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Editorial comment

How good is a model?

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One of the most famous paintings by Belgian surrealist artist René Magritte (1898–1967) is an image of a smoking pipe with the text "Ceci n'est past une pipe" under it. Indeed, an image of a pipe is not a pipe. When the painter was asked about this, he replied: "Obviously it is not a pipe, just try to fill it with tobacco!". This would represent the face validity aspect of a model: does the model seem to function as the situation modelled? In the present issue of Scand J Pain there are two papers from the research group of Per Hartvig Honoré that go one level deeper on the validity of neuropathic pain models. The first one "Neuropathic pain models in the development of analgesic drugs" [1] discusses the construct validity of the models: are the models biologically representative to the conditions studied? The second paper [2] is more specifically on the predictive validity of the neuropathic pain models for different drug groups. For development of (human) drugs this is the highest level of validity: if something works in the model, it should also work in the patients, and if another molecule fails in the animal testing, it may not be a possible cure wasted. In rational drug development, any compound that fails in the early preclinical phase will never be administered to humans. On the other hand, this limits the information available on the specificity of these models.

In the IASP World Congress in San Diego 2002, we looked at the predictive validity of the most commonly used neuropathic pain models [3]. In a systematic review of published evidence, the picture looked rosy, even too good to be true. Since then, the pharmacological horizon for neuropathic pain treatments has widened tremendously, and with the new mechanisms and biological systems involved the question of predictive validity has become much more difficult. In addition, the old problems remain. Clinical efficacy is clearly not a yes/no—question, but a dichotomous answer is needed for quantitative assessment of validity. Most clinical studies of neuropathic pain are performed in postherpetic neuralgia or painful diabetic neuropathy, but surgical nerve lesions are used in many laboratory models. Mainly evoked responses are measured in the animal models, but also ongoing and spontaneous pain are important for the patient. In clinical practice, patients satisfied with tricyclic antidepressants for neuropathic pain may report that their pain intensity has not changed much, but sleep quality has improved significantly. This aspect has been studied very little in the animal models of neuropathic pain. The main limitation of the predictive validity paper by Honoré et al. [2] is that most of the interesting new pharmacological approaches have not yet been tested in humans.

How well the findings in the model predict (or in some cases, just repeat) the reality of a clinical trial in humans seem to depend both on the qualities of the model and on the properties of the drug group or the pharmacological mechanism that is studied. The match between the results of simple thermal nociceptive tests in rodents seem to reflect the analgesic efficacy of spinal opioids in postoperative pain almost perfectly [4], but it has been very difficult to find even a human model where paracetamol could be studied, as it is completely ineffective in many models. We do not know how well the present rodent models of neuropathic pain can predict the effects of e.g. modulation of cytokine or neurotrophin systems in human patients.

The quality of the data obtained from animal models of pain can be improved by controlling the test environment. The testing conditions should be reported in detailed manner [5], so that if e.g. habituation before testing would seem to be important, reader of a report of any behavioural pain paper could easily find out how the animals were habituated in that study. In reality, this is not yet a common level of reporting. Even ethical committees could request more detailed reporting based on the "reduce" part of the 3R principles (replacement, reduction, refinement): a well reported study could make another similar experiment redundant and thus reduce the number of animals used for drug development.

In several Magrittes' paintings, such as "The Human Condition" series from 1933 to 35, the image on the painter's canvas drawn in the picture and sky surrounding it are perfectly similar, blending seamlessly. We will never have such a match with laboratory findings in pain models and clinical reality. It has been claimed that not a single new drug for neuropathic pain has been developed using the laboratory models of neuropathic pain. This may be true at the moment, but rather reflects the slow pace of pharmacological development from target identification to a new product on the market than fundamental problems with the animal models of neuropathic pain. Pathophysiological mechanisms and new targets that are relevant for more effective treatment of neuropathic pain have been and will be identified using these models. Because drug development often fails due to problems unrelated to efficacy *per se*, such as with adverse effects in human use or bioavailability issues, the most important findings from animal models of neuropathic pain are, probably also in the future, mechanisms of action rather

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than exact efficacy of a given compound. This is further emphasised by the differences in the properties of receptors or other target molecules and in pharmacokinetics and pharmacodynamics between humans and laboratory animals.

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