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THE QUEST FOR MORE RESEARCH ON PAINFUL DIABETIC NEUROPATHY

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Abstract—A 62-year-old diabetologist diagnosed himself to have diabetes type-2, with an HbA1c of 9.5. Five months after lifestyle intervention and a multi-drug approach, HbA1c was 6.3, systolic blood pressure was below 135 mmHg and BMI reduced to 27. But he suffered from severe painful diabetic neuropathy. Therefore he decided to visit his friend, a famous neuroscientist at an even more famous university. He asked him several plain questions: 1. What is the natural course of painful diabetic neuropathy? 2. Why do I have, despite almost normalizing HbA1c, more problems than before? 3. Are you sure my problems are due to diabetes or should we do a nerve biopsy? 4. Are there imaging techniques helpful for the diagnosis of this diabetic complication, starting in the distal nerve endings of the foot and slowly moving ahead? 5. Can you suggest any drug, specific and effective, for relieving painful diabetic neuropathy? This review will use the experts' answers to the questions of the diabetologist, not only to give a summary of the current knowledge, but even more to highlight areas of research needed for improving the fate of patients with painful diabetic neuropathy. Based on the unknowns, which exceed the knowns in diabetic neuropathy, a quest for more public support of research is made.

Key word: painful diabetic neuropathy, patho-mechanisms of diabetic neuropathy.

WHAT IS THE NATURAL COURSE OF PAINFUL DIABETIC NEUROPATHY?

This is a difficult question to answer (Boulton et al., 2004; Llewelyn et al., 2005; Said, 2013), because this would require large cohorts of patients with recent manifestation of diabetic polyneuropathy (DPN) followed over more than 10 years. While diabetic neuropathy seems to be frequent, pain is much less frequent (van Hecke et al., 2014). Most cohorts have only been studied for a relatively short time and thus there is a lack of longitudinal data. Even the prevalence of DPN reported is surprisingly different in the various studies, pointing to effects of subgroups and methodological problems, such as the diagnostic tools used and whether or not small fiber functions are included (Davis et al., 2008; Ziegler et al., 2009; Kärvestedt et al., 2009; Roth et al., 2016; Blankenburg et al., 2012). The estimates on the prevalence of painful diabetic neuropathy are sparse and vary from 8% to 26%, depending on the diagnostic criteria and population studied (Davies et al., 2006; Ziegler 2008). We do not know whether the patients first showing cramps go on to develop tingling and spontaneous pain as symptoms later on. We do not know whether hyperalgesia or allodynia is a predictor of a diabetic foot syndrome. We do not know how many patients start with tingling in their toes and have cramps that are more proximal later on. We also do not know how many patients start to have numbness and then go on to develop diabetic foot syndrome later. Finally, we do not have sufficient longitudinal data describing the connection between distal symmetric sensory and autonomic neuropathy, but there is evidence that 10-year mortality is higher in those patients that have pain (Torrance et al., 2010). What we have are cross-sectional data and data from pharmacological studies. But the patients in clinical trials are mostly preselected with respect to the syndrome to be addressed and by the drug that is being studied, in order to give the drug the highest chance to show effectiveness. We have some data with respect to the role of hyperglycemia

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(DCCT, 1995; UKPDS Group, 1998; Pierson et al., 2003; Sima 2003; Roth et al., 2016), data on the simultaneous occurrence of neuropathy and other diabetic complications and data on the correlation of loss of nerve fibers with diabetic neuropathy (Ziegler et al., 2014a). In addition, while in some studies symptom and deficit scores are used, others report quantitative sensory testing, with or without nerve conduction velocity measurements. There are very few cross-sectional studies, in which a complete and deep phenotyping of patients was performed. What we are missing is a longitudinal study of patients, fully characterized with quantitative sensory testing (Backonja et al., 2013), autonomic function tests, nerve conduction velocity measurements, symptom description and a comprehensive list of all other diabetic complications, including the clinical chemistry needed for characterization of the status of complications. All these parameters are needed with a yearly follow-up. Only then an adequate answer to your question will be possible.

Furthermore, in most statistical analyses, the term DPN stands for very different symptoms, ranging from tingling, cramps and pain, to thermal hyperalgesia, allodynia and other symptoms, to loss of pain perception and non-healing ulcers. In some studies, the positive and negative symptoms and signs are not clearly distinguished. The longitudinal study outlined above, in which each symptom and sign is followed separately rather than scores of accumulated complaints, will help to unequivocally clarify the natural course of this devastating diabetic complication. I personally believe it is time to look at each aspect of DPN separately, because different anatomical structures have different functions in the neuronal system. Even though our knowledge about structure – function relationship to each symptom is limited, as is our knowledge of the interaction of peripheral and central nervous circuits in diabetes-associated painful symptoms, we can still assume that the term DPN does not stand for one disease, but rather encompasses several very distinct diseases. Probably we should not talk about DPN in general, but we do need to define the mechanisms of each single symptom as a prerequisite to give each distinct symptom the status as a bona-fide diagnosis criterion by itself. While such extensive work is needed for scientific purposes, because only this will allow to understand the distinct nature of the plethora of neuropathic problems, a much easier screening tool for routine diagnostic purposes has been developed (Bongaerts et al., 2015). A basic score, asking for age, height, weight, pain or discomfort in the feet and or legs and duration of diabetes, yielded a sensitivity of 87%, but only a specificity of 67% with a positive predictive value of 33%. Thus, it should not happen any longer that patients with DPN are not diagnosed.

WHY DO I HAVE, AFTER ALMOST NORMALIZING HBA1C, MORE PROBLEMS THAN BEFORE?

Diabetes type-1 and type-2 is defined by increased glucose levels, HbA1c or a pathologic oral glucose tolerance test. This suggests that hyperglycemia is the driving force of painful neuropathy. Indeed, for a very long time, the field of diabetes, including drug development, has been hampered by the misunderstanding that a parameter used to define a disease is a primarily surrogate parameter, until it has been proven to be a parameter causing a complication. If hyperglycemia were to be the prime and driving cause of all complications, then glucose normalization should entirely prevent diabetic neuropathy along with all the diabetic complications as well. Or at least, glucose normalization should significantly (and meaningfully, from the patient's point of view) reduce symptoms in all patients. However, the real-life situation has turned out to be much more complex than predicted. Even though there is some evidence that lowering glucose levels reduces the risk of DPN in type-1 diabetes, the data on type-2 diabetes are somewhat disappointing (Gaede et al., 2003; UKPDS Group, 1998; Ismail-Beigi et al., 2010; Callaghan et al., 2012; Martin et al., 2014). Rather, prospective data from the Femantle Diabetes Study showed that treatment with lipid-lowering agents, such as the statins or fibrates, may protect against the development of DPN (Davis et al., 2008). This points to a complex network of risk factors, in addition to glucose levels, giving rise to DPN. To test whether this is simply a correlation or a causative connection, a Danish study group performed an intervention trial and reported the outcome of an early intensive multifactorial treatment in patients with type 2 diabetes (Charles et al., 2011). After 6 years, they did not find any effect of the intensive multifactorial treatment on the prevalence of DPN. This points to a more complex pathophysiological basis of DPN involving factors that have not yet been addressed in the multifactorial approach used.

Furthermore, there is not a single study on diabetic complications reflecting what you have done. You changed your lifestyle, lost weight, and using drugs for blood pressure and metabolic control. Few small studies reported an improvement of painful neuropathy and neuropathic deficits by increasing physical activity (Singleton et al., 2015). But you reduced glucose very rapidly and quite aggressively, believing that the surrogate hyperglycemia is also the sole and most important cause of your symptoms. But this has not yet been proven. Even worse a recent study showed, that there is an entity called ''treatment-induced diabetic neuropathy" (Gibbons and Freeman, 2015). This includes dizziness, erectile dysfunction, abdominal problems, pain and other symptoms. Thus, it might even be harmful to lower glucose not only too fast, which has been known for years with respect to diabetic retinopathy, but also too low. Whatever the precise pathomechanism might be, physiological analyses show that there are differences between neuronal and other cells in glucose uptake and handling. Neuronal cells depend on the Warburg mechanism, a process by which neurons will predominantly produce energy from a high rate of glycolysis followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in the mitochondria. As consequence, neurons take up and metabolize more glucose than other cells within the

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body. Therefore, they might be more vulnerable than other cells to low glucose plasma levels that may occur frequently while rapidly lowering glucose. Furthermore, even *in vitro*, there is a lack of data indicating that glucose levels of 200 milligrams per 100 milliliters are harmful for neuronal cells. In contrast, neuronal cells are cultured under higher glucose levels than other cells. But as said before: The precise mechanism why your symptoms got worse rather than better after lowering glucose is unknown. My recommendation would be: Try to adjust your HbA1c to the range studied and therapeutically reached in the UKPDS study and the Steno-2 study (UKPSD Study Group, 1998; Gaede et al., 2003).

The role of hyperglycemia has also been questioned with respect to the very early manifestation of DPN in the course of type 2 diabetes that occurs frequently, sometimes even before diabetes is diagnosed (Adler et al., 1997; Tesfaye et al., 2010). This indicates that not hyperglycemia alone, but also other factors associated with diabetes drive the development of DPN. Interestingly, several studies have shown that the sequelae of events contributing to pain and loss of pain perception are not specific for diabetes. It has been shown that the expression of the receptor for advanced glycated end products (RAGE), its ligand CML and the RAGE-CML-mediated downstream activation of NFkBp65 are upregulated in a similar fashion in endoneurial vessels in diabetes, while in Schwann cells, RAGE is upregulated, while its ligand or NFkBp65 remain unchanged in expression (Haslbeck et al., 2007). This indicates that upregulation of RAGE might have different consequences in different cells, illustrating the underestimated fact that a nerve is a complex organ, in which only the well-orchestrated function of different cells assure normal function. Neuronal changes may therefore be present before hyperglycemia develops (Kennedy and Zochodne 2000; Polydefkis et al. 2004), suggesting non-hyperglycemic factors, but also not excluding glucose as a driving force, because also glucose-derived neurotoxic or metabolites altering neuronal function may accumulate in the absence of hyperglycemia. In short, neuronal changes might occur when glucose and its metabolites are not correctly handled within a cell, even under euglycemic conditions. These data are interesting, because they highlight the profound difference between what is measurable in the plasma and what happens within a cell. Furthermore, pain perception, which can be induced by the glucose-derived metabolite methylglyoxal (Bierhaus et al., 2012) and loss of nerve fibers (Bierhaus et al., 2004), are very separate events. In STZ-treated mice lacking the receptor RAGE, neuronal function is intact and DPN-associated degeneration of nerve fibers occurs normally. This supports the notion that the term DPN is misleading and that in the future, it will be more meaningful and relevant to characterize the different entities on the structural, biochemical and clinical levels, encompassing the many distinct pathologies of neuronal dysfunction that are possible in patients with diabetes.

A similar picture evolves looking at reduced heart rate variability (HRV), a symptom of autonomic neuropathy. About 20% of patients with known diabetes have a pathologic HRV (Hilsted, 1982; Vinik and Ziegler, 2007), predicting major cardiovascular events (Liao et al., 2002; Astrup et al., 2006; Young et al., 2009; Humpert et al., 2009). As stated before with respect to peripheral neuropathy, a reduced HRV was shown in prospective studies to predict the development of diabetes itself (Carnethon et al., 2003a; Carnethon et al., 2003b). The good news is that lifestyle modification seems to improve the reduced HRV (Carnethon et al., 2006). Therefore, neuronal dysfunction precedes diabetes manifestation (Adler et al., 1997) and indirectly explains why lowering glucose cannot automatically reverse neuronal dysfunction developed prior to hyperglycemia. Even though elevated glucose does not seem to be the initial driving cause, this does not mean that glucose does not play any role. There is ample data that glucose-derived metabolites can drive neuropathic abnormalities. For example, a reduction or acquired dysfunction of glyoxalase leads to accumulation of methylglyoxal, which can induce pain by modification of neuronal ion channels (Bierhaus et al., 2012; Eberhardt et al., 2012). Since neuronal cells are heavily dependent on glucose for their energy demand, it is not surprising that in addition to glyoxalase, the triose phosphate controlling transketolase (Ziegler et al., 2016b) seems to be also associated with some aspects of diabetic neuropathy. Further support for this hypothesis comes from an observational study showing that while HRV is reduced in patients with type-1 and type-2 diabetes, only patients with type-1 diabetes have a reduced cardiorespiratory fitness (Röhling et al., 2016). All this points to events downstream of hexokinase metabolizing glucose and an acquired disorder of detoxification of reactive glucose-derived metabolites, which are currently not addressable by glucose-lowering therapies (Hidmark et al., 2014). Furthermore, some, but not all inflammatory markers are associated with cardiac autonomic dysfunction in recent onset type-2 diabetes, making an anti-inflammatory therapeutic approach almost impossible (Herder et al., 2017). How complex the downstream handling of hexokinase-triggered glucose metabolites may be is shown in a recent study: Upon comparing an intense multifactorial treatment with routine care in patients with type 2 diabetes, the intensive diabetes treatment was not capable of reducing levels of the pain-inducing metabolite, methylglyoxal, to a larger extent than the routine treatment (Jensen et al., 2015). This indicates that hyperglycemia alone is not responsible for neurotoxic glucose-derived metabolites in the plasma. Albeit currently out of reach, it is crucial to clarify these pathomechanisms, not only on the neuronal cellular level, but also in non-neuronal cells that establish the neurovascular unit. In addition, treatment with statins, known to be beneficial in diabetes therapy, was reported to increase plasma levels of methylglyoxal by a yet unknown mechanism. Whether, as shown for ROS, a certain level of this metabolite has protective functions, and thereby exceeding this protective level leads to loss of function, remains unknown. This indicates that you may affect molecules by the multifactorial treatment used in type-2 diabetes, which are relevant for neuronal function, while treating other risk factors for diabetic complications.

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The mouse and human studies showing an association of methylglyoxal with pain were performed relatively early after diabetes manifestation (Bierhaus et al., 2012). Other studies, done in serum, using stored samples from a biobank, yielded different results (Hansen et al., 2015). This might be due to many different reasons, including differences in the assay method, the storage, the material used and the patient characteristics. Since all patients with uremia have elevated methylglyoxal levels, but only rarely develop pain, the simple measurement of methylglyoxal by itself will not suffice to predict pain. Other parameters, more stable than methylglyoxal, and parameters differentiating the various routes of methylglyoxal detoxification, such as D-lactate, acetol and lactaldehyde, might shed more light on this issue (Morgenstern et al., 2016). And, of course, methylglyoxal is not the only reactive metabolite affecting the nerve; there are many more, such as ROS, acrolein, and others (Fleming and Nawroth, 2014). Furthermore, not all mediators of neuronal dysfunction come from glucose metabolism, also lipid-derived and metabolites of other energy sources can affect neuronal function. Some of these remain totally unknown, because clinical studies have confirmed some expected risk factors of distal symmetric sensorimotor polyneuropathy, which include duration of diabetes, hyperglycemia and age, followed by prediabetes conditions, hypertension, dyslipidemia and obesity. But there are also some surprising risk factors, such as height, smoking and insulin resistance (Papanas and Ziegler, 2016). Not mentioned in this review are all the parameters affecting renewal and regeneration of the various neuronal cells in diabetes. This predicts that treatment of diabetic neuropathy will remain quite difficult, especially because although so many different risk factors are known, their causative role is yet unexplored. Furthermore, the term DPN stands for so many clinically different entities, making it very likely that at the end there will not be a single drug capable of resolving all painful and painless symptoms of DPN.

ARE YOU SURE MY PROBLEMS ARE DUE TO DIABETES OR SHOULD WE DO A NERVE BIOPSY?

Your clinical history makes it very likely that you suffer from painful DPN. The diagnosis is mainly made based on history and clinical examination, other tests are only needed for studies, but not in clinical routine for patients with diabetes and typical manifestation of polyneuropathy (Ziegler et al., 2014b; Tesfaye et al., 2010; Papanas and Ziegler, 2013; Papanas and Ziegler, 2014; Papanas and Ziegler, 2015; Papanas et al., 2013; Ziegler et al., 2011a; Papanas and Ziegler, 2011; Körei et al., 2016). Nerve biopsies are not the method of choice to assess neuropathic pain, because routine analysis without electron microscopy does not address small fiber function; punch skin biopsies are a better standard for structural analyses of peripheral nerve fibers (Haanpää et al., 2011). If there is any doubt about the diabetic neuropathy, the diagnosis can be differentiated by less invasive routine tests, such as serum electrophoresis, vitamin levels, and analysis of cerebral spinal fluid. A nerve biopsy or punch skin biopsy would not change the potential therapy; therefore, it is not recommended. When nerve biopsies from patients with alcoholic neuropathy, chronic inflammatory demyelinating polyneuropathy, Vitamin B12 deficiency, CIPD, Charcot-Marie-Tooth disease I and II and monoclonal gammopathy were compared, a distinct local expression of the receptor for AGE's and its downstream target NFkBp65 was seen (Haslbeck et al., 2007). This is only one example for differences between diabetic and non-diabetic neuropathy, but these are findings of interest for the scientist, but not helpful for relieving your symptoms. Furthermore, familial amyloid polyneuropathy (FAP), which exhibits a clinical and electrophysiological phenotype, that shares many features with DPN, is unlikely to cause your complaints. In vivo imaging by MR neurography revealed some similarities, but also distinct differences, between these entities. For both diseases, increased proton spin density in the proximal nerve trunks is present resulting in a nerve signal increase. However, in FAP, an entirely diffuse pattern of proximal nerve fascicle signal increase was present (Kollmer et al., 2015), while in DPN, a focal/multifocal pattern was observed (Pham et al., 2011). The extent of these signal changes is directly related to the severity of clinical symptoms. These findings are interesting for several reasons: First, both diseases have similar clinical patterns, but distinct morphologic appearances. Second, while the amyloid deposition is generalized and the pattern in magnetic resonance neurography is therefore diffuse, there is a focal or multifocal pattern in DPN (Pham et al., 2015). This is surprising given the fact that hyperglycemia is not a focal event, thus pointing to other local reactions which must take place to trigger DPN. Therefore, research is needed to understand the focal pattern observed in DPN and to understand why some regions react while others do not react to the metabolic disorder. On the other hand, this means that while some areas of the nerve are vulnerable, others are protected, i.e. there must be effective defense systems, which have not been delineated so far. One might even discuss that while circulating glucose is elevated throughout the whole body, the intracellular changes needed for initiating diabetic complications might be very local and not uniform, even within an organ or a nerve.

These open questions around DPN indicate that it is still premature to simply label DPN as a microvascular complication of diabetes. Some histopathologic data (see above) indicate that this might be true, but even in mouse models, the data are conflicting. The simultaneous occurrence of DPN in association with retinopathy and nephropathy does not prove that DPN can be entirely understood on the level of a mere microvascular disease. If some of the vessels supplying the nerve are affected, this does not mean that the vessel only is relevant for DPN and other cells besides the endothelial cells are irrelevant. This holds especially true for the symptoms of painful DPN. Ultimately, pain is the result of a change of neural circuits involving the peripheral as well the central nervous system (Treede, 2016). Diabetic neuropathic pain may be spontaneous,

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but also includes enhanced pain sensitivity to external test stimuli (evoked pain: allodynia or hyperalgesia). We do not have any histological marker in peripheral nerves helping to understand these different symptoms, nor do we have a marker helping to understand on the structural basis as to why painful diabetic neuropathy is worse at night. This is indicative of a contribution of the central nervous system, possibly involving alterations in thalamic gating or descending controls. As a bottom-up mechanism, the thalamus serves functions as a ''pain generator and amplifier" (Fischer et al., 2009; Silva et al., 2016; Freeman et al., 2016). As a top-down mechanism, the rostroventromedial medulla mediates pain modulation by descending inhibition and facilitation (Yarnitsky et al. 2012; Silva et al., 2016). Consistent with this hypothesis are post-mortem studies in patients, which showed increases in the content of serotonin in the medial and lateral hypothalamus in diabetic patients (Lackovic et al., 1990). How all this correlates with the complex neuronal circuits, in which reappraisal of pain controls the magnitude of pain, and as a recent review stated ''you are getting the pain you expect", is still unknown (Tracey, 2010).

ARE THERE IMAGING TECHNIQUES HELPFUL FOR DIAGNOSIS OF THIS DIABETIC COMPLICATION, STARTING IN THE DISTAL NERVE ENDINGS OF THE FOOT AND SLOWLY MOVING AHEAD?

Patients sense the DPN mostly at the distal region of the lower extremities. Therefore, it is understandable that researchers focused on the distally dominant, mixed axonal loss of nerve fibers (Behse et al., 1977; Dyck et al., 1986a; Dyck et al., 1986b; Johnson et al., 1986; Llewelyn et al., 1991; Malik et al., 2001; Said et al., 1983; Wilbek et al., 2016). Accordingly the term ''dying back neuropathy" has been used (Said et al., 1983; Said, 2007). An alternative hypothesis is that early proximal axonal loss results at later stages in distal length-dependent degeneration. This hypothesis is supported by histological data generated already many years ago (Dyck et al., 1986a; Dyck et al., 1986b; Johnson et al., 1986; Sugimura and Dyck, 1982), but due to the availability of skin biopsies and the counterintuitive proximal symptom location - the symptoms occur distally – the proximal origin of DPN has not become a mainstream explanation of DPN. However, recently imaging techniques have changed this view, since a significant signal increase on T2-weighted MR images in the proximal nerve at thigh level corresponded to the severity of DPN. There was a strong proximal to distal gradient of these findings (Pham et al., 2011; Pham et al., 2015). The changes seen were focal or multifocal, which corresponds well to the histopathologic findings reported earlier (Dyck et al., 1985; Dyck et al., 1986b; Sugimura and Dyck, 1982; Johnson et al., 1986). Therefore, the evidence based on MR neurography and histological findings challenge the hypothesis of the distal origin of DPN and rather suggest a proximal primary injury, with severe distal consequences being secondary. In addition, the availability of such a sensitive imaging method might allow not only defining morphologic markers specific for distinct symptoms of DPN, but also locating these focal lesions in nerves and study the molecules and structures altered by histopathologic means. This might help to understand not only the biochemical events behind these MR neurographic lesions, but also the events in the proximal nerve leading to distal axonal loss. Morphologically, these lesions are reminiscent of ischemic insults as seen in human vasculitic neuropathy (Dyck et al., 1972). The combinatory approach of MR neurography and histology might solve this question and shed new light on the contribution of the epi- vs. endoneuronal vessels to some symptoms of DPN. Yet, the success of a combined approach including clinical characterization, neurography and, where available, histology in terms of revealing the distinct mechanisms leading to distinct symptoms remains speculative.

CAN YOU SUGGEST A DRUG, SPECIFIC AND EFFECTIVE FOR RELIEVING DIABETIC NEUROPATHY?

From the comments made above, you can already tell how sceptic I am. Too much remains unknown. There are several options for symptomatic treatment of neuropathic pain associated with diabetic neuropathy as listed in several excellent meta-analyses and guidelines (Finnerup et al. 2010), but there is no disease-modifying treatment available yet. Drug development has been hampered by incomplete understanding of the different structural and biochemical events underlying each symptom of DPN (Chizh et al. 2008). Pain, tingling, cramps on the one hand, hyperalgesia and allodynia on the other hand, are so distinct from loss of pain perception, non-healing ulcers and neuronal degeneration, that it can hardly be expected that one drug can solve all problems. Furthermore, the mechanisms behind pain in diabetes are so diverse that a simple concept is not going to work (Woolf et al. 1998). This holds true for the anti-inflammatory analgesic approaches, or the attempts to inhibit NFκB, RAGE signaling and others. One reason is that cellular activation parameters, such as inflammation or NFκB activation, represent a part of a complex regulatory network, affecting not only excitability, but also tissue regeneration and other cellular properties needed to counteract diabetic complications. Furthermore, the effects on inflammation, apoptosis and other mechanisms described in diabetes affect many organs, yet the individual organs may respond differently.

Symptomatic management of painful diabetic neuropathy is possible with systemic medications such as duloxetine or pregabalin, or topical treatment with lidocaine of capsaicin. Many analgesic drugs used have undesired side effects (Ziegler et al., 2015a; Moulin et al., 2014; Peltier et al., 2014; Snedecor et al., 2014; Ziegler and Fonseca, 2015). The majority of patients treated experience less than a 50% reduction in pain. In almost all studies conducted, patients treated ''successfully" still fulfill the criteria for entry into the study, even after ''successful" treatment. Therefore several new compounds are currently in development (Papanas and

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Ziegler, 2016; Jin et al., 2016). Some studies compare these new drugs against Pregabalin, approved for the management of neuropathic pain associated with diabetic neuropathy (Ziegler et al., 2015a). But Pregabalin has shown inconsistent results over the time of the trial in several studies, even within periods as short as 6 weeks (Pfizer, 2007a,b; Tolle et al., 2008; Ziegler et al., 2015a). Reviewing several trials with different drugs reveals a major disconnect between promising animal data and disappointing human studies. One main obstacle is the lack of reliable biomarkers, perhaps because neuron-specific biomarkers have a concentration too low to be detected (Chizh et al., 2008). Moreover, the abnormal spontaneous activity of nociceptive C-fibers in patients with diabetic neuropathic pain is also a marker not perfectly predicting whom to treat and whom not to treat (Serra et al., 2015). Resistance to analgesic treatment, in part due to loss of opioid receptors, is not a rare event the clinician is encountering (Ziegler et al., 2014c; Ziegler and Fonseca, 2015; Moore et al., 2014; Wiffen et al., 2013; Zhang et al., 2015).

Among the many drugs used, alpha-lipoic acid and benfotiamine (Hammes et al., 2003; Stracke et al., 2008; Seyit et al., 2016) are drugs believed to address important pathogenic mechanisms of painful neuropathy, as has been reported in some, but also contradicted in other studies (Várkonyi et al., 2013; Papanas and Ziegler, 2014; Papanas and Maltezos, 2012; Ziegler et al., 2011b; Ziegler et al., 2004; McIlduff and Rutkove, 2011; Mijnhout et al., 2012; Çakici et al., 2016; Garcia-Alcala et al., 2015; Ziegler et al., 2016a). The complex nature of DPN is indicated by the fact that optimal control of cardiovascular risk factors was associated with an improved efficacy of alpha-lipoid acid (Ziegler et al., 2016a). An explanation for this observation is still missing. There are many pathways known to be contributing to DPN, including the above mentioned AGE-RAGE pathway, detoxification of reactive metabolites, hyperglycemia, increased glucose metabolism through the polyol pathway, resulting in sorbitol and fructose accumulation and myoinositol depletion, but also thiamine depletion, activation of protein kinase C or depletion of the nerve growth factor, among others (Boulton et al., 2013; Ziegler et al., 2015b; Várkonyi et al., 2013; Albers et al., 2010; Papanas and Maltezos, 2012; Ziegler et al., 2011b). The challenging complexity of developing a mechanistic treatment based on pathogenesis is best exemplified by the side effects of aldose reductase inhibitors. One should expect that aldose reductase inhibitors should reduce the increased flux through the polyol pathway and thus ameliorate DPN (Bril and Buchanan, 2004; Bril and Buchanan, 2006; Giannoukakis, 2006; Matsumoto et al., 2008). However, the blocked polyol pathway is also crucial for DNA repair, known to be required for prevention of diabetic complications (Bhatt et al., 2015), and moreover, the aldose reductase inhibitors can also block the AKR needed to detoxify methylglyoxal in neuronal cells (Morgenstern et al., 2016). Thus, it appears that neuron-specific modulation of biochemical pathways is required to improve likelihood of successful clinical trials. However, it remains to be seen whether more specific drugs, targeting ion channels such as Nav1.7 or Nav1.8, will be more successful. Several studies are on the way, but the large number of failed studies make pharmaceutical companies somewhat cautious to invest their money into a complex field, in which disconnect between animal and human data is frequent and biomarkers predicting the therapeutic efficacy are sparse. One of the reasons contributing to this problem is the wide use of the streptozotocin (STZ) animal model for diabetes research. Certainly, STZ is particularly toxic for beta-cells in the pancreas, finally leading to an increase in glucose – comparable to type 1 diabetes. But STZ is also a DNA-chelating agent and induces many proinflammatory effects. One study showed recently that STZ-dependent and high glucose-independent immunologic effects persist even weeks after STZ-induced diabetes. Therefore, one can conclude that many studies have not specifically studied diabetes, but rather STZ effects, if they study their endpoint too early. This might be one explanation, among others, why so many drugs looked promising in animal studies, in which the non-glucose-dependent STZ effect was studied, but failed in the real world clinical study. The perfect target addressing diabetic neuropathy and especially the active symptoms, such as spontaneous pain, hyperalgesia, allodynia, tingling and cramps, has yet to be discovered. You may wonder how complex the pathophysiology is that finally results in pain, involving proximal nerve dysfunction, later distal nerve dysfunction, a variety of histologically and functionally very different nerve fibers, very different cell types within a nerve, but also mechanisms in the central nervous system and cardiovascular risk factors: miraculously, almost 50% of patients enjoy a meaningful reduction of their discomfort (Humpert et al., 2009) following muscle stimulation, but as you may expect to hear – the mechanism remains to be clarified.

IN CONCLUSION

You told me your complaints, I reported my current state of knowledge. It is by far less than what you anticipated. For the scientist, the open questions behind painful diabetic neuropathy are a wonderful world to be discovered, for the patient it is still a tragedy. What can we do? Ultimately, the most important issue at hand is to secure sufficient funds for pain research, especially pain induced by acquired disorders of metabolism, relevant in diabetes, but also other pain states.

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PS: The article focuses on questions relevant from the authors' perspective but other questions might be equally relevant.

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