Abstract (Deadline: May 7, 1999)

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OXIDATIVE STRESS AND CYTOTOXICITY OF PHENOL AND AMVN IN HUMAN KERATINOCYTES: EVIDENCE FOR ENHANCED LIPID AND THIOL OXIDATION AND ANTIOXIDANT DEPLETION.

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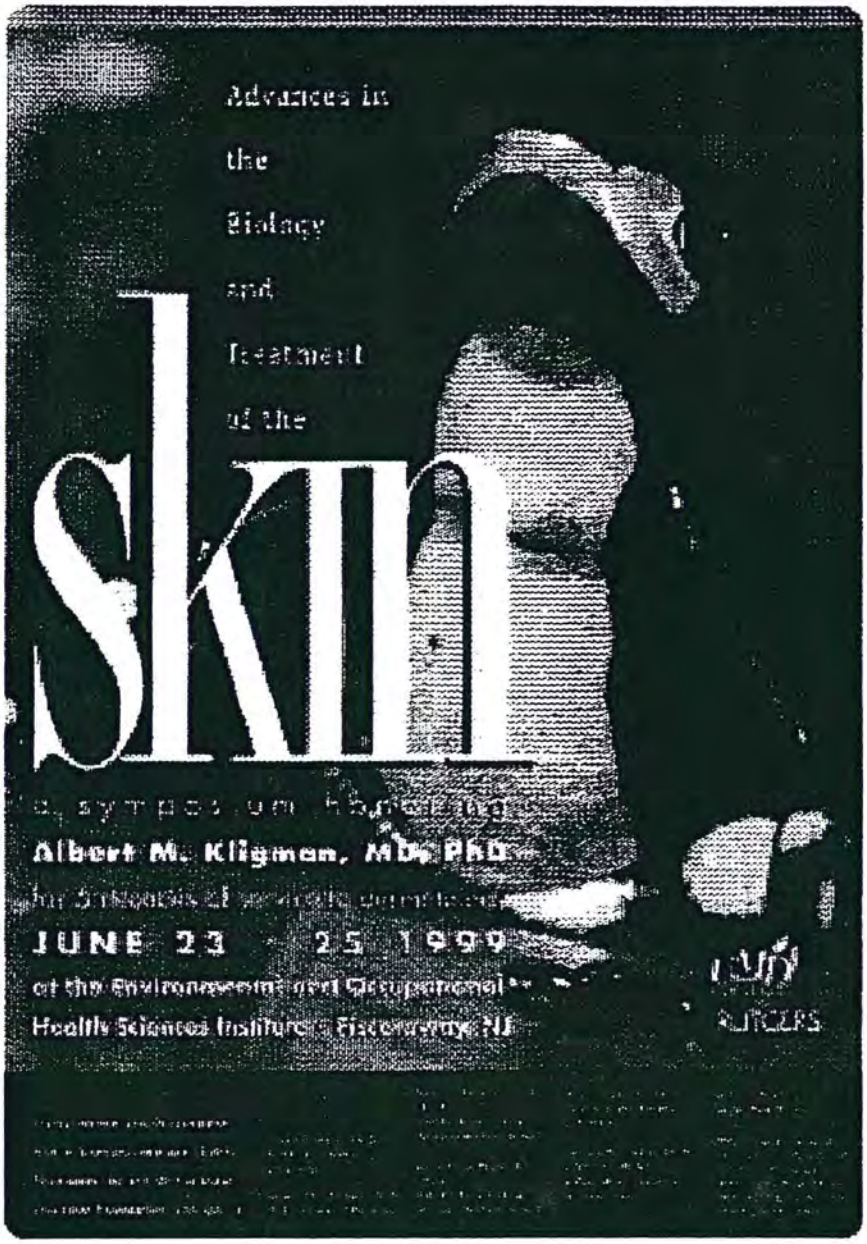
A variety of phenolic compounds that are utilized in industry (e.g., for production of phenol-formaldehyde resins, paints and lacquers, cosmetics and pharmaceuticals) are toxic to skin (i.e., may cause rash, dermal inflammation, contact dermatitis, leucoderma, or cancer promotion). The biochemical mechanisms of cytotoxicity of phenolic compounds are not well understood. We hypothesized that enzymatic one-electron oxidation of phenolic compounds resulting in generation of phenoxyl radicals may be an important contributor to their cytotoxic effects. Phenoxyl radicals are readily reduced (regenerated) by thiols, ascorbate and other intracellular reductants (e.g., NADH or NADPH). Hence, phenolic compounds may undergo enzymatically-driven redox-cycling, thus causing oxidative stress. To experimentally test the hypothesis, we performed measurements of thiols, lipid peroxidation and total antioxidant reserves in normal human keratinocytes incubated with phenol and compared the effects to those produced by an azo-initiator of peroxyl radicals, AMVN, 2,2'-azobis(2,4-dimethyl-valeronitrile). Using a newly developed cis-parinaric acid-based procedure to assay site-specific oxidative stress in membrane phospholipids, we found that phenol at subtoxic concentrations (50 μM and 500 μM) caused oxidation of phosphatidylcholine and phosphatidylethanolamine (but not of phosphatidylserine) in keratinocytes. The magnitude of the phenol-induced changes in phospholipids was quantitatively comparable to those induced by AMVN. Measurements with ThioGlo™-1 showed that phenol dramatically depleted GSH. Luminol-enhanced chemiluminescence assay demonstrated a significant decrease in total antioxidant reserves of keratinocytes exposed to phenol. Incubation of ascorbate-preloaded keratinocytes with phenol produced an EPR-detectable signal of ascorbate radicals. We conclude that redox-cycling of the one-electron oxidation product of phenol, its phenoxyl radical, is involved in the oxidative cytotoxic effects.


Advances in
the
Biology
and
Treatment
of the
Skin
Albert M. Kligman, MD, PhD
JUNE 23
25 1999
at the Environmental and Occupational
Health Sciences Institute - Piscataway, NJ

We are Grateful to the Following Organizations for their Sponsorship of the *Advances in the Biology and Treatment of the Skin* Symposium

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Biersdorf, AG

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