Open Questions and Potential Answers

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As of this writing, Dupuytren questions far outnumber answers.

58.1 What *Is* Dupuytren Disease?

Is it one disease or several similar appearing conditions? Is it a discrete disease, or simply part of the spectrum of the biology of aging, along with gray hair, smile lines, and loss of hearing? Or is it exactly the opposite, a failure of aging, a failure of cell senescence? Normal fibroblasts divide about 60 times before becoming senescent. Do Dupuytren myofibroblasts simply fail to age and die gracefully? Are Dupuytren, Ledderhose, knuckle pads, frozen shoulder, and Peyronie disease imposters, or cousins, or clones? Why does this disease develop in the hand and not in the thigh or earlobe? In the pursuit of understanding Dupuytren biology, is it helpful or is it misleading to use data from other localized fibroses such as desmoid tumor, keloid, or hypertrophic burn scar? Is it helpful or is it misleading to use data from more generalized fibroses such as cirrhosis, pulmonary fibrosis, scleroderma, or arteriosclerosis? Could Dupuytren be a protein-folding disease? How could that question be answered? Where does collagen lie on the line between cause and consequence?

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58.2 What *Accompanies* Dupuytren Disease?

It's not a simple tally. Dupuytren research has spawned answers for questions which do not yet exist – data, factoids, and anecdotal observations which beg the question "what does this mean?" It's not surprising that Dupuytren Disease has been found to be associated with abnormalities in the collagen metabolism arena: autoantibodies to type 1 collagen and elastin (Menzel et al. 1994), abnormal levels and ratios of matrix metalloproteinase-2, matrix metalloproteinase-14, tissue inhibitor of metalloproteinase-14 (Wilkinson et al. 2012), and circulating fibrocyte levels (Iqbal et al. 2014). What remain unexplained are associations of seemingly unrelated issues and Dupuytren Disease. What is the molecular relationship of Dupuytren Disease to diabetes (Noble et al. 1984)? To hyperlipidemia (Sanderson et al. 1992)? To having a low body mass index (Gudmundsson et al. 2000)? To sympathetic dystrophy (Dickson 1964)? To hypothyroidism (Macaulay et al. 2012)? To depression (Macaulay et al. 2012)? To early mortality (Gudmundsson et al. 2002)? To cancer risk (Gudmundsson et al. 2002)? To psoriasis (Patel et al. 2014)? To Caucasian heritage? To tissue iron deposits (Berg et al. 1972)? To the Charlson comorbidity index (Macaulay et al. 2012)? HLA type (McCarty et al. 2010)? IgA immune complexes (Houghton et al. 1983)? DR+ T cells and CD5+ B cells (Gudmundsson et al. 1998)? *All* of these associations have been reported; *almost none* have received the type of in-depth additional investigation needed to confirm, refute, or make sense out of the finding.

58.3 What Do Dupuytren Patients Want?

More importantly, what do they *not* want? Dupuytren patients *don't* want to be told that they have an incurable disease. They *don't* want to be rushed through a surgical evaluation because their hands are not "bad enough yet." They *don't* want their research into alternative treatments dismissed without discussion. They *don't* want to be told and told that there is nothing that they can do. They *don't* want to be treated by specialists who tell them that theirs is the only successful treatment or who are not familiar with other treatment options or who can't provide expertise on possibly associated diseases. Dupuytren patients want what *all* people want: respect, hope, empowerment, and complete, objective information. These are things that we can and should provide, even as the search for a cure continues.

58.4 Why Is There a Patient-Driven Movement Pushing for Better Dupuytren Treatments?

People, in general, are risk averse and aren't comfortable unless potential benefits greatly outweigh potential risks (Kahneman and Tversky 1979). This creates a problem for Dupuytren patients, because current Dupuytren treatment doesn't fit that model: the most common treatment (fasciectomy) offers temporary gains with moderate risk of prolonged recovery and moderate risk of permanent complications. It's no surprise that patients are so willing to embrace treatments which provide even shorter projected periods of improvement (collagenase, needle fasciotomy) or are discouraged by some surgeons despite promising benefits (radiotherapy), because these approaches have much less perceived risk than fasciectomy. The motivation is that people don't like what their doctor recommends for their Dupuytren Disease. They come home from the doctor's office and reach out online with the thought that there *must* be something better.

58.5 What Is Really Going on with Dupuytren Care?

The long-term outcome of Dupuytren treatment has not changed in decades despite many flurries of activity in the technical treatment of Dupuytren contracture deformity. We must recognize that

we have reached an impasse, an invisible wall which must be breached. The invisible wall is the misperception that Dupuytren Disease is a hand condition, that contracture is the disease and not the end result of the disease, and that procedures for contracture are the only option. As long as these misconceptions persist, a cure for Dupuytren Disease will remain out of reach.

58.6 How Does One Approach a Traditionally Insoluble Problem?

Move things around!. That's the advice I received as a child when I complained that I couldn't find what I was looking for in my messy bedroom. Dupuytren Disease is the same: we can't find what we are looking for because we mistake obstacles for boundaries. At the same time, we see things that aren't there: we confuse change for progress, anecdote for insight, wishful thinking for strategy, good luck for success, and tradition for understanding. This must stop. It's time to move things around, to solve what only *appears* to be an insoluble problem. We can use three strategies: examine failure, question convention, and engage outsiders.

- *Examine failure*. What are some of the failures of Dupuytren care? So far, we have failed to provide a permanent solution. We have failed to develop an objective, predictive measure of Dupuytren Disease severity. We continue to fail to provide patients an acceptable set of treatment choices. We fail to grasp the number of people with Dupuytren Disease who are undocumented, or who are unhappy with the results of their treatment, or who avoid any treatment evaluation because they have heard stories of unhappy Dupuytren treatment outcomes. We (hand surgeons) have overestimated the happiness our Dupuytren patients have with their outcomes. We need to keep these issues in our view: they are the most obvious areas which need improvement.
- *Question convention*. Does it make sense to accept a high-morbidity procedure with unpredictable outcome and limited duration of control as the standard of care for a benign, painless disorder? Does it make sense to ignore all aspects of an inherited systemic connective tissue disorder other than the late effects it has on the palms and fingers? Does it make sense to evaluate treatment effectiveness of an ongoing chronic progressive disease by lumping together outcomes evaluated at a wide range of follow-up durations after treatment as if recurrence rates were linear and uniform? Does it make sense to evaluate overall treatment effectiveness based on selected outcomes segregated by posttreatment criteria? None of these make sense if the goal is what is the best interest of the patient. We should question on how these flawed approaches became acceptable standards and work to correct these flaws.
- *Engage outsiders*. If the cure for Dupuytren Disease could be found in a local procedure, it would exist. Instead, there are a great number of procedural variations which address only a small aspect of Dupuytren Disease and provide nearly identical outcomes. Further progress is unlikely unless investigation broadens to address aspects of Dupuytren Disease other than deformity. Vascular surgery evolved dramatically with new surgical approaches, but real progress in outcomes came from better understanding of disease risk factors, biomarkers, and systemic interventions. The same is true for rheumatoid arthritis, peptic ulcer disease, and most bacterial diseases. Surgeons must escape their Dupuytren procedure-centered tunnel vision and engage their rheumatology, gerontology, cell biology, and genetic colleagues to take on the challenge.

58.7 Why Aren't More People Doing Dupuytren Research?

Why do people do medical research in the first place? Curiosity isn't enough. Profit, fame, self-interest, and altruism all factor in, but ultimately, it is a matter of time and money. Dupuytren Disease is not a good fit for practice-based

surgical registry research. Surgeons, in general, are busy. Compared to patients with other common non-emergent benign hand conditions such as tendinitis, neuritis, or arthritis, care of Dupuytren patients tends to be labor-intensive relative to reimbursement. This discourages surgeons from developing a Dupuytren focus to their practice, a disincentive to participating in a surgical registry. At the same time, funding drives research, and research funds are scant for what is perceived to be an uncommon benign nuisance experienced only by seniors.

58.8 What Needs to Be Done?

We need to raise awareness of Dupuytren Disease, its health implications and potential impact of effective Dupuytren medication on other fibrotic disorders. By doing so, Dupuytren research funding can be increased, and a greater number of researchers can be recruited to study the disease. We need to leverage the efforts of Dupuytren patients to raise awareness by social media and by direct engagement with their politicians to increase government funding of Dupuytren research. We need to keep reminding ourselves that the only reason that there is not yet a cure for Dupuytren Disease is that no one has yet put the pieces together on the necessary scale to achieve the task. What needs to be done is to plan in reverse: assume that a cure is possible and then outline the steps needed to develop a cure. This is the basis of the International Dupuytren Data Bank, discussed elsewhere in this text (Eaton 2016).

And finally, *why is there not a poem about Dupuytren Disease?*

Well, now there is.

Dupuytren Disease

Just Dupuytren. Though hard to say in fluent French, your name became an eponym, your curse cliché for fingers bent, coerced to clench, the wrench you throw into the hand, intention no one understands, entrenched, you never go away.

How Dupuytren, to classify your lumps and cords, skin gone awry, the strings of joints curved out of line turn fingertips to pointed swords to score the face when washing up. You pour the palm into a cup. Disorder, strange and undefined.

Your Dupuytren biology lies in the guise of normalcy, yet collagens, T-I-M-Ps and MMPs somehow devise a plot with myofibroblasts to modify their mien en masse to what and when? A mystery.

The Dupuytren inebrium – your lid's ajar, you're out of plumb, near or far, where are you from, just scar disequilibrium? You hide inside a next of kin, not diet nor a vitamin, but in the lines of dad and mum.

Oh, Dupuytren, you fight defeat, by any means, you're hard to treat. Surgery, so incomplete, cannot delete your secret genes resisting pharmacology, persisting after therapy, existing only to repeat.

Now, Dupuytren. You need a cure for everyone who must endure and dynasties yet immature. Yes, you can hide, but you can't run: We'll learn your scheme like Aristotle, put your genies in a bottle, lay to rest your nom de guerre. Yes, Dupuytren. You need a cure.

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