Alice in Wonderland fell down the rabbit hole, at least that is what I am told. I never did like that book. The analogy is perfect though for much research, where pursuing the answer to a single question (and its related parts) might seem like a good idea. It is also appropriate for some aspects of molecular research aimed at discovering single-cause reasons for disease (for example tyrosine kinase inhibitors for chronic myeloid leukaemia).

Clinical musculoskeletal (MSK) conditions are not like that, they have a multifactorial aetiology complicated by individual factors such as genetics and co-morbidities and it is unlikely that pursuing any one question about pathology will impact on the condition across the population. So resolving the minutia is not only unlikely to inform the clinician about the condition, but more importantly, will not help them manage the condition in the complex body in which it exists. Clinicians need to stay above the ground and out of rabbit holes, taking key messages from each rabbit hole and integrating the research into a management strategy for MSK pain.

What is most critical is that pain (the key clinical musculoskeletal domain and discussed here in a clinical context, not from a pain science perspective) is poorly related to pathology and structural change (although it remains an important risk factor for pain). Often, the primary (misguided) aim for both researchers and clinicians is to restore normalcy, most commonly thought of from a structural or pathoanatomical perspective. We want to measure everything to within an inch of its life and then ascribe benefit to restoring normal levels. But most MSK pain is poorly related to pathology, making the pursuit of normal structure and absence of pathology senseless.

If we only consider MSK pain, normalcy (for the patient) is the absence of pain. But MSK pain can be ameliorated by reducing use – impossible to do in many organic diseases but certainly a common response in MSK conditions. Reducing use may be beneficial for MSK pain, but it comes with a range of negative health consequences – because of physical inactivity – that are likely worse in the long-term than living with the pain (for example increased risk of non-communicable disease). Clinicians are paid to manage MSK pain but the aim should be to do that in the context of full

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function for each person. Reducing use is likely to negatively impact on the strength and capacity of tissues and therefore will affect function, further reducing ability to exercise and quite possibly reducing the threshold for pain. All this is considered without accounting for the central contributions to the pain experience.

So where does research sit in this complex clinical environment? There are those who preach that most research provides meaningless findings\(^2\) with small effect sizes\(^3\), and many clinicians would agree that most is not helpful for their patients and practice. What seems apparent is that much research pursues single ideas to death (down the rabbit hole), whereas clinicians need a broader perspective and helpful evidence-based ideas for their patients. If research is not helpful, clinicians are vulnerable to falling down clinical rabbit holes, where complex conditions are managed with simplistic and unimodal treatments.

Let’s examine one condition—tendinopathy—to illustrate that there are innumerable rabbit holes in research and clinical practice. These have direct implications (not always positive, in fact mostly negative) for clinical management.

**COMMON RABBIT HOLES IN TENDON RESEARCH AND THEIR COROLLARIES**

**Molecular miracle**

There are 28 matrix metalloproteinases (and several inhibitors of them) that are responsible for the turnover of the tendon matrix\(^4\). There are also 36 interleukins, all active across a range of tissue responses to disease and injury\(^5\). It is crazy to think that fixing levels/expressions/half-life of one will immediately have a positive effect on the tissue as a whole and, of course, the complex individual with the condition. Of course in this rabbit hole, it is also essential that there are no interactions between any of these molecular substances.

The clinical corollary of this is injecting tendons with these magical mixtures and expecting that not only will it normalise structure, but that in turn it will fix pain and therefore will return the tendon/kinetic chain/person to full function. We have spent a lifetime looking for simple cures for complex problems, it is time to let it go and move on to flexible, multimodal research that allows us to investigate MSK conditions in a real world environment.

We can image pain

I was brought up on the pathoanatomical model and it is so hard to let go of the relationship between structural pathology and pain. Surgeons may struggle more than most as their treatments are directed at ‘normalising’ structure. Interestingly, the injured population is also wedded to this idea, having been exposed to multiple scans and reports of their abnormal structure and struggle with the concept that function and pain can be corrected without structural change.

We also have to be so careful of using pejorative words in radiology reports; tears and degeneration imply poor outcomes and have been shown to influence response to treatment\(^6\). More and better imaging is unlikely to change this, any imaging that may shed light on local drivers of pain will be invasive and expensive and are unlikely to become feasible in the near future. In
tendons, where the local nociceptive driver is not known and potentially cell-based, this is even less likely to be possible regardless of advances in imaging.

The corollary of nociception is that the brain is responsible for the generation of pain without a tissue-based nociceptive driver. This is currently fashionable (another bandwagon), but loses sight of the concept that a key driver of MSK pain is tissue-based nociception. In tendon, athletes can have 20 years of patellar tendon pain, that hurts when they jump (and only then) and for a short (tissue) time after, making the likelihood of a nociceptive driver, although not yet found, overwhelming. Ignoring the nociceptive driver and only addressing the central modulation is unlikely to have a positive long-term effect.

The rabbit response is exactly the same as the human response

Research in humans is complex and research in complex conditions in humans is impossible, especially if the comparison is not drug A to drug B. It is easy to control animal experiments perfectly and perhaps the military model (where many factors that might influence outcomes are more controlled than in general population research) is the best in humans.

Even in animal models the study design may not reflect human disease. The Backman model of inducing tendon pathology has been used extensively to investigate tissue responses. The model is a repetitive plantar and dorsiflexion movement in an anaesthetised rabbit, so does not involve any energy storage and induces peritendinous inflammation rather than overuse tendon pathology we see in humans.

PUTTING THE BUNNIES IN WITH THE HARES AND GUINEA PIGS

It may be surprising to some that there is limited agreement on the diagnostic criteria for tendinopathy. In 2007, it was first recognised that set research diagnostic criteria were needed, and that is also true for clinicians. In tendons, if imaging and palpation tenderness are not always associated with tendon pain, then these criteria are not sufficient to diagnose tendinopathy and include participants in a study. Today, we still have no consensus on inclusion criteria of participants in studies. If there is no agreement on the inclusion criteria – how can the researcher know if the findings reflect a response of the true condition to the treatment? Following on from this, how can the clinician know the treatment is applicable to the person in front of him or her?

WHAT DRIVES RESEARCHERS DOWN RABBIT HOLES?

Pragmatic clinical research that allows for individual choices and clinical prescriptions based on presentation is not considered worthy of publication because of inherent biases in the study design. This results in effective interventions in trials that lack effectiveness in the real world.

Grant and publication imperatives

Simple questions with clear answers get funded and published, or at least get through the review process without a mauling. Introduce biases (such as co-morbidities in a real world population) then the numbers necessary for a research study would have to be huge to satisfactorily account for them.

It is easy to follow on from previous research

Question A leads to question B which leads to question C, and so on. The researcher does not care if it is not helping the clinician, it is being funded and published; end of story.

WHAT ABOUT CLINICAL RABBIT HOLES? (OR IS THAT A BANDWAGON?)

Applying a single, simplistic treatment is an easy response to the complexity of clinical practice and the research results that are not easily translated into meaningful clinical practice. There is also an imperative to use the newest and most exciting treatment – what I would call a bandwagon. These treatments become ‘hot’ in the media,
Researchers in clinical medicine should have a perspective on clinical practice. Similarly, clinicians need to determine the direction of research.
If research is not helpful, clinicians are vulnerable to falling down clinical rabbit holes, where complex conditions are managed with simplistic and unimodal treatments.

References