PAINFUL AND PAINLESS DIABETIC NEUROPATHY: ONE DISEASE OR TWO?

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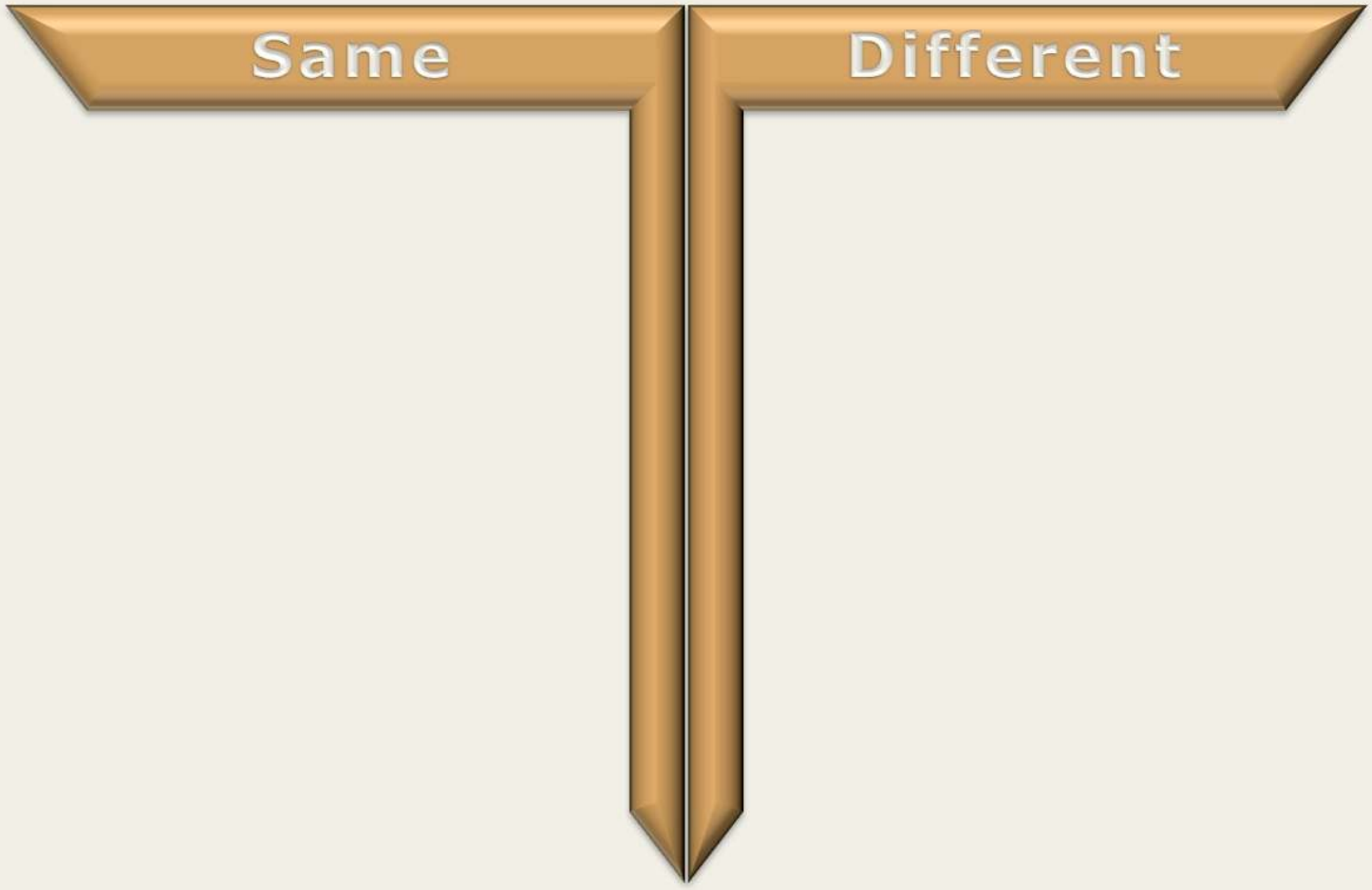
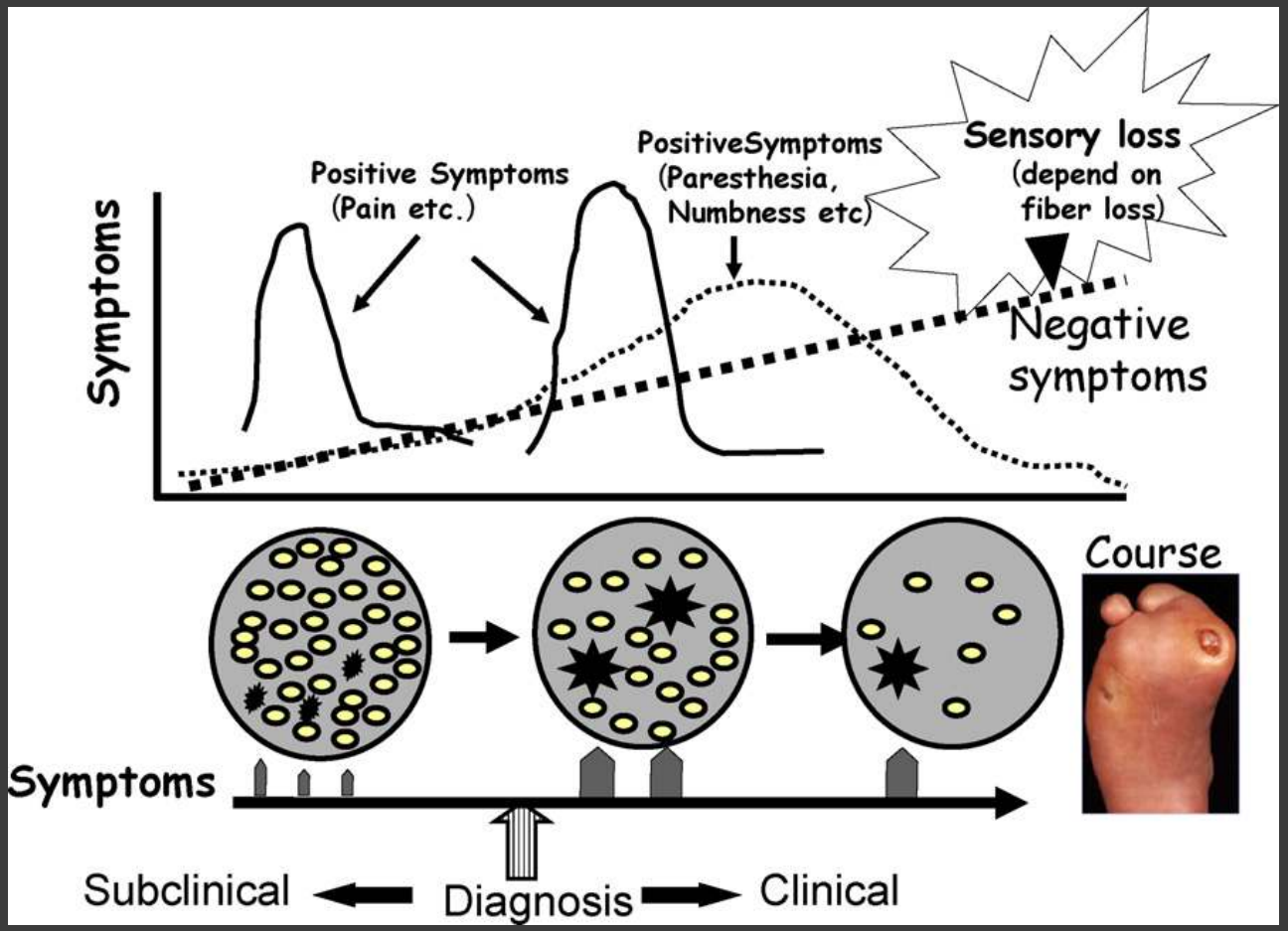
Same and Different



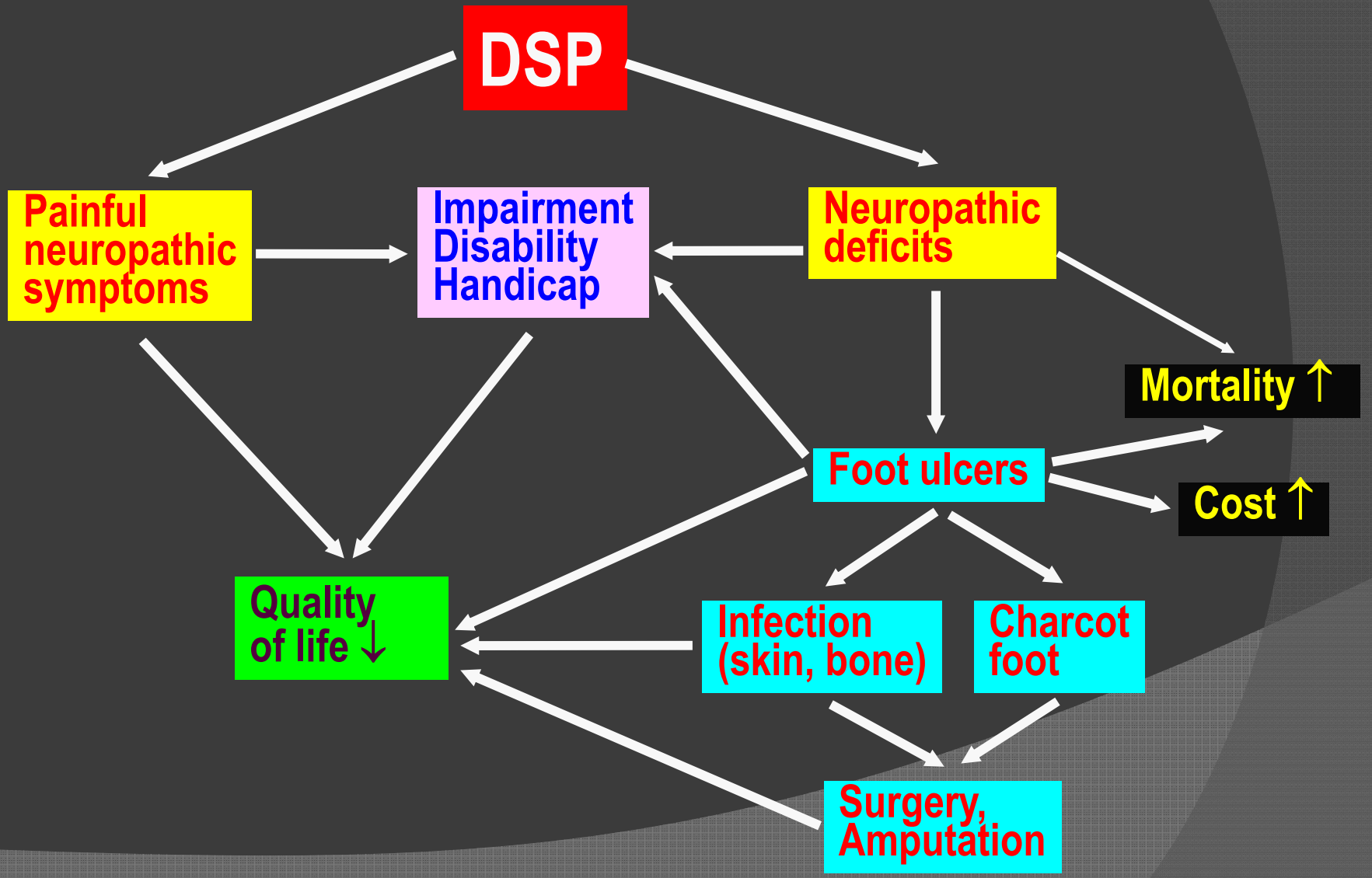
Natural history of diabetic neuropathy



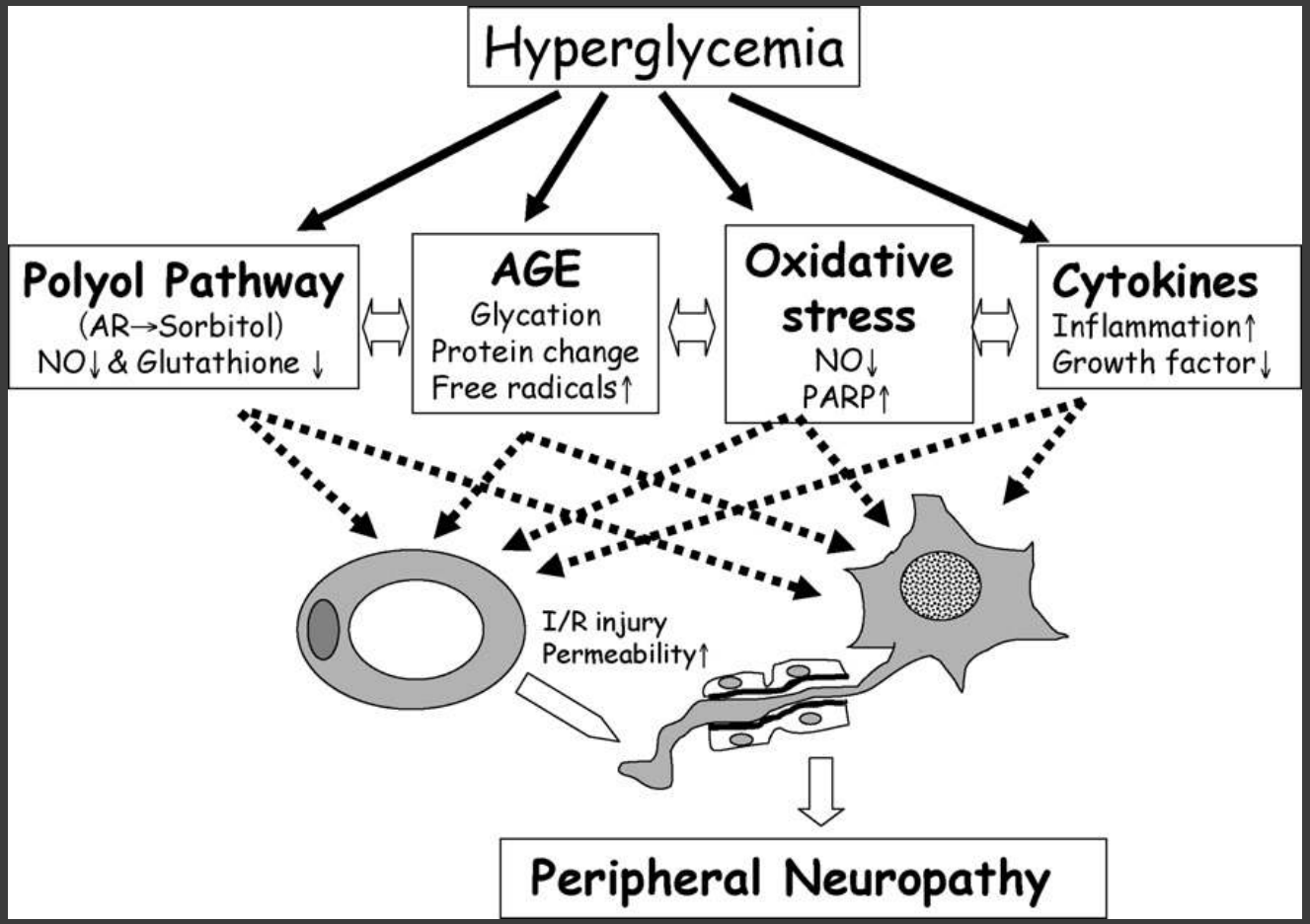
- With increasing stage of neuropathy, there is a progressive loss of nerve fibers that convey sensation.
- When the fibers undergo degeneration or impaired remyelination, they release impulse of positive symptoms.
- With progression of disease, negative symptoms of sensory loss are increased.

DRCP 77S (2007) S184–S189

Clinical Impact of Diabetic Distal Symmetric Polyneuropathy (DSP)



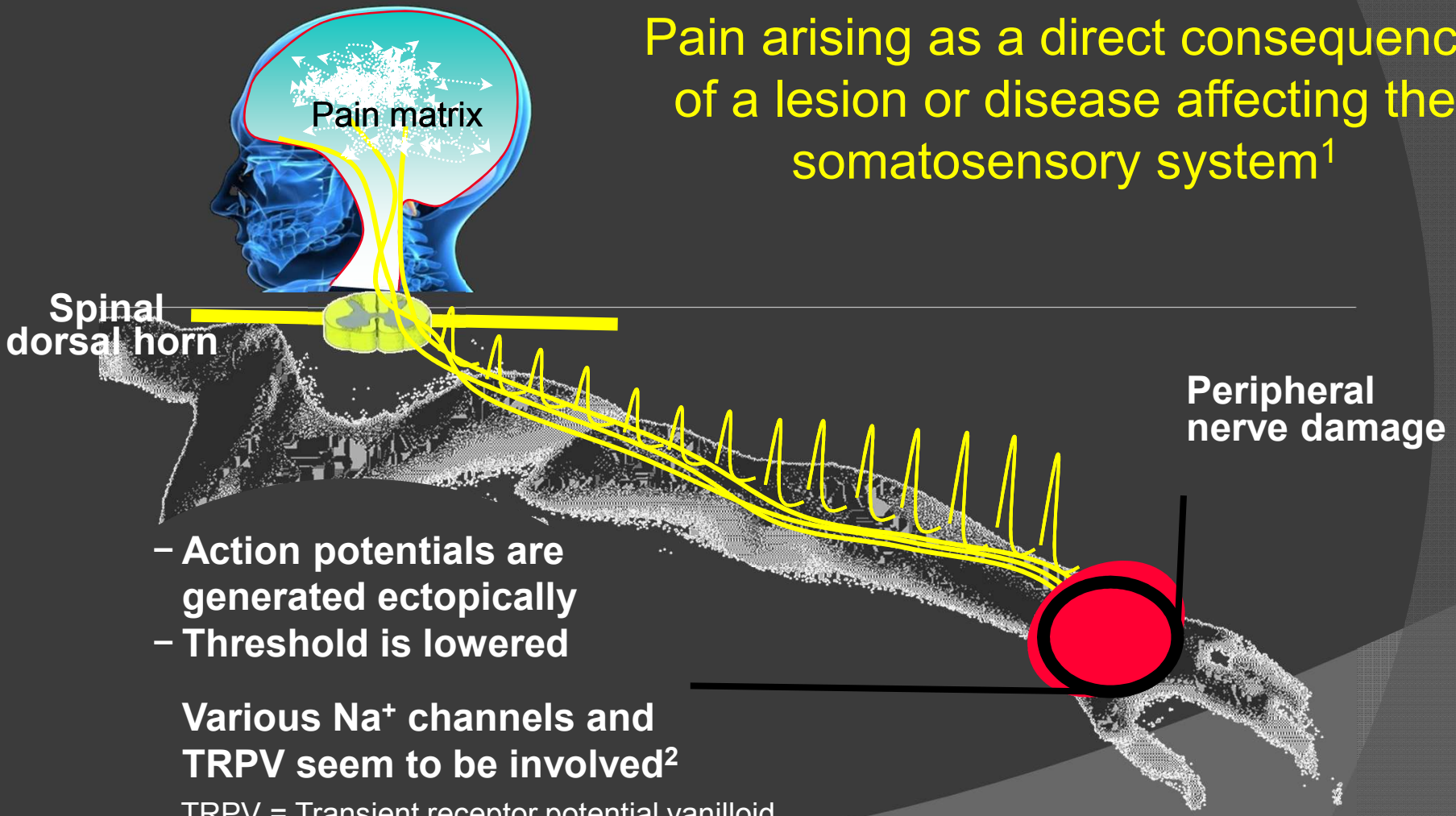
Multifactorial etiology of diabetic neuropathy



- Hyperglycemia exerts increased polyol pathway, enhanced AGE formation, increased oxidative stress as well as cytokine release.
- These factors are complicatedly interactive or independently operate for the cause and development of diabetic neuropathy directly affecting nerve tissues or through nutrient vascular tissues.

Neuropathic Pain

Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system[1]



- Action potentials are generated ectopically
- Threshold is lowered

Various Na^+ channels and TRPV seem to be involved[2]

TRPV = Transient receptor potential vanilloid.

1. Treede et al. *Neurology* 2008;70(18):1630–5. 2. Scholz et al. *Nat Neurosci* 2002;5 (Suppl):1062-67.

Slide courtesy of Walter Zieglgänsberger, Max Planck Institute of Psychiatry, Munich, Germany.

Nociceptive Versus Neuropathic Pain[1–2]

Nociceptive pain

- Adaptive
- Identifiable stimuli that normally produce tissue damage
- Usually self-limiting
- Transmitted by structurally and functionally intact pain pathways
- Examples: post-operative pain, burns, ischemic pain

Neuropathic pain

- Maladaptive
- Often spontaneous (occurring without identifiable stimuli)
- Often chronic
- May involve structural and functional changes in pain pathways
- Examples: polyneuropathy (e.g., diabetic, HIV), trigeminal neuralgia, central post-stroke pain

– Clinical pain syndromes occur along a spectrum from nociceptive to neuropathic

– Nociceptive and neuropathic pain may coexist in the same patient

1. Portenoy RK and Kanner RM. *Pain Management: Theory and Practice*. Philadelphia, PA: FA Davis; 1996:4. 2. Galer BS and Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, MN: McGraw-Hill; 2000:8–9.

Definition and assessment of negative and positive sensory symptoms and signs

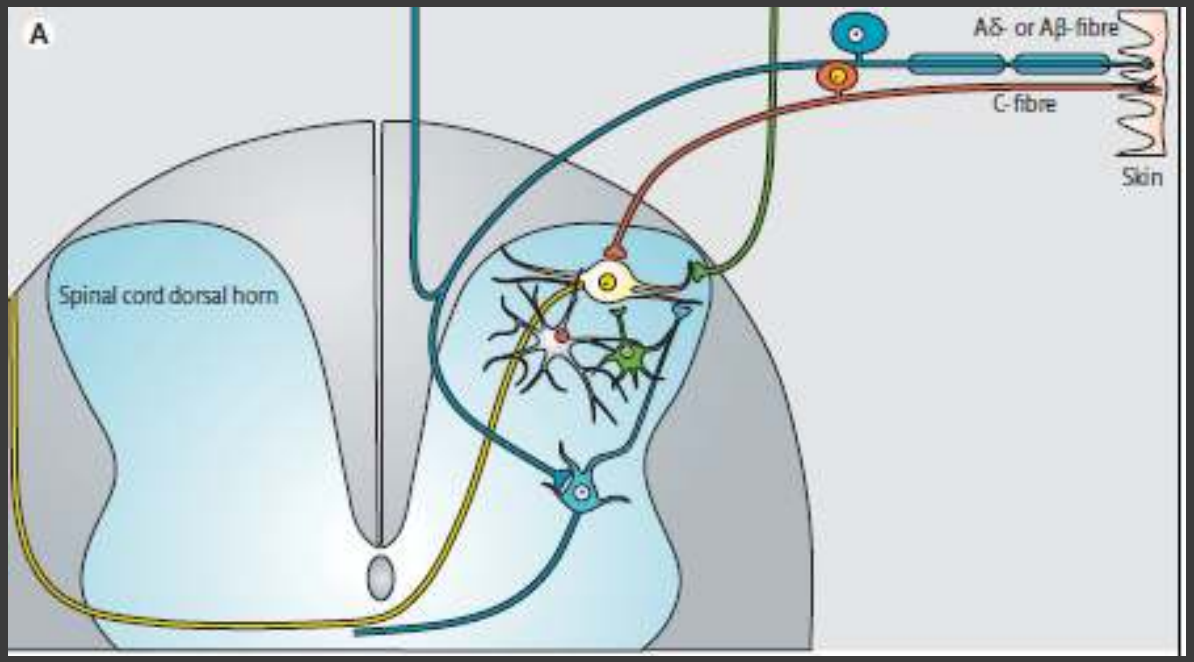
	Definition	Bedside assessment	Expected pathological response
Negative symptoms and signs			
Hypoaesthesia	Reduced sensation to non-painful stimuli	Touch skin with painter's brush, cotton swab, or gauze	Reduced perception, numbness
Pall-hypoaesthesia	Reduced sensation to vibration	Apply tuning fork on bone or joint	Reduced perception threshold
Hypoalgesia	Reduced sensation to painful stimuli	Prick skin with single pin stimulus	Reduced perception, numbness
Thermal hypoaesthesia	Reduced sensation to cold or warm stimuli	Contact skin with objects of 10°C (metal roller, glass with water, coolants such as acetone); contact skin with objects of 45°C (metal roller, glass with water)	Reduced perception
Spontaneous sensations or pain			
Paraesthesia	Non-painful ongoing sensation (skin crawling sensation)	Grade intensity (0–10); area in cm^2	..
Paroxysmal pain	Shooting electrical attacks for seconds	Number per time; grade intensity (0–10); threshold for evocation	..
Superficial pain	Painful ongoing sensation, often a burning sensation	Grade intensity (0–10); area in cm^2	..

Multiple Mechanisms of Pain Dysfunction

- Peripheral nervous system input:
  - Peripheral sensitization
  - Ectopic excitability
- Central nervous system processing:
  - Central sensitization
  - Structural reorganization
  - Disinhibition

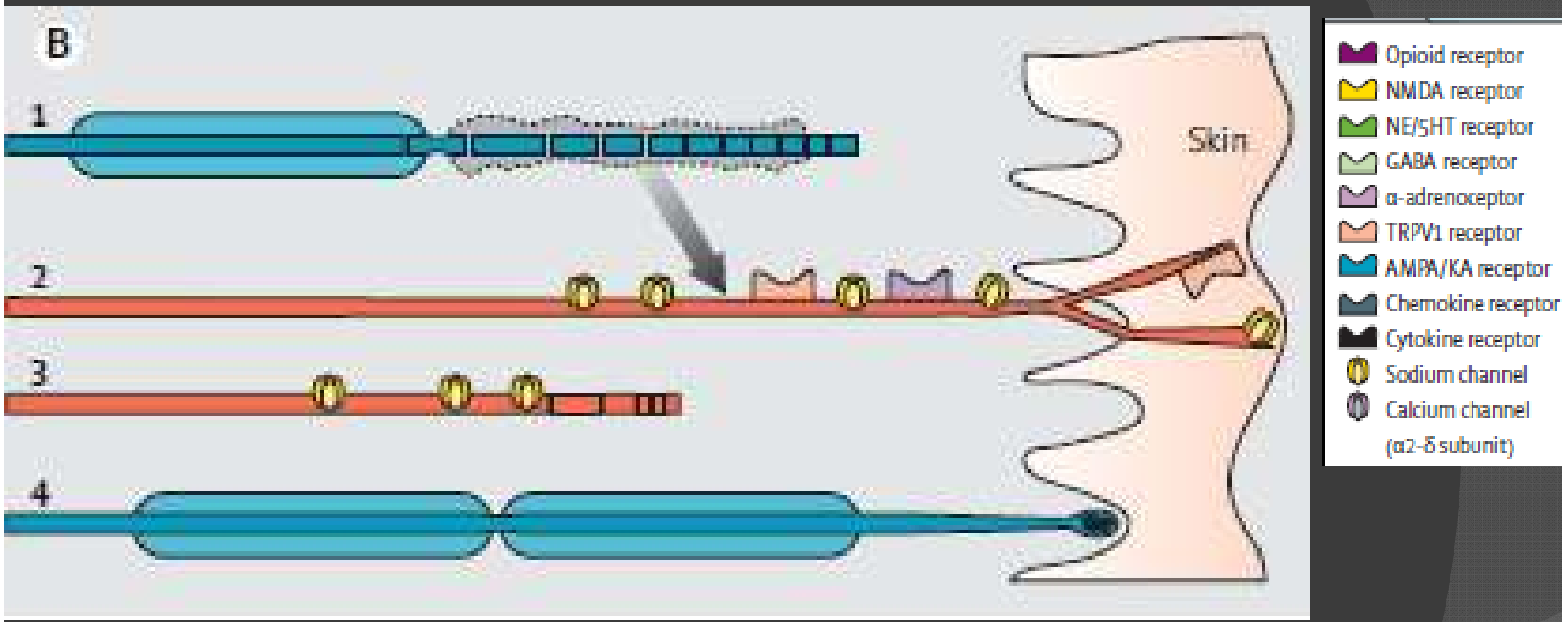
Woolf CJ. *Ann Intern Med*. 2004;140:441–451.

Primary afferent pathways and their connections in the spinal cord dorsal horn



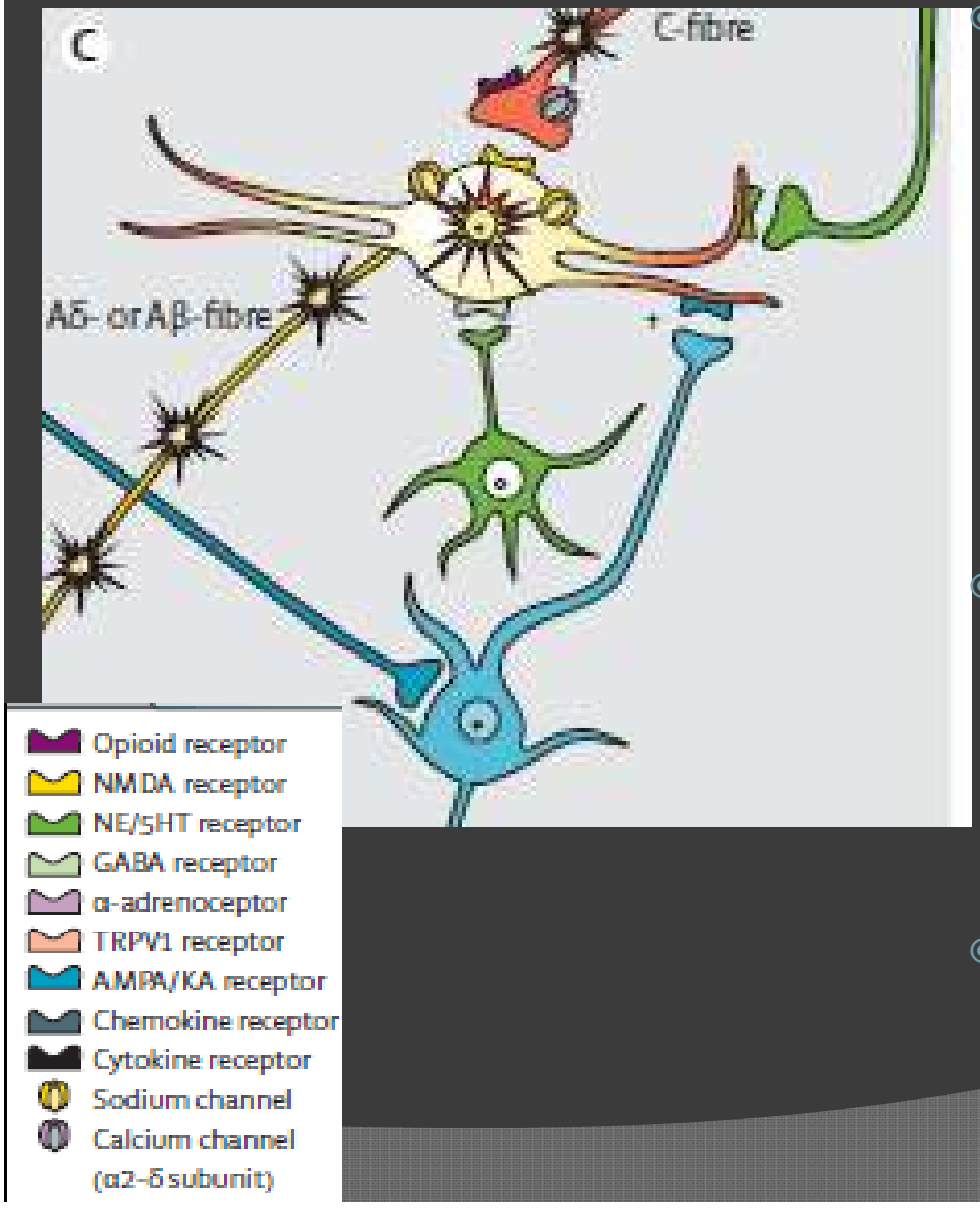
- Nociceptive C-fi bres (red) terminate at spinothalamic projection neurons in upper laminae (yellow neuron). Non-nociceptive myelinated A-fibres project to deeper laminae.
- The second-order projection neuron is a WDR type—it receives direct synaptic input from nociceptive terminals and also multisynaptic input from myelinated A-fibres (non-noxions information, blue neuron system).
- Interaction with microglia (grey cell) facilitates synaptic transmission.
- GABAergic interneurons(green neuron) normally exert inhibitory synaptic input on the WDR neuron.
- Furthermore, descending modulatory systems synapse at the WDR neuron (only the inhibitory projection, green descending terminal).

Peripheral sensitisation



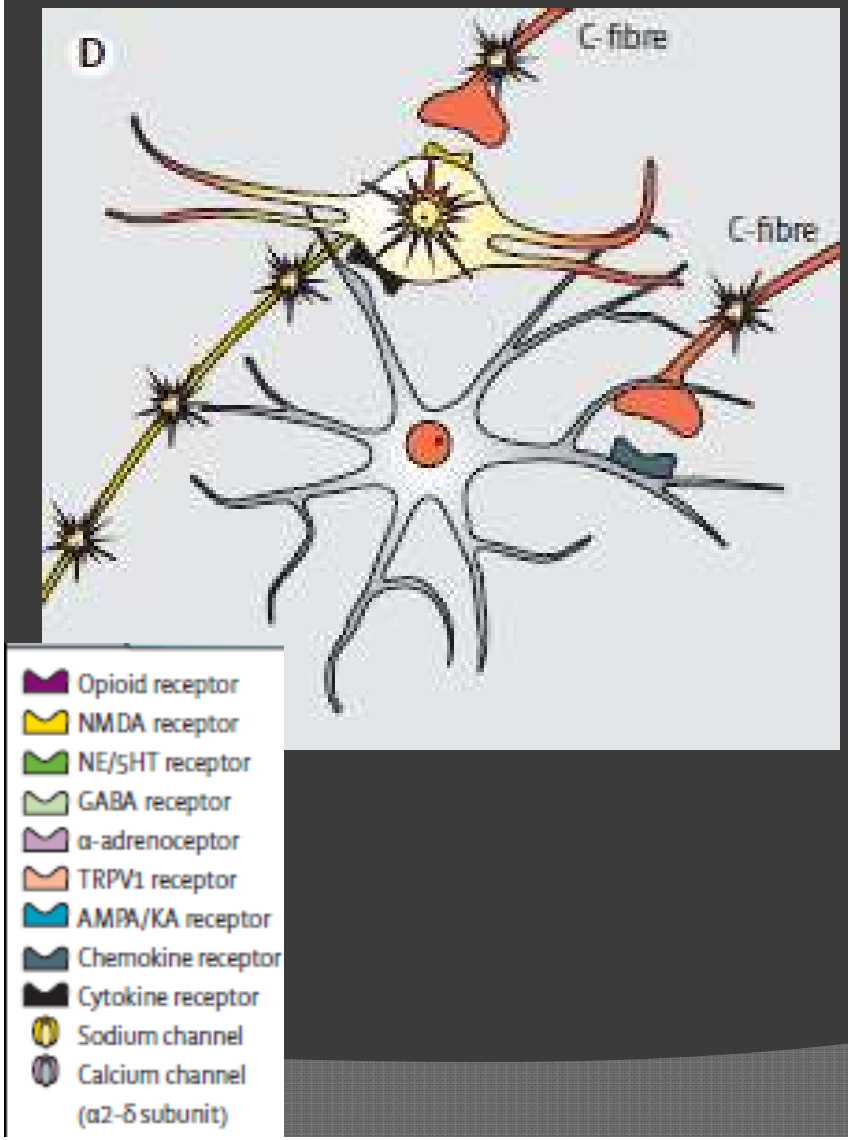
- Some axons are damaged and degenerate (axons 1 and 3) and some are still intact and connected to the peripheral end organ (skin; axons 2 and 4).
- Expression of sodium channels is increased on damaged neurons (axon 3), triggered as a consequence of the lesion.
- Furthermore, products such as nerve growth factor, associated with Wallerian degeneration and released in the vicinity of spared fibres (arrow), trigger expression of channels and receptors (eg, sodium channels, TRPV1 receptors, adrenoreceptors) on uninjured fibres.

Spontaneous activity & disinhibition & central sensitisation



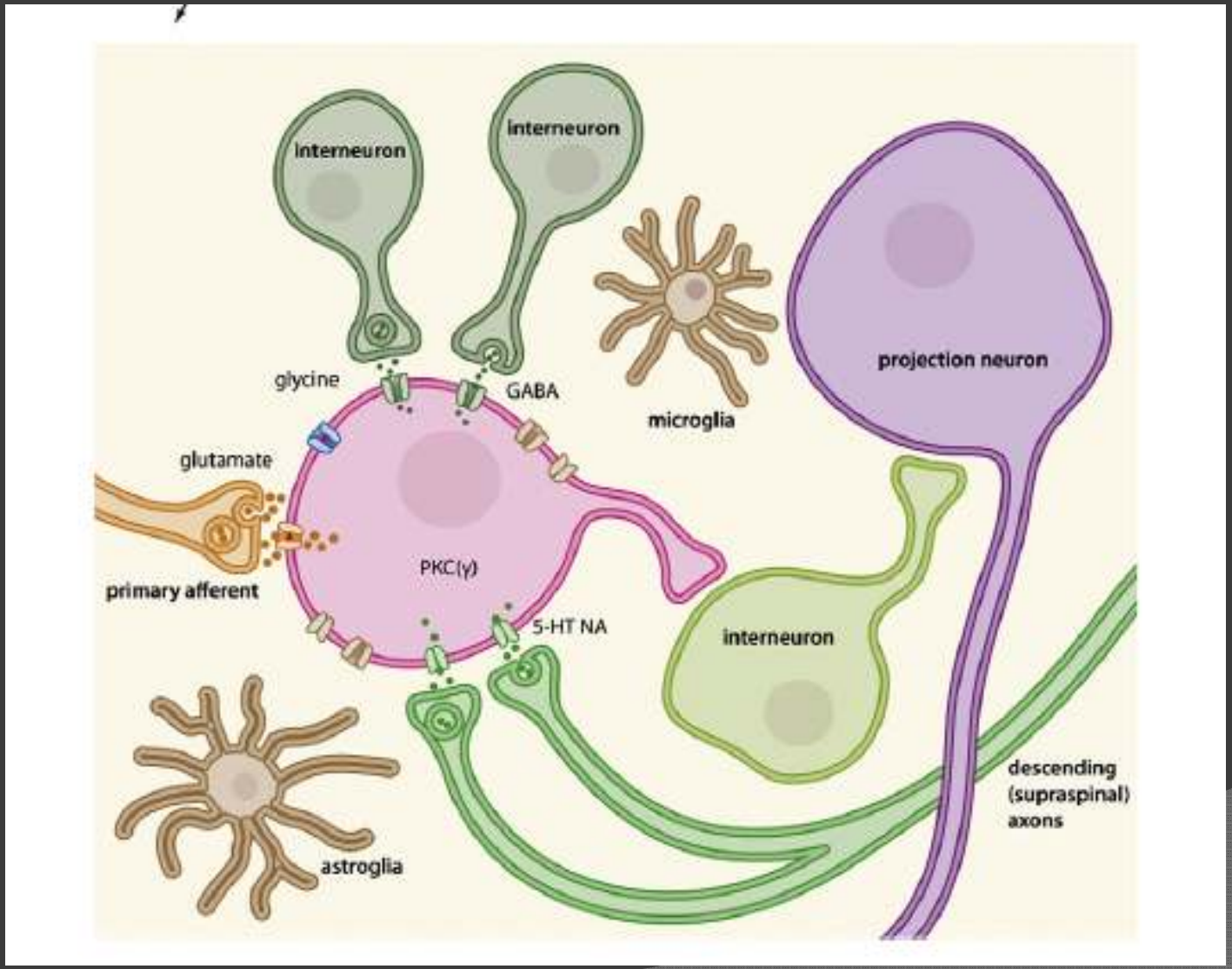
- Spontaneous activity in C-nociceptors induces secondary changes in central sensory processing, leading to spinal cord hyperexcitability (central sensitisation of second-order nociceptive neurons, star in yellow neuron) that causes input from mechanoreceptive A-fibres (blue neuron system, light touching and punctate stimuli) to be perceived as pain (dynamic and punctate mechanical allodynia, indicates gating at synapse).
- Several presynaptic (opioid receptors, calcium channels) and postsynaptic molecular structures (glutamate receptors, AMPA/kainate receptors, sodium/5HT receptors, GABA receptors, sodium channels) are involved in central sensitisation.
- Inhibitory interneurons and descending modulatory control systems (green neurons) are dysfunctional after nerve lesions, leading to disinhibition or facilitation of spinal cord dorsal horn neurons and to further central sensitisation.

Ectopic nerve activity



- Peripheral nerve injury activates spinal cord glial cells (grey cell) via chemokines, such as CCL2 acting on chemokine receptors.
- Activated microglia further enhance excitability in WDR neurons by releasing cytokines and growth factors (eg, tumour necrosis fator α, bone-derived nerve factor) and increasing glutamate concentrations

Superficial dorsal horn in physiological situations



	Definition	Bedside assessment	Expected pathological response
Evoked pain			
Mechanical dynamic allodynia	Pain from normally non-painful light moving stimuli on skin	Stroke skin with painter's brush, cotton swab, or gauze	Sharp burning superficial pain; present in the primary affected zone but spreads beyond into unaffected skin areas (secondary zone)
Mechanical static hyperalgesia	Pain from normally non-painful gentle static pressure stimuli on skin	Apply manual gentle mechanical pressure to skin	Dull pain; present in the area of affected (damaged or sensitised) primary afferent nerve endings (primary zone)
Mechanical punctate, pin-prick hyperalgesia	Pain from normally stinging but non-painful stimuli	Prick skin with a safety pin, sharp stick, or stiff von Frey hair	Sharp superficial pain; present in the primary affected zone but spreads beyond into unaffected skin areas (secondary zone)
Temporal summation	Increasing pain sensation (wind-up-like pain) from repetitive application of identical single noxious stimuli	Prick skin with safety pin at intervals of <3 s for 30 s	Sharp superficial pain of increasing intensity
Cold hyperalgesia	Pain from normally non-painful cold stimuli	Contact skin with objects of 20°C (metal roller, glass with water, coolants such as acetone); control: contact skin with objects of skin temperature	Painful, often burning, temperature sensation; present in the area of affected (damaged or sensitised) primary afferent nerve endings (primary zone)
Heat hyperalgesia	Pain from normally non-painful heat stimuli	Contact skin with objects of 40°C (metal roller, glass with water); control: contact skin with objects of skin temperature	Painful burning temperature sensation; present in the area of affected (damaged or sensitised) primary afferent nerve endings (primary zone)
Mechanical deep somatic hyperalgesia	Pain from normally non-painful pressure on deep somatic tissues	Apply manual light pressure at joints or muscles	Deep pain at joints or muscles

Epidemiological aspects

- Is it possible to isolate distinct clinical correlates of PDPN?
- The available studies—a few of which are now quite dated—give estimates of PDPN prevalence ranging from 3.3 % to 26.8 %.
- A prevalence of about 17.5 % corresponds to the median of the figures obtained when the diagnosis was based on the presence of both neuropathic pain and DPN
- Risk markers or factors for DPN

Diabet Med. 2004;21:976–82.
Diabetes Metab. 2009;35:206–13.

Epidemiological Aspects

Table 1 Epidemiological studies on prevalence and clinical correlates of PDPN: author, study characteristics, number of patients, diagnostic criteria for PDPN, prevalence of PDPN, and correlates of DPN and PDPN (in **Bold** those found in multivariate analysis)

Author (year)	Study design/setting	Number (type)	Diagnostic criteria for PDPN	Prevalence (%)	Correlates and predictors of DPN	Correlates and predictors of PDPN
Chan 1990 [146]	Hospital diabetic clinic; UK	962 (type 1 and 2)	Neuropathic pain in the lower limbs	7.4	Not provided	Not provided
Harris 1993 [38]	Population based study (NHIS); US	124 (type 1) 2268 (type 2)	Painful sensation or tingling in hands and feet (personal household interviews)	26.8	Not provided	Diabetes duration, **hypertension** (OR = 1.58), **hyperglycemia** (OR = 2.51), **glycosuria** (OR = 2.31)
Partanen 1995 [28]	University hospital diabetes center (longitudinal study); Finland	132 (type 2) (aged 45–64, newly diagnosed)	Pain in the limbs + 4 NCS abnormalities	6 at diagnosis, 20 at 10 years	Poorer glycemic control, low serum insulin	Not provided
Sorensen 2002 [29]	Hospital diabetes center; Australia	2610 (type 2)	Bilateral and symmetrical foot pain; criteria for DPN: VPT≥30	3.3	**Age** (OR = 1.09), **diabetes duration** (OR = 1.09), **height** (OR = 1.05), **HbA1c** (OR = 1.2)	**Diabetes duration** (OR = 1.09), **VPT** (OR = 1.06)
Daousi 2004 [3]	Community-based study in 3 urban general practice surgeries; UK	350 (type 1 and 2)	PDPN [typical neuropathic pain >1 year + PSS≥3 + (NDS≥6) or (NDS≥3 + NSS≥5)]	16.2	Not provided	No clinical correlates among sex, age, duration, type, BMI, HbA1c, smoking, alcohol, PAD, CAD, foot ulceration, depression
Davies 2006 [4]	Population-based study in an urban community; UK	353 (type 2) in phase 1; 269 in phase 2	Typical neuropathic pain (phase 1: postal survey; phase 2: clinical neurologic history and examination + TCSS)	26.4 (23.4 and 19 when excluding patients with TCSS<5 and mixed pain)	**Diabetes duration** (OR = 1.06), **HbA1c** (OR = 1.28)	No clinical correlates apart from severity of DPN (TCSS score) (in univariate analysis)
Wu 2007 [40]	Population-based study (random sample of households); France	1023 (type 1 and 2)	Neuropathic symptoms and pain (MNSI-Q ≥7 + average pain on BPI >0); computer-aided telephone interviews;	8	Type 1, age >65 years, gender (female) (only in univariate analysis)	Age >65 years, gender (male) (only in univariate analysis)
Ziegler 2009 [5]	Population-based study (MONICA/KORA); Germany	195 (type 1 and 2)	PDPN (positive answer to question 2 and/or question 6 of MNSI-Q + MNSI score>2)	13.3	Not provided	**Age** (OR = 1.08), **weight** (OR = 1.03), **PAD** (OR = 9.27)
Ziegler 2009 [32]	Population-based study (KORA Myocardial Infarction Registry); Germany	214 (type 1 and 2, post-Myocardial Infarction)	PDPN (positive answer to question 2 and/or question 6 of MNSI-Q + MNSI score >2)	21	Not provided	**Waist circumference** (OR = 1.05), **physical activity** (OR = 0.31), **PAD** (OR = 5.61)
Van Acker 2009 [6]	40 outpatients diabetes clinics; Belgium	344 (type 1); 767 (type 2)	PDPN (DN4 ≥4 + abnormal sensitivity to 10 g monofilament and/or insensitivity to pinprick)	14.1	**Gender** (female) (OR = 0.7), **age** (per 10 years OR = 1.56), **type 2** (OR = 1.65), **diabetes duration** (per 5 years OR = 1.16), **low HDL** (OR = 2.12)	**Age** (OR = 1.47), **diabetes duration** (per 5 years OR = 1.14), **obesity** (OR = 1.62), **low HDL** (OR = 2.17), **high triglycerides** (OR = 1.76), **nephropathy** (OR = 1.69)

ORs of risk factors associated with the presence of DPN using logistic-regression analysis

Variables	OR (95% CI)	*P* value
Age (yr)	1.01 (1.00, 1.02)	0.01
Duration of diabetes (yrs)	1.03 (1.01, 1.04)	< 0.01
Current smoker (%)	1.41 (1.08, 1.85)	0.01
Hypertension (%)	1.48 (1.21, 1.79)	< 0.01
Dyslipidemia (%)	1.28 (1.07, 1.55)	< 0.01
Any retinopathy (%)	1.88 (1.50, 2.35)	< 0.01
History of CVDs (%)	1.45 (1.07, 1.94)	0.01
History of PADs (%)	5.53 (3.17, 9.64)	< 0.01
Foot ulcer or amputation (%)	3.82 (1.03, 14.16)	< 0.01
MNSI scores (≥ 2.0)	4.66 (3.49, 5.14)	< 0.01

Diabetic Medicine .vol29(9) e290–e296, September 2012

Odds ratios of risk factors associated with the presence of PDPN

Variable	OR (95% CI)	p-Value
Age	1.02 (1.00–1.03)	0.03
Gender, female	1.49 (1.08–2.07)	0.02
Duration of diabetes	1.01 (0.99–1.03)	0.51
Diabetes treatment		
Oral hyperglycemic agent(s)	1.20 (0.77–1.86)	0.42
Insulin	0.93 (0.53–1.64)	0.80
Insulin + oral hypoglycemic agent(s)	1.28 (0.64–2.58)	0.43
Obesity	0.84 (0.48–1.49)	0.55
Fasting plasma glucose	1.00 (1.00–1.01)	0.03
HbA1c	0.94 (0.88–1.01)	0.10
Diabetic retinopathy	1.30 (0.93–1.83)	0.13
Diabetic nephropathy	1.20 (0.82–1.76)	0.36
Cardiovascular disease	1.01 (0.65–1.56)	0.97
Cerebrovascular accident	1.81 (1.02–3.22)	0.04
Peripheral artery disease	1.52 (0.87–2.67)	0.14
Hypertension	1.59 (1.14–2.23)	<0.01
Dyslipidemia	0.90 (0.66–1.23)	0.51
Current smoker	1.28 (0.70–2.34)	0.43

Standardized ORs are expressed per SD increase in each continuous variable, and those for categorical variables have as a reference group without the respective risk factor. CI, confidence interval; ORs, odds ratios; PDPN, painful diabetic peripheral neuropathy.

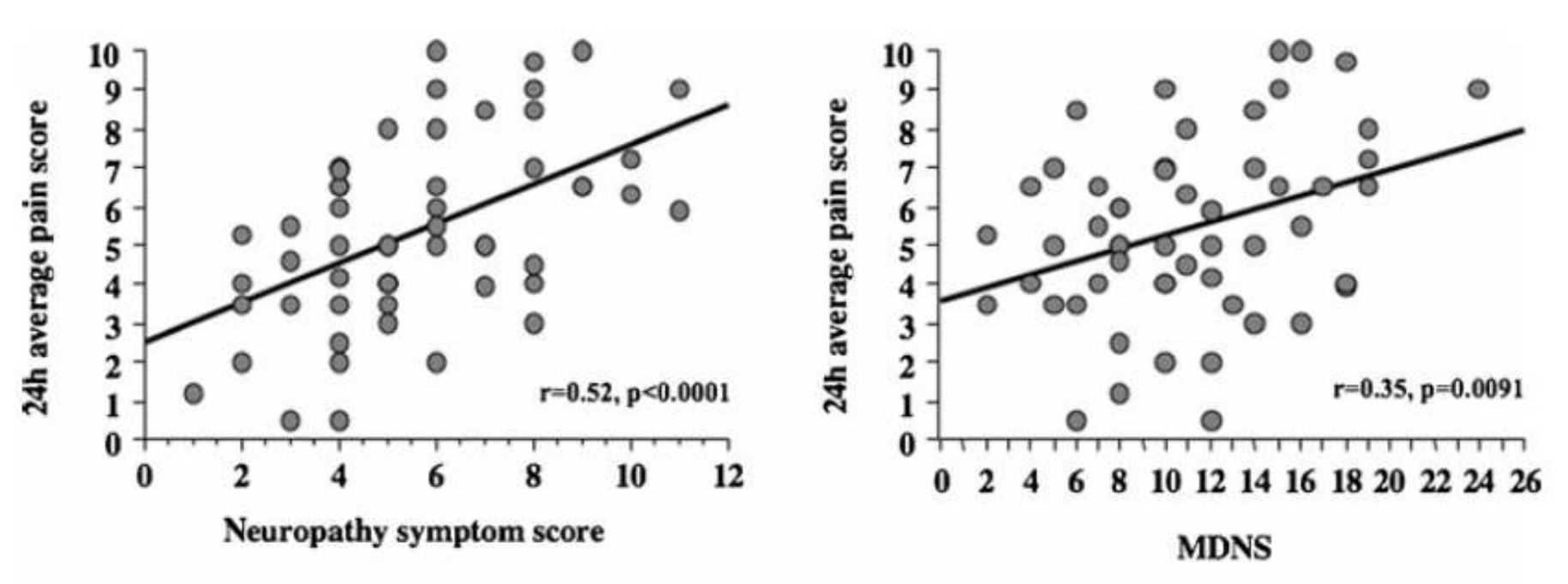
Neurologic aspects: Is there a particular neurologic phenotype of Painful vs Painless DPN?

- The Association between sensorimotor deficits and PDPN
- Coexistence of pain with plausible distribution,
- History of peripheral or central neuropathy,
- Objective demonstration of neurologic signs concordant with the distribution of pain
- Objective confirmation of the diagnosis of the neurologic disease.

Positive & negative symptoms

- Generally, positive sensory symptoms, such as pain and paresthesia, are considered the consequence of fiber neuropathic damage with active degeneration or impaired regeneration,
- Where as with increasing loss of sensory fibers, negative symptoms occur, ie, sensation loss

Clinical correlates of painful diabetic neuropathy and relationship of neuropathic pain with sensorimotor nerve function



- Correlation between average 24-h pain score and some sensorimotor indexes of diabetic neuropathy, ie, neuropathy symptom score, Michigan Diabetic Neuropathy Score (MDNS).

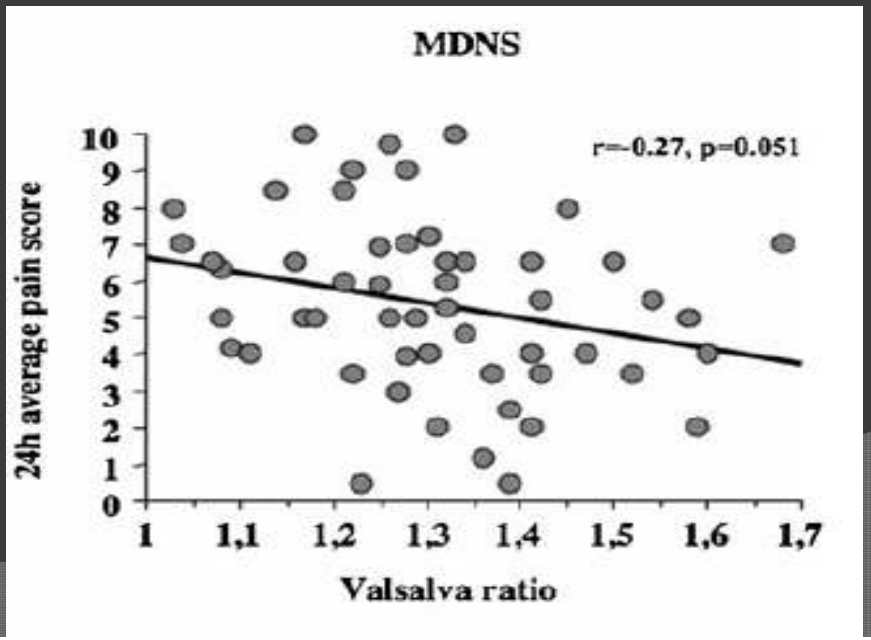
Eur J Pain. 2011;15:153–60

The Association between Neuropathic Pain and Small-fiber function and Morphology

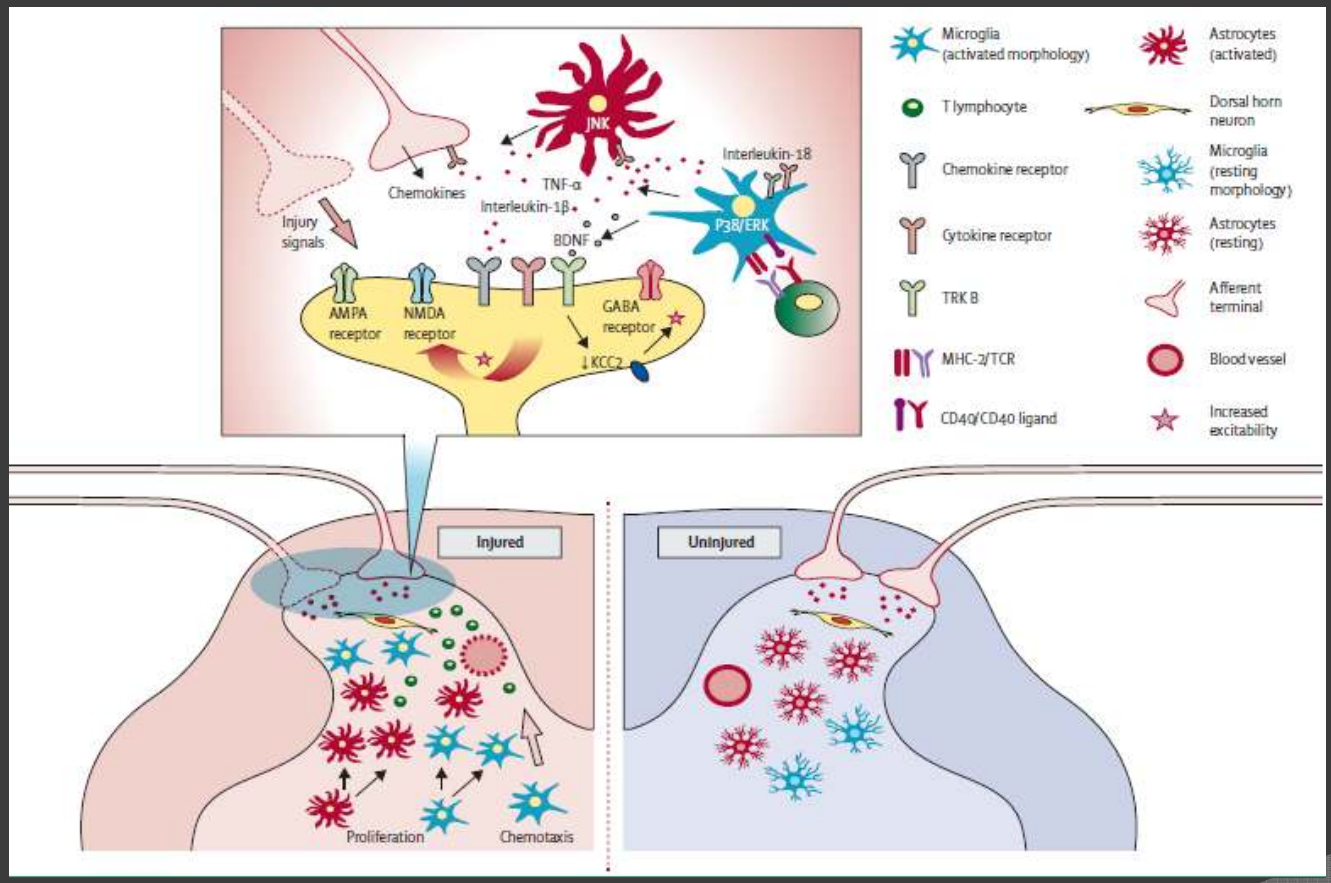
- A number of studies have described in PDPN pain-related sensory dysfunction using QST to assess large (Aβ) and mainly small-fiber (Aδ and C) function.
- They yielded, however, contradictory results with regard to a predominant or exclusive involvement of small fibers (responsible for nociceptive and thermal sensation) in PDPN
- Slightly reduced IENF and corneal nerve fiber lengths (but not density) were also observed in painful DPN compared with its painless equivalent .
- However, also using skin biopsy some studies failed to find a close or constant link between the presence of neuropathic pain and IENF morphology

The Association between Diabetic Neuropathic Pain and Autonomic Neuropathy

- The relationship between autonomic involvement and PDPN has been evaluated with 2 possible implications:
- Involvement of autonomic fibers inside a spectrum of small fiber damage
- Possible role of autonomic - mainly sympathetic - dysfunction as a pain generating mechanism.



The role of the immune system in the generation of neuropathic pain



- Synaptic transmission between sensory neuronal terminals and dorsal horn neurons enhanced by newly recruited microglia, T lymphocytes, and astrocytes after nerve injury

Lancet Neurol 2012; 11: 629–42

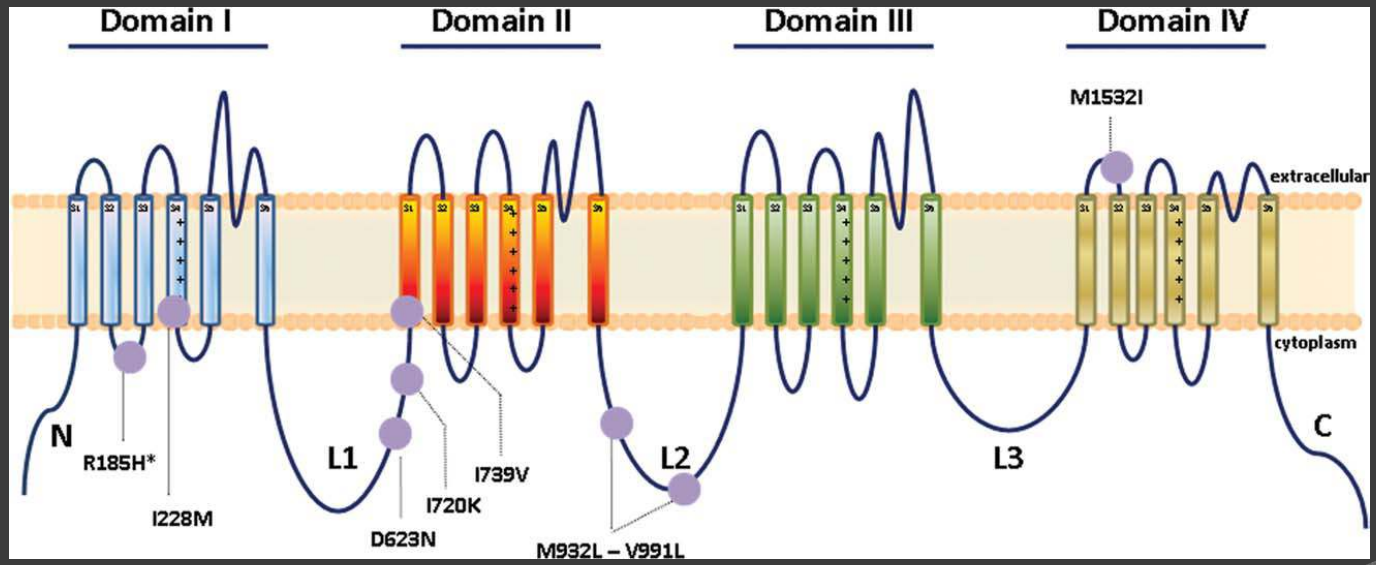
Hyperglycemia-Dependent Mechanisms of Pain

- Several hyperglycemia-related mechanisms clearly involved in the pathogenesis of DPN & have also been implicated in experimental conditions in neuropathic hyperalgesia and abnormal sensation, such as increased aldose reductase activity, oxidative-nitrosative stress, protein kinase C, poly(ADP-ribose) polymerase (PARP), p38-MAP kinase activity, proinflammatory response (increase in TNF-α and COX-2 activity):
- Dysregulation of neuronal Ca2+ homeostasis, produced by reduced stimulation of insulin receptors
- Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy
  - Altered glyoxalase 1
    : late diabetic complication.

Nat. Med. ***18, 926–933 (2012)***

Genetic Susceptibility to Pain

- Gain of function mutations in the SCN9A gene encoding Nav1.7
- Mutations of Nav1.8
- Genes coding for tetrahydrobiopterin (BH4), including GCH1



Clin Genet. 2012;82:367–73
Proc Natl Acad Sci U S A. 2012;109:19444–9.

Pain in RCTs in Diabetic Neuropathy

- Why is pain more responsive to disease-modifying intervention than other neurologic endpoints?

Acetyl-L-Carnitine	Acetyl salicylic acid	Actovegin	α-Lipoic acid
Alpha-Tocoferol	Alrestatin	Amitriptyline	Baclofen
BDNF	Benfotiamine	Beraprost	Calcitonin
Capsaicin	Carbamazepine	Chininsulfate	Chlorpromazine
Citalopram	Clomipramine	Clonazepam	Clonidine
Colchicin	C-Peptide	Cronassial	CT-3
Cyanocobalamine	Cyclandelat	Cytidin	Desipramine
Dextromethorphan	Dipyridamole	Doxepine	Duloxetine
Epalrestat	Erythropoietin	Fidarestat	Fluoxetine
Fluphenazine	Gabapentin	γ-Linolenic acid	Ginkgo biloba
Goshajinkigan	Haloperidol	Ibuprofen	Iloprost
Imipramine	Interleukin-6	Isaxonine	ISDN
Lacosamide	Lamotrigine	Levodopa	Levomepromazine
Lidocaine	Lidorestat	Lisinopril	Madopar
Maprotiline	Memantine	Methylcobalamine	Mexiletine
Mianserine	myo-Inositol	NGF	Nortriptyline
Org 2766	Oxcarbazepine	Oxycodone	Paroxetine
Pentoxifylline	Phenytoine	Ponalrestat	Pregabalin
Promethazine	Prostaglandin E1	Protriptyline	Pyridoxine
Ranirestat	Ruboxistaurin	Sabeluzole	Sorbinil
Sulindac	Tetrazepam	Thiamine	Thioridazine
Tolrestat	Topiramate	Tramadol	Trandolapril
Trazodone	Trifluopromazine	Uridin	Valproate
Venlafaxine	VEGF	Zenarestat	Zopolrestat


SAME SAME
BUT DIEFERENT

Conclusions

- While painful and painless DPN share most risk markers,the relationship with obesity, however, would appear more prominent for the painful form.
- Neuropathic pain can develop or persist also at advanced stages of DPN, and an increasing severity of sensory deficits is associated with an increased risk of developing neuropathic pain.
- Although somatic small fiber damage is considered a prerequisite for neuropathic pain development in diabetes, there is no definite evidence of an exclusive or prominent involvement of small fibers in PDPN.

Conclusions(II)

- Multiplicity of pain mechanisms that despite stemming from the common soil of peripheral nerve damage (at the level of small and usually also large nerve fibers) can take different directions, in a dynamic way that might change through the subsequent stages of nerve disease.
- Peculiar role in neuropathic are pain generation of genetic susceptibility, inflammation, direct hyperalgesic effect of hyperglycemia, and central processing of neuropathic pain.
- PDPN probably needs, for its development, the intervention of distinct contributors: gender, genetics, particular nuances of metabolic derangement (greater glycemic oscillations, more dyslipidemia, more oxidative stress, more inflammation), psychological and behavioral interactions, and environment.

As Winston Churchill said, "We need to go from failure to failure without losing our enthusiasm and ultimately we will succeed."

Thank you for your attentions