PROHAPTENS ARE NOT A NEW IDEA!

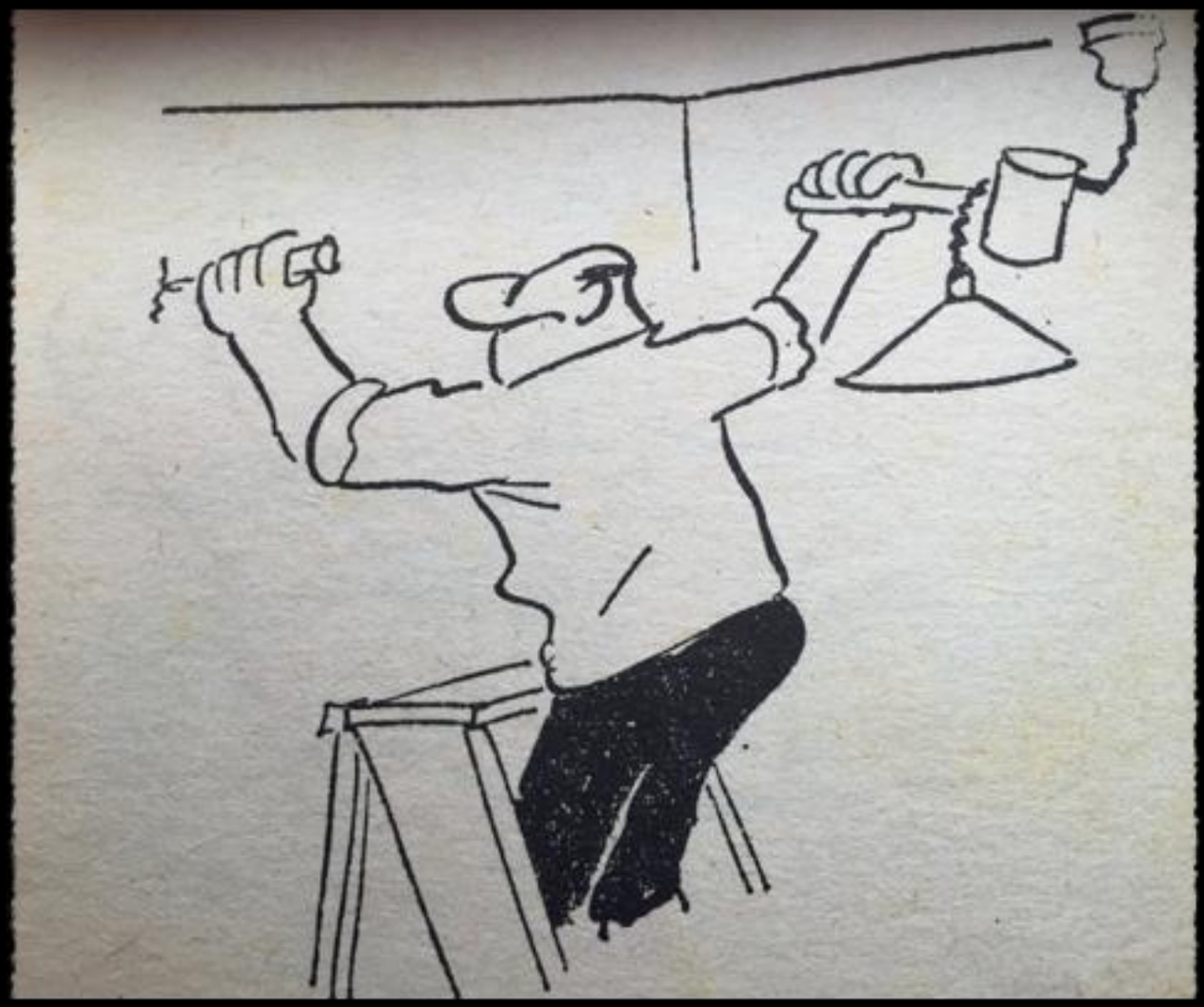
WHAT IDENTIFIES A CHEMICAL SENSITISER AS A PROHAPTEN

- Evidence/opinion that it is not a direct (re)acting chemical, i.e. an electrophile
- Evidence/opinion that is not susceptible to air oxidation to produce an electrophilic species
- Comparison with known activation systems, e.g. carcinogens, typically based on liver metabolism data
- An absence of any other explanation for its action

Characterisation of a contact allergen as a “prohapten” is a “diagnosis of exclusion”

?HOW MANY PROHAPTENS?

- We used to suggest 30% (ACD: Chemical and Metabolic Mechanisms, Smith and Hotchkiss, 2001)
- Increasing evidence of the relative importance of air oxidation lowers this figure substantially (e.g. work on geraniol from Karlberg and colleagues)
- Also, the evidence that some supposed “prohaptens” are positive in reactivity tests forces us to rethink
- Perhaps 10% is closer to our current view of reality…



IN VIVO PREDICTIVE TESTS

- In the guinea pig methods, it was simply assumed that the animal was a good model – the only real debate was on test sensitivity.
- With the mouse (LLNA), validation demonstrated that predictivity for the human hazard was acceptable (about 85%), but again no specific consideration was applied regarding metabolic differences.
- Both species did detect many substances believed not to be direct acting haptens.

THE QUESTION I ASKED ORIGINALLY AND STILL ASK TODAY IS "WHAT DO WE KNOW ABOUT THE REALITY IN MAN, AND HOW CAN WE INVESTIGATE THE TOPIC?"

ORIGINALLY, MY IMPRESSION WAS THAT ***ALL*** **OF** OUR APPARENT KNOWLEDGE WAS BASED ALMOST ENTIRELY ON CHEMICAL THEORY.

WHAT IS THE CURRENT STATUS?

- A PubMed search in early 2015 for "prohaptens and skin" yields only 25 hits; add "metabolism" and its falls to just 21
- Of these, just 2 involve research on which enzymes are involved in murine/human skin (in)activation of prohaptens
- Enzymes implicated: NADPH-dependent reductase and N-acetyl transferase
- NAT role is supported by work in 2009 from Blomeke and colleagues on NAT1 and 2 genotypes (fast versus slow)

WHAT IS THE CURRENT STATUS?

- Other searching yields these:

So, we have now a much better knowledge of the metabolic capabilities of skin, but that does not tell us which (pro)haptens are activated, nor how!

- Götz C, Pfeiffer R, Tigges J, Blatz V, Jäckh C, Freytag EM, Fabian E, Landsiedel R, Merk HF, Hewitt N, Fritsche E, Xenobiotic metabolism capacities of human skin in comparison with a 3D epidermis model and keratinocyte-based cell culture as in vitro alternatives for chemical testing: phase II enzymes. Exp Dermatol. 2012: 21: 358-363.

- Götz C, Pfeiffer R, Tigges J, Blatz V, Jäckh C, Freytag EM, Fabian E, Merk HF, Krutmann J, Edwards RJ, Abel J, Pease C, Goebel C, Hewitt N, Fritsche E. Xenobiotic metabolism capacities of human skin in comparison with a 3D-epidermis model and keratinocyte-based cell culture as in vitro alternatives for chemical testing: phase II enzymes. Exp Dermatol. 2012: 21: 364-369.

- van Eijl S, Zhu Z, Cupitt J, Gierula M, Götz C, Fritsche E, Edwards RJ. Elucidation of xenobiotic metabolism pathways in human skin and human skin models by proteomic profiling. PLoS One. 2012; 7(7): e41721.

CROSS REACTIONS: WHAT CAN WE LEARN?

- Cinnamal and cinnamic alcohol: positivity to both could be concomitant contact allergy…but the common failure to react to both is important
- …but very few dual positives to eugenol and isoeugenol occur, suggesting these do not share a common in vivo hapten

PROHAPTENS - THE OPPORTUNITY

chemistry of haptens

immunogenic adduct formation

reality

clinical data

skin metabolic capability

We should focus on deriving the information that is needed, not on what we can generate easily!

Considering in vivo and in vitro tests,, one might ask whether a confirmatory HRIPT is the only way to be sure that a prohapten has not been missed prior to consumer use/dermatologist feedback.