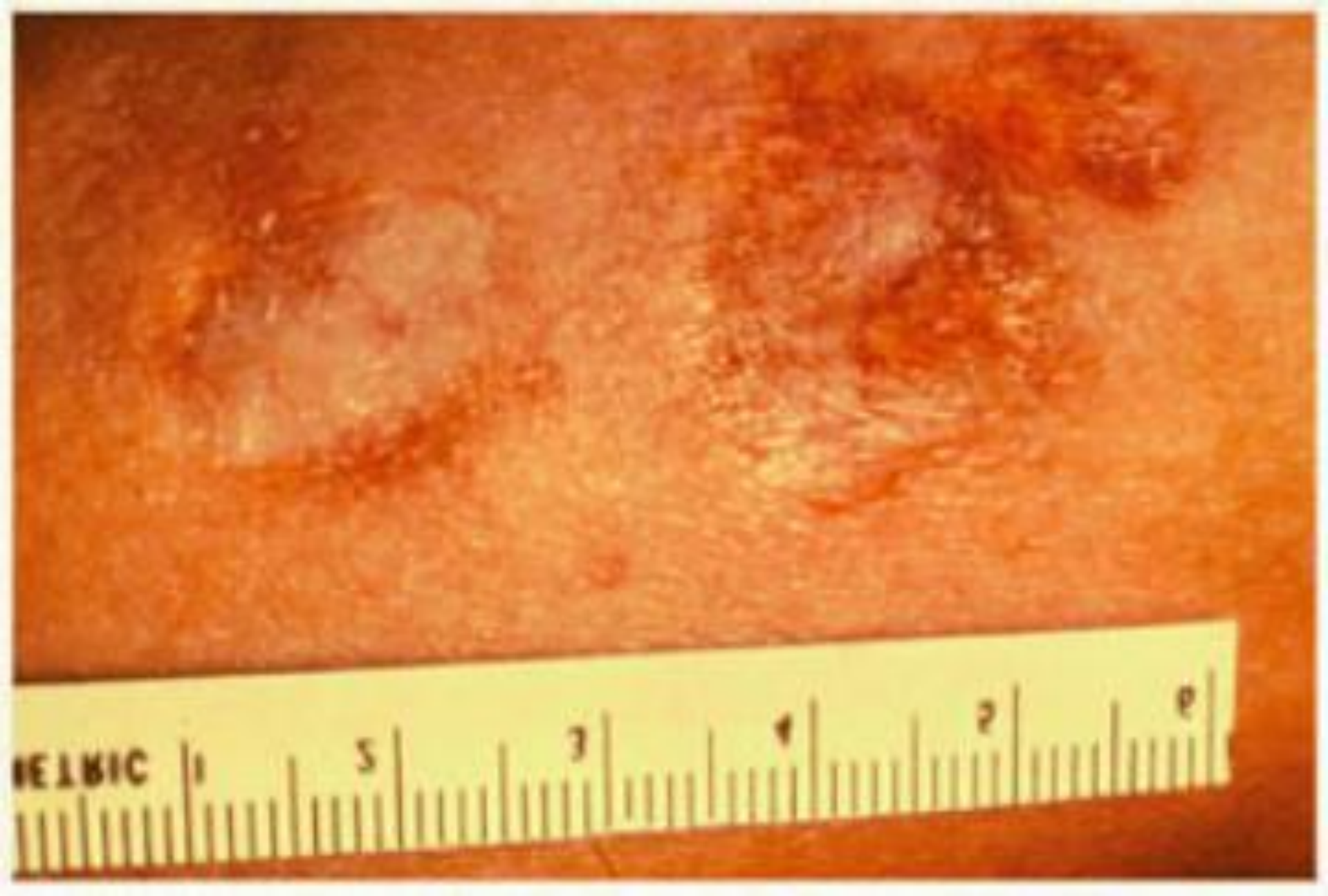
- The ability of the skin to metabolize chemicals that diffuse through it contributes to its barrier function.
- The epidermis and pilosebaceous units are the most relevant and, indeed, are the major sources of such activity in the skin.
- On a body-weight basis, phase I metabolism in this organ usually is only a small fraction (~2%) of that in the liver.
- The epidermis of the neonatal rat is treated with benzo(a)pyrene, P450 activity in the skin can exceed 20% of that in the whole body.



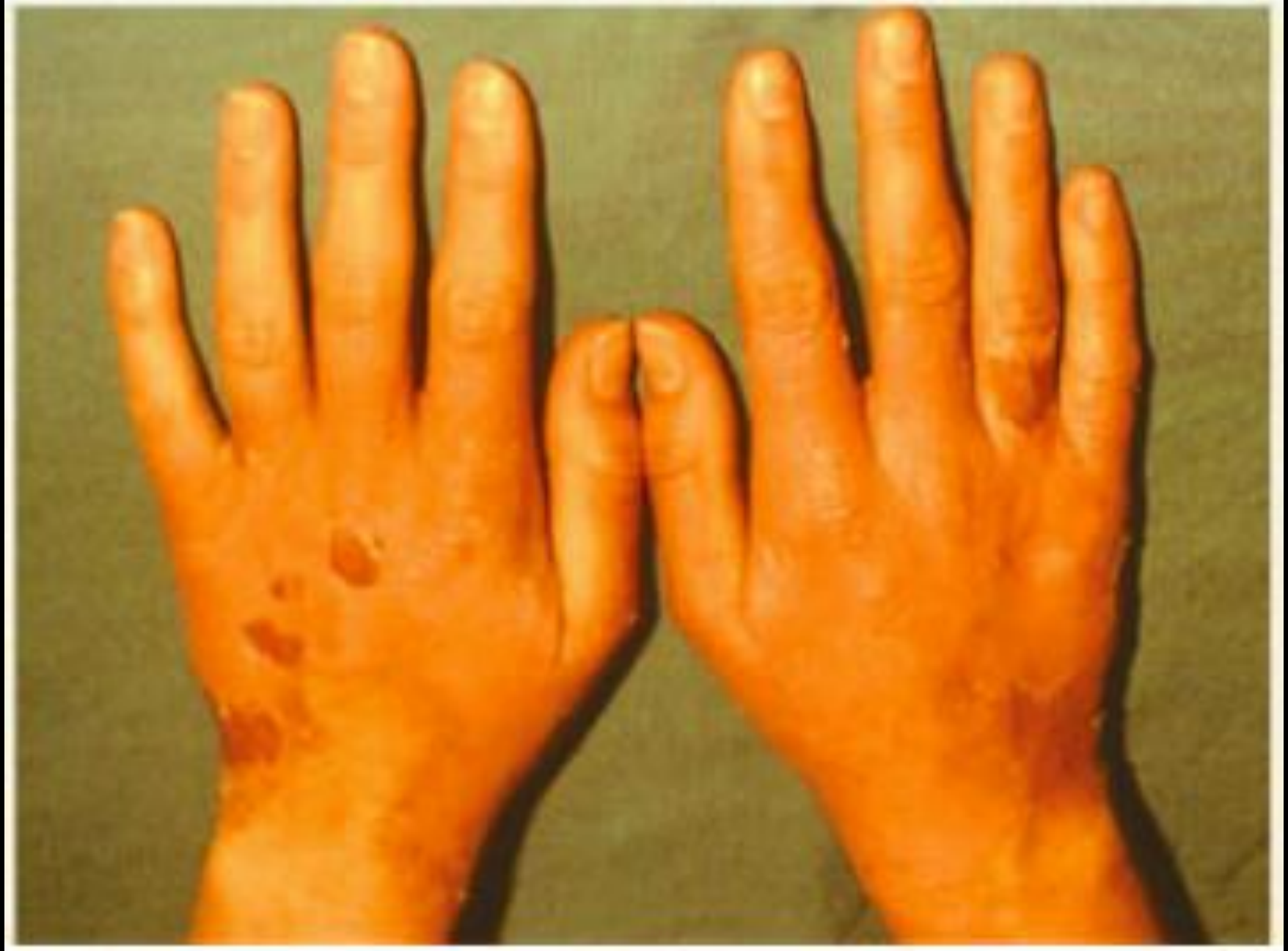
Burn from alkali exposure



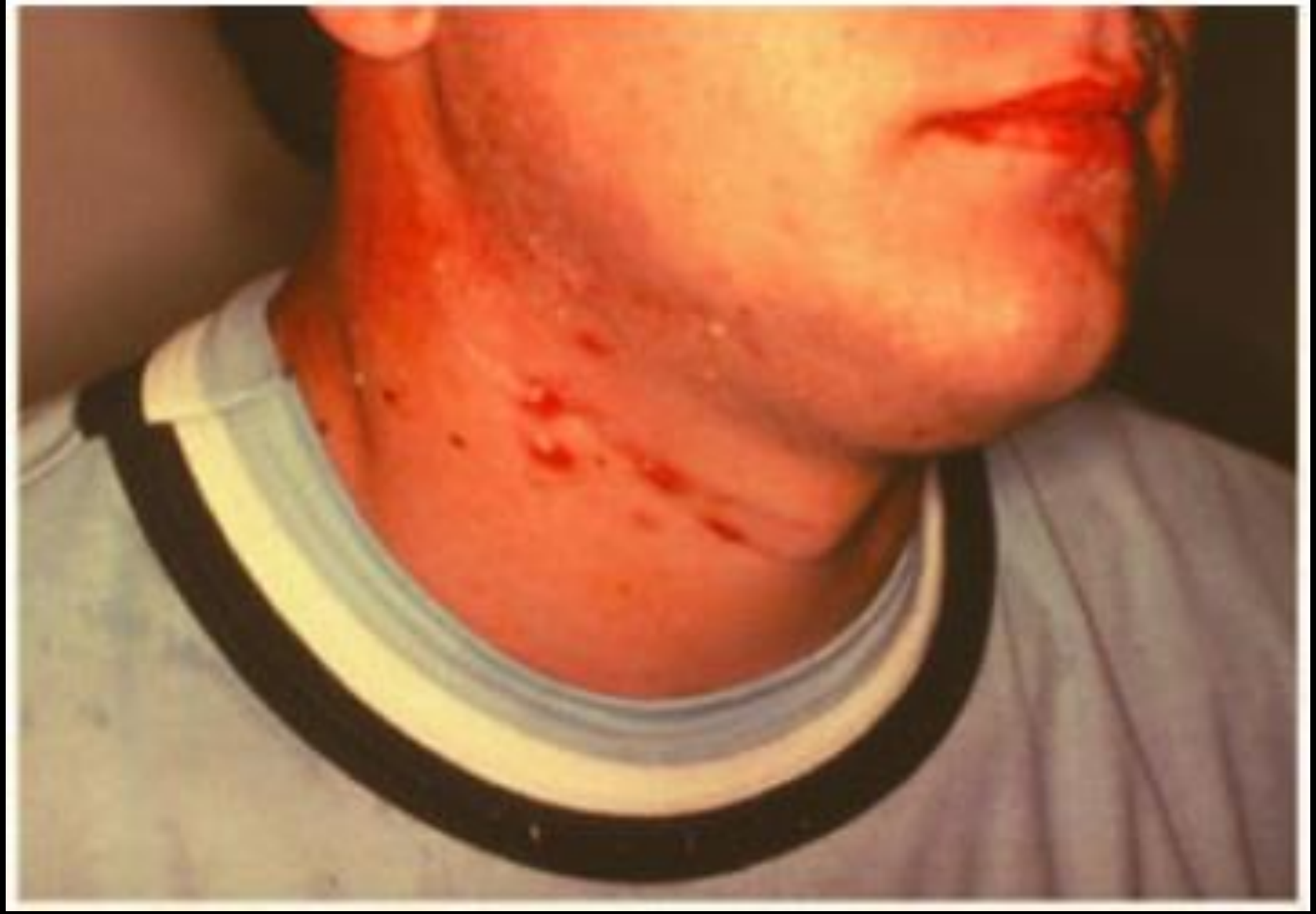
Sensitization to dichromate



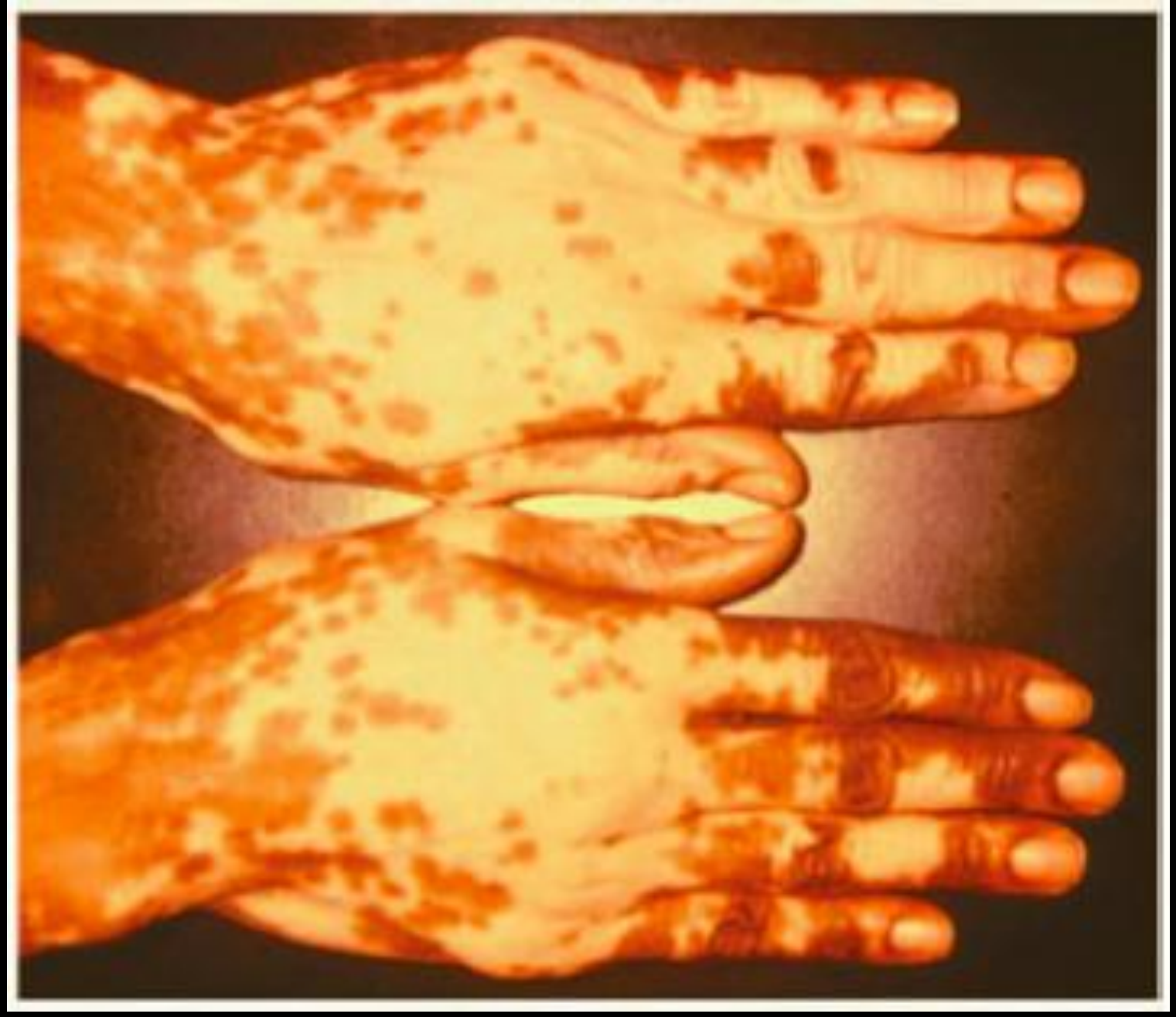
Beryllium granulomas



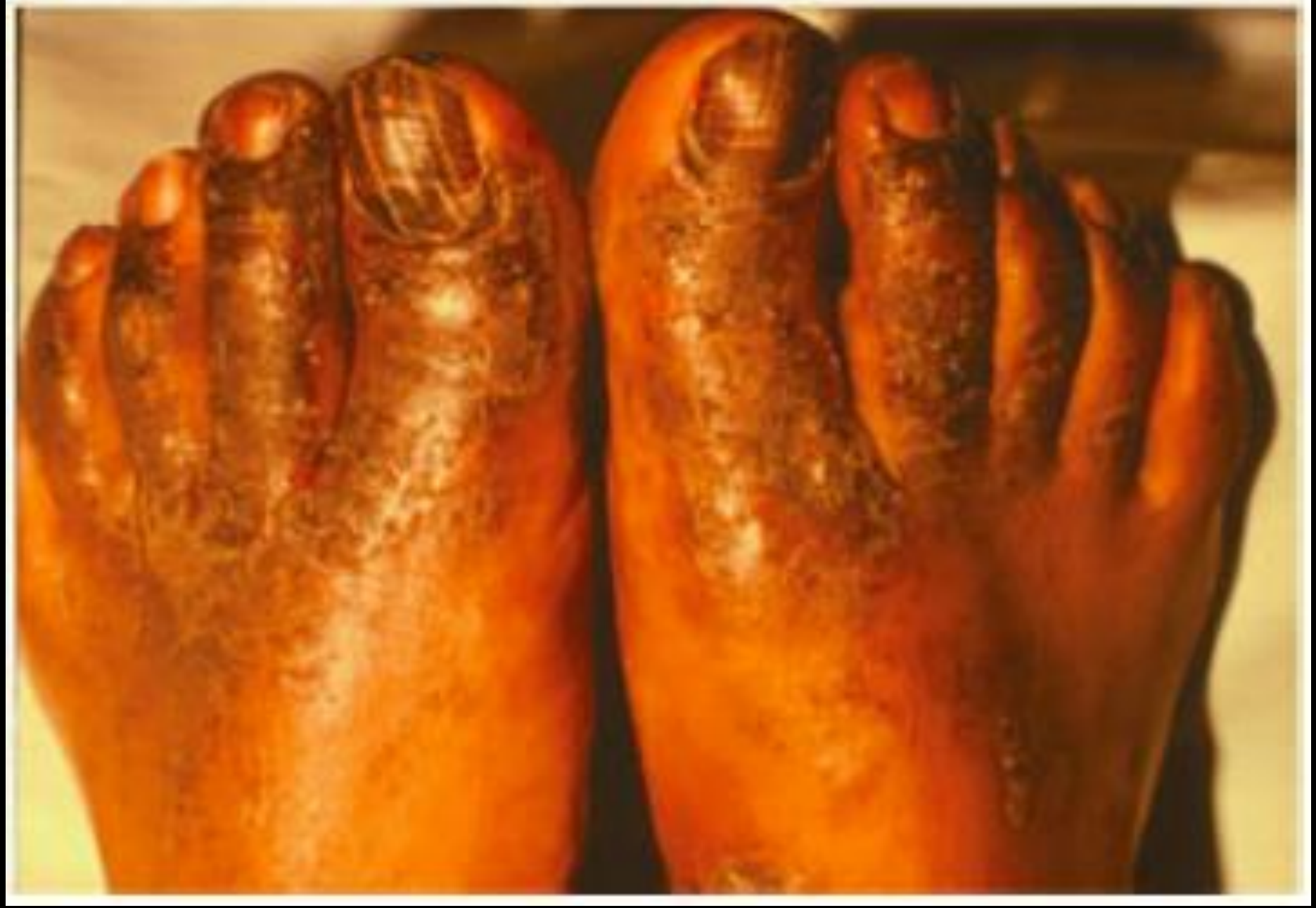
Phototoxicity from lime juice



Acne from cutting oil



Leukoderma from rubber antioxidants



Hyperpigmentation from mercaptobenzothiazole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