BENZON SYMPOSIUM No. 57

ACUTE PAIN - PATHOPHYSIOLOGY AND RISK FACTORS FOR CHRONIFICATION

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Organizing committee:
Henrik Kehlet (Copenhagen), Troels Staehelin Jensen (Aarhus), Arne Svejgaard (Copenhagen) & Povl Krogsgaard-Larsen (Copenhagen)

Abstracts - MONDAY, October 4, 2010

Opening lecture
Chronic Pain after Surgery - how the Problem Evolved

Macrae WA; Step Rock House, The Scores, United Kingdom

It is a paradox that people have suffered chronic pain after injuries, including surgery, since ancient times, but it has received scant attention in the medical literature until the last twelve years. Pain after amputation has been recorded through the years, and was first described by the French surgeon Amboise Paré in 1551 as "dolor membri amputati" - the pain that remains after amputation. Admiral Lord Nelson, who lost his arm at the Battle of Santa Cruz de Tenerife in 1797, suffered phantom pain, including a feeling of the fingers digging into his palm. He proclaimed that his phantom was: "direct proof of the existence of the soul. If an arm can survive physical annihilation why not the entire person.". During and after the American Civil War Silas Weir Mitchell studied soldiers who had been injured, and published on the subject of gunshot wounds, chronic pain and amputation. He was the first person to use the term phantom pain, but interestingly published his account in Lippincott's literary magazine, not a medical journal. In 1938 René Leriche, the eminent French surgeon wrote about chronic pain caused by surgery (1), but the subject continued to be ignored, until epidemiological studies in Scotland and the North of England found that about 22% of patients coming to Pain Clinics implicated surgery as one of the causes of their chronic pain and in half of these, the sole cause (2).

Why such a common and distressing condition should have been given so little attention is an important question for several reasons. First, chronic pain after surgery causes an immense burden of pain and suffering in the community (3), which has a significant effect on patients' quality of life (4-6) and serious economic consequences (4, 7). Secondly, because the subject is ignored, patients who suffer chronic pain after an operation often feel that they are to blame, as they don't realize that it is a common occurrence. This can be compounded by the attitude of medical staff, who may feel guilty that something they might have done has caused or contributed to the patient's suffering. These feelings of guilt and recrimination can lead to poor outcomes for the patient (8), poor relationships between doctors and their patients and medical litigation. Lastly, if the problem is ignored then research into this area will not happen, so there will be little hope of improvement in this lamentable situation.

It is only by understanding the problem and its origins that these difficulties can be addressed, hence the importance of this Symposium. Pain after an injury is normal. It is a vital physiological response with deep evolutionary roots. The

pain of a broken leg for example draws attention to the fact of injury, and makes further use of the injured limb aversive, hence allowing healing and union to take place. The mechanisms are complex and involve long term amplification of pathways in the nervous system. This amplification is necessary and useful during the period of injury and healing, but becomes pathological when it persists after injury. Elucidating these mechanisms is the key to understanding chronic pain after injury and surgery and the necessary precursor to better treatments.

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Peripheral Mechanisms of Acute and Chronic Post-injury Pain

Brennan TJ; Department of Anesthesia, University of Iowa Hospitals and Clinics, USA

Peripheral mechanisms for acute and chronic pain can be caused by release of factors that activate or sensitize nociceptors and by an increase in nociceptor responsiveness, i.e., sensitization. To understand peripheral nociceptor mechanisms, the normal and the post-injury state are studied. Nociceptors in the normative state rarely have spontaneous, ongoing action potentials. Usually they are quiescent, with minimal ongoing activity in the absence of any stimuli. Nociceptors not only signal potential tissue-damaging stimuli but also become sensitized; that is, they develop increased responses to noxious and innocuous stimuli after injury.[1] Characteristics of nociceptor sensitization after injury include: increased spontaneous activity, decreased threshold, increased response to a suprathreshold stimulus, after-discharge, expansion of the receptive field and an increase in the proportion of afferents responding to a stimulus.[2] This lecture will examine mediator release, nociceptor activation and nociceptor sensitization in acute incisional tissue injury and after chronic nerve injury.[3]

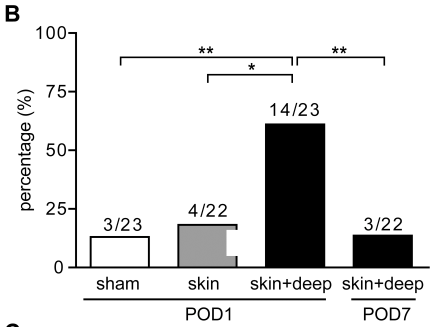

Fig. 1 Percentage of nociceptors with spontaneous activity after incision. POD=postoperative day.

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Central Signalling Systems in Dorsal Horn Neuroplasticity

Salter MW; Neurosciences & Mental Health, Hospital for Sick Children, Canada

A body of evidence has emerged indicating that pain behaviors resulting from injury to peripheral nerves are critically dependent upon interactions between neurons and glia in the dorsal horn of the spinal cord. Microglia has been found to play a causal role in neuropathic pain behaviors resulting from peripheral nerve injury, and specific neuron-microglia-neuron signaling pathways have been elucidated. Within the dorsal horn, microglia suppresses neuronal inhibition by a sequence of steps involving activation of microglial P2X4 receptors causing the release of BDNF. BDNF acts on trkB receptors which lead to a rise in intracellular chloride concentration in dorsal horn nociceptive output neurons, transforming the response properties of these neurons.

In addition to suppressed inhibition, evidence indicates that following nerve injury there is activity-dependent facilitation at dorsal horn glutamatergic synapses which enhances nociceptive transmission. This enhancement is mediated by intracellular signaling networks involving serine/threonine and tyrosine kinases within nociceptive transmission neurons. Key for this enhancement is facilitation of NMDA receptor function by the non-receptor tyrosine kinase Src. Src is anchored within the NMDA receptor complex by the protein ND2. Disrupting the ND2-Src interaction *in vivo* attenuates behavioral pain hypersensitivity without the deleterious consequences of directly blocking NMDARs.

Thus, understanding of the pathological signaling not only within neurons but also in glial cells, and, as well, the interactions between neurons and glia within the dorsal horn may lead to novel strategies for the management of chronic pain states, strategies not previously expected from a solely neuron-centric view of pain.

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Proinflammatory Cytokines and Sphingolipids at the Crossroad between Nociceptors and the Immune System

Kress M; DPMP, Div. of Physiology, Medical University Innsbruck, Austria

While acute pain serves as an essential alarm system to protect our body's integrity, tissue injury including inflammation, nerve lesion and cancer generate pathological pain states characterized by mechanical and/or thermal (heat, cold) hyperalgesia and/or allodynia in humans. A number of animal models have been developed to study the associated changes within the nociceptive system and investigate peripheral mechanisms of thermal and mechanical hypersensitivity. Proinflammatory mediators which signal inflammation have been found to sensitize or excite nociceptors and cause hypersensitivity in animal models. Regarding neuroimmune interactions, cytokines have emerged as the most important link between the immune system and nociception. Among the cytokine gene products associated with proinflammatory and proalgesic effects are several families including tumor necrosis factor (TNFα) and members of its superfamily, IL-1alpha, IL-1beta, IL-6, and others. Besides acting as inflammatory mediators increasing evidence suggests that cytokines act on nociceptors where they specifically interact with neuronal receptors. They regulate thermosensitive ion

channels to increase sensitivity to noxious heat stimuli (1-3). Neutralization strategies, e.g. for TNFα, may be helpful to prevent induced thermal hypersensitivity but seem to be unable to reverse hypersensitivity once it has been established (2). Further possible candidates for regulators of nociception may be sphingolipids which are generated downstream of TNFα or nerve growth factor. In the nervous system sphingolipids like LPA and sphingosine 1-phosphate (S1P) act on neurons via specific membrane receptors (4). Local LPA injections induce pain (5) and LPA receptors are involved in the generation of neuropathic pain (5). S1P potentiates the excitability of sensory neurons (6) and mRNA for specific S1P receptors has been found in rat dorsal root ganglia (DRG) (7). We found that S1P induced pain like behavior and nociceptor sensitization in mice via neuronal $S1P_1$ receptor and propose that cytokines and sphingolipids are important regulators of nociception for pain chronification.

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Neurotrophic Factors in Inflammatory and Neuropathic Pain

McMahon S; Wolfson Centre for Age-Related Diseases, King's College London, United Kingdom

Neurotrophic factors (NTFs) are secreted proteins that exert long-term effects on the survival, growth and properties of discrete neuronal sub-populations. In the sensory nervous systems many NTFs are secreted from the peripheral targets of primary sensory neurons (e.g. keratinocytes) where they play a well established role in development as survival factors.

Over the past decade, considerable evidence has accumulated from both humans and animals that one NTF, nerve growth factor (NGF), additionally acts as a peripheral pain mediator, particularly in inflammatory pain states. NGF is up-regulated in a wide variety of inflammatory conditions, and NGF neutralizing molecules are effective analgesic agents in many models of persistent pain. Such molecules are now being evaluated in clinical trials with positive results. NGF regulates the expression of a second NTF, brain-derived neurotrophic factor (BDNF), in nociceptors. BDNF is released when nociceptors are activated, and it acts as a central modulator of pain.

In neuropathic conditions, the role of NTFs is less clear. Sensory neurons that are axotomised loose their target-derived supply of neurotrophic factors and some of the pathophysiological changes occurring in damaged sensory neurons can be normalized by giving exogenous NTFs. For nociceptors, the most relevant NTF is NGF, but giving this factor has the confound of sensitizing the pain signaling pathway, as above. Some nociceptors – ones that are not axotomised - may be exposed to increased levels of NGF and in this case, anti-NGF strategies might be of some use. The weight of evidence in pre-clinical studies for the use of NGF or anti-NGF will be discussed.

Mechanisms of Visceral Hypersensitivity

Gebhart GF; Center for Pain Research, University of Pittsburgh, USA

Functional visceral disorders such as irritable bowel syndrome (IBS) and painful bladder syndrome (PBS) are characterized by altered bowel/bladder habits, discomfort, pain and organ hypersensitivity associated with an expanded area of referred abdominal tenderness. Organ hypersensitivity in IBS and PBS patients exists in the absence of a demonstrable organic cause. Thus, the hypersensitivity that characterizes IBS and PBS differs from somatic hyperalgesia, which is commonly associated with tissue injury and inflammation. Local anesthesia of the colorectum or bladder relieves IBS/PBS symptoms, revealing significant peripheral afferent drive contributing to the pain and hypersensitivity of these visceral disorders.

The mechanosensitive afferent innervation of the colorectum and bladder has been widely studied over the past 30 years. There exist both low and high threshold mechanosensitive endings in these organs, both of which possess the ability to sensitize and to encode into the noxious range. Accordingly, mechanosensitive endings are likely contributors to the discomfort and pain present in IBS and PBS. Recently, we have characterized mechanically *in*sensitive afferents (MIAs, 'silent' nociceptors) in the colorectal innervation. These MIAs acquire mechano-sensitivity after experimental exposure to an inflammatory soup and their proportion in the pelvic nerve innervation of the colorectum (normally ~25%) is reduced significantly (by 50%) in models of colorectal hypersensitivity. These findings suggest a previously unappreciated contribution of MIAs to organ hypersensitivity and potentially to the altered sensations that characterize functional disorders such as IBS and PBS.

Specificity in the Processing of Pain Messages

Basbaum A; Department of Anatomy, University of California, San Francisco, USA

The primary afferent nociceptor expresses a host of molecules that are not found or are only minimally expressed elsewhere in the CNS. Among these molecules are subtypes of sodium channels, G protein-lined receptors, purinergic receptors and even water channels. Studies in mice with gene deletions established that several of these molecules are important contributors to the processing of pain messages. Another approach to the problem asks whether subtypes of nociceptor, which express a variety of these molecules, contribute to submodalities of pain (e.g. heat, cold, mechanical) or whether any given population is multimodal in its contribution to pain behavior. Our studies indicate that the peptidergic population contributes only to heat pain sensitivity and the non-peptidergic population to mechanical pain. We also found that these subsets of nociceptors can be differentially regulated. In these studies, we reexamined the distribution and function of the mu (MOR) and delta (DOR) opioid receptors in primary afferent nociceptors. Contrary to the prevailing view, which was based almost exclusively on immunocytochemical grounds, using a DOReGFP reporter mouse, we now show that the DOR and MOR are expressed by largely non-overlapping populations of primary afferent fiber. Peptidergic nociceptors express the MOR, and myelinated and non-peptidergic unmyelinated afferents express the DOR. This segregated DOR and MOR distribution is paralleled by a remarkably selective functional contribution of the MOR to the control of heat pain and the DOR to mechanical pain and nerve injury-induced mechanical

hypersensitivity. More recently, we found that the somewhat enigmatic low threshold C mechanoreceptor is also an important contributor to mechanical allodynia. Whether this remarkable degree of specificity for the processing of pain messages at the level of the primary afferent nociceptor is manifest at the level of the circuits engaged by these fibers remains to be determined.

Poster No. I-01

Characterization of a New Selective Sigma-1 Receptor Antagonist (S1RA) that Inhibits Neuropathic Pain and Potentiates Opioid Analgesia – From Rodents to Human

Vela JM, Abadias M, Escriche M, Sust M, Farran R, Encabo M, Vidal A, Romero L, Zamanillo D, Encina G & Plata C; Drug Discovery and Preclinical Development, Esteve, Spain

Reduced neuropathic pain behaviours and reduced activity-induced spinal sensitization have been described in sigma-1 receptor deficient mice. Sigma-1 receptors are also known to modulate opioid analgesia. On these bases, the sigma-1 receptor has been recognized as a new potential molecular target for drugs designed to alleviate pain.
Given the attractive therapeutic potential of targeting this receptor, ESTEVE has developed a new chemical entity, a selective sigma-1 receptor antagonist (S1RA), and its effects have been assessed in different animal models of acute and chronic pain. S1RA dose-dependently attenuates neuropathic pain-related behaviours secondary to sciatic nerve injury. The development of thermal (heat) hyperalgesia and cold and mechanical allodynia induced by the nerve injury is suppressed following chronic treatment. No pharmacodynamic tolerance to its analgesic effects appears in chronic treatments (up to 21 days). In fact, repeated treatment with S1RA resulted in increased analgesic activity overtime (with respect to acute treatment). S1RA also significantly enhances the analgesia elicited by opioids including morphine, remifentanyl, fentanyl, oxycodone and tramadol in different rodent pain models.
The safety, tolerability, pharmacokinetic and pharmacodynamic profiles of S1RA have also been assessed in Phase I trials after single and multiple oral doses to healthy male and female volunteers. S1RA administration is associated with good safety and tolerability profiles. No serious adverse events have been observed. The overall profile of S1RA in human is compatible with a fast onset of action and once-a-day administration.

Poster No. I-02

Prolonged duration of nerve block to oppose long-term pain vulnerability development in a incisional model of pain in rats

Richebe P, Xu M, Rivat C & Cahana A; Department of Anaesthesiology and Pain Medicine, University of Washington Medical Center, USA

Background and goal of the study: High doses of opioids are known to induce higher postoperative early and acute hyperalgesia after plantar incision in rats (*Richebé P. et al, Anesthesiology 2005*), but also long-term pain vulnerability that can be assessed by a simple test as a stress (Stress Induced Analgesia: **SIA** *versus* Stress Induced Hyperalgesia: **SIH**; *Rivat C. et al, NeuroPsychoPharmacology 2007*). The aim of our study was to evaluate the preventive effect of locoregional anaesthesia on the development of long-term pain vulnerability in rats. **Material and Methods:** **6** groups were evaluated: **G1**:

plantar incision (PI; *Brennan T.J. et al, Pain 1996*) without Fentanyl, **G2**: PI under high doses of fentanyl (**F**) (4x100µg/kg s.c.), **G3**: PI + single shot Sciatic Nerve Blockade (SNB) (ropivacaïne 0.5% 0.2ml), **G4**: PI + SNB 4 injections (4 x ropivacaïne 0.5% 0.2ml), **G5**: PI + SNB 4 injections + F (4x100µg/kg s.c.), **G6**: control without PI nor SNB nor F on D0. Nociceptive threshold (**NT**) was evaluated with mechanical stimulation (g) (Randall Selitto) from D0 until postoperative D10. On **POD10**, while nociceptive threshold of all rats returned to preoperative basal values, one stress was applied. The variation of the **NT** after such a stress aimed to evaluate the development of long-term pain vulnerability after surgery. **Results:** On D0, **SNB** analgesic effect (G4 and 5) lasted 6hs. G3 only benefited from one single injection of ropivacaïne and presented shorter analgesia duration (2hs). In the long-lasting analgesia group without **F** (G4), the early postoperative hyperalgesia was reduced as compared to G1. The groups that received high dose of opioids on D0 (G2 and 5) showed a higher and longer hyperalgesia. Finally, the pain vulnerability test (stress) performed on POD10 showed that **SIH** was deeper and lasted longer in groups that benefited from **F** analgesia on D0 (G2 and 5) as compared to the two groups that benefited from loco-regional analgesia on D0 without opioids (G3 and 4). As previously observed and reported, the control group (no **PI**, no **F**, no **SNB** on D0) showed **SIA** and not **SIH** as in the other groups with a history of surgery and pain (*Rivat C. et al, NPP 2007*). **Conclusion:** Perioperative pain management with long-lasting loco-regional analgesia (**SNB**) was able to diminish the early postoperative hyperalgesia but also to decrease the risk of developing long-term postoperative pain vulnerability assessed by **SIA** or **SIH** development in rats.

Poster No. I-03

Potential role for the alphα−2−δelta sub-unit in pain chronification

Jay G, Donevan S & Cheung RY; Research & Development and Medical Affairs, Pfizer Inc., USA

The alphα−2−δelta (α–2–δ) protein is an accessory sub-unit of voltage gated calcium channels (VGCC). In animal models of neuropathic pain, mechanical injury of afferent sensory nerves results in increased expression α−2−δ sub-units[1]. Evidence from these models suggests that there is increased trafficking of VGCC from the dorsal root ganglion (DRG) to the presynaptic terminals at the dorsal horn[2,3]. This is associated with hyperalgesia and allodynia[2,3], probably resulting from increased calcium-dependent release of pro-nociceptive neurotransmitters such as glutamate and Substance P. These neurotransmitters are thought to play an important role in Central Sensitization and possibly the development of chronic pain[4]. Inhibition of VGCC trafficking using α−2−δ ligands such as pregabalin reduces hyperalgesia and allodynia in the test animals[3]. In other rodent models of neuropathic pain, injury to the afferent nerve increased Inhibitory Post Synaptic Currents (IPSC) at the locus coeruleus (LC), resulting in reduced noradrenergic descending inhibition at the dorsal horn[5,6]. Treatment with α−2−δ ligands restored descending inhibition[5,6], this is associated with reductions in the IPSC at the LC[6]. There is also evidence that α−2−δ ligands can modulate synaptogenesis in the CNS[7]. In an animal model of Post Herpetic Neuralgia, acute administration an α−2−δ ligand at day 5-10 following the herpes infection reduced the number of animals that went on to develop hyperalgesia and allodynia[8] 30 days following infection. Data from these animal models suggest that the α−2−δ sub-unit may play an important role in pain chronification. Consistent with this hypothesis, Buvanendran and colleagues showed that 2 weeks treatment with pregabalin, beginning peri-operatively,

significantly reduced the incidence of pain persisting for 6 months following total knee arthroplasty[9].

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Poster No. I-04

Brainstem and spinal interactions in visceral pain

Sikandar S & Dickenson AH; NPP Pharmacology, University College London, United Kingdom

The relative lack of understanding of visceral nociceptive signalling compared to somatic pain is a challenge in successfully treating visceral pain syndromes. A better understanding of the mechanisms of visceral nociception can advance translational research for producing effective analgesic treatments.
We investigate brainstem mechanisms mediating visceral nociception in a model of acute visceral pain using colorectal distension (CRD). Evoked visceromotor responses (VMR) were quantified with EMG recordings of the external oblique muscle following CRD. CRD produced graded VMR responses that were facilitated by intracolonic mustard oil (MO). Spinal ondansetron and systemic PGB reduced VMR in naïve rats and MO-pre-treated rats. Thus, a descending, facilitatory 5-HT3 receptor drive mediates evoked visceral pain responses, and the neuropathic pain drug, PGB, produces analgesia in animals lacking pathophysiology in an acute model of visceral pain.
RVM ON-cells, likely to be pro-nociceptive in somatic pain, were selectively ablated with Dermorphin-Saporin injections. Derm-SAP pre-treatment reduced VMR, although PGB remained effective in the absence of these neurones, which are permissive for pregabalin analgesia in neuropathy.
Differential brainstem processing of noxious somatic and visceral stimuli may underlie the unique lack of state-dependent actions of PGB in this visceral pain model. Recordings in the serotonin-rich RVM verify that brainstem processing of somatic and visceral stimuli differs. The effects of CRD on RVM cells classed as ON, OFF, or NEUTRAL was independent of their somatic responses. PGB markedly reduced the visceral responses of RVM ON-cells.
These results illustrate clear differences in the central processing of visceral and somatic stimuli, yet a common role for descending modulation by brainstem activity in mediating evoked pain measures partly through serotonergic facilitations.

Poster No. I-05

Cold allodynia induced by repeated topical menthol applications for testing analgesics in healthy volunteers

Schmidtko A, Altis K, Kuczka K, Angioni C, Lötsch J, Tegeder I & Geisslinger G; Institut of Clinical Pharmacology, Goethe-Universitaet, pharmazentrum frankfurt/ZAFES, Germany

Cold allodynia is a frequent clinical phenomenon in patients with neuropathic pain, but validated experimental models are still lacking for humans. Recent studies indicate that topical menthol application on human skin evokes a short-lasting cold allodynia. Here, we demonstrate that the duration of menthol-evoked cold allodynia can be extended by repeated topical menthol applications, and we assessed the effects of standard doses of ibuprofen, tramdol and pregabalin on menthol-evoked cold allodynia in a randomized, placebo controlled 4-way cross-over study in 20 healthy volunteers. Tramadol (100 mg) significantly reduced menthol-evoked cold allodynia, whereas effects of ibuprofen (600 mg) and pregabalin (100 mg) were not significant. Analgesic effects of tramadol were associated with minor side effects, particularly fatigue and nausea. Minor side effects also accompanied analgesic effects of pregabalin and ibuprofen in subjects responding to these drugs, mostly fatigue, dizziness and difficulties to concentrate for pregabalin and gastric upset for ibuprofen. Five out of 18 subjects had a ≥50% reduction of cold hyperalgesia with tramadol, three of these additionally responded to pregabalin, and two with all three drugs. The number needed to treat largely agree with the reported efficacy of these drugs in patients with peripheral or central neuropathic pain suggesting that menthol-evoked cold allodynia may represent a valid model for neuropathic pain, particularly cold allodynia.

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Poster No. I-06

Effects of pig tail docking and docking length on the formation of neuromas

Herskin MS[1], Holm B[2], Waag R[2], Thodberg K[1] & Jensen HE[2]; [1]Dept. Animal Health and Bioscience, Aarhus University, Denmark; [2]Dept. Vet. Disease Biol, University of Copenhagen, Denmark

In pig production, piglets are tail docked at birth in order to prevent tail biting later in life. One cause for this effect might be hyperalgesia due to formation of neuromas leading to increased avoidance behaviour.
In order to examine effects of tail docking and docking length on formation of tail neuromas, we used 65 pigs and four experimental treatments: intact tails (I); removal of 25% (Q); 50% (H); or 75% (T) of the tail length. The piglets were docked at d 2-4 using a gas heated apparatus, and kept under conventional conditions until slaughter at the age of 22 weeks, where the tails were removed and examined macroscopically and histologically.
The results show that tail lengths and diameters differed at slaughter (lengths: 30.6±0.6; 24.9±0.4; 19.8±0.6; 8.7±0.6 cm; $P<0.001$; diameter: 0.5±0.03; 0.8±0.02; 1.0±0.03; 1.4±0.04 cm; $P<0.001$, for I, Q, H and T, respectively). Docking resulted in a higher proportion of tails with neuromas (64 vs. 0%; $P<0.001$), number of neuromas per tail (1.0±0.2 vs. 0; $P<0.001$), size of neuromas (3.3±0.5 vs. 0 cm; $P<0.001$), proportion of tails with neuroma tissue (70 vs. 0%; $P<0.01$), as well as number of neuroma tissues per tail (1.2±0.2 vs. 0; $P<0.001$). The occurrence of neuroma tissue was affected by docking length, as shown by a significantly lower proportion of tails with neuroma tissue in Q compared with H or T (41 vs. 79 and 100%, respectively; $P<0.05$) and a lower number of neuroma tissue per tail in Q and H compared with T (0.6±0.2 and 1.1±0.2 vs. 2.2±0.3, respectively; $P<0.001$).

The results showed that tail docking in pigs caused formation of neuromas in the tail tip. The formation of neuroma tissue is suggested to increase with increased docking length. The presence of neuromas might lead to hyperalgesia, however the existence of changes in tail sensitivity in pigs after docking need to be confirmed.

Poster No. I-07

VOLTAGE-GATED SODIUM CHANNELS 1.7 AND 1.8 AS THERAPEUTIC TARGETS FOR PACLITAXEL-INDUCED HYPER-ALGESIA

Salengros J-C, Bandekala P & Sosnowski M; Department of Anesthesiology, Institut Jules Bordet, Belgium

INTRODUCTION: Paclitaxel, commonly known as Taxol, is a chemotherapy drug that is given as a treatment for some types of cancer (ovarian, breast and non-small cell lung cancer). Side effects, such as: mechanical allodynia and hyperalgesia are almost inevitable. Voltage-gated sodium channels (Nav 1.7 and 1.8) seem to play an important role in this particular setting. Ranolazine targets, among others, these particular voltage-gated sodium channels in neurons.
MATERIALS AND METHODS: Paclitaxel (2 mg/kg) was administered intraperitoneally to adult male rats at day 0, 2, 4 and 6. Mechanical pain threshold was tested with two different methods: von Frey hairs (15g) and Paw pressure test (Randall-Selitto). At day 29, hyperalgesic rats were randomized to two groups: Placebo group (P) and Ranolazine group (R) for the two test paradigms. Pain threshold was evaluated 30 minutes, 60 minutes and 24 hours after the administration of Ranolazine or Placebo.
RESULTS: von Frey hairs: 28 rats/90 (31.1%) were hyperalgesic (P=13, R= 15). Thirty minutes after the injection, 62% (8/13) in group P and 33% (5/15) in group R remain hyperalgesic (p= 0,13). Paw pressure test (Randall-Selitto): 23 rats/30 (76,7%) were hyperalgesic (P= 10, R= 13). No differences in pain threshold before or after treatment (median increase of 0%) in group P. Median increase of 150% in pain threshold 30 minutes after treatment in group R.
CONCLUSIONS: In this rat model, Ranolazine was efficient to treat paclitaxel-induced hyperalgesia. Paw pressure test (Randall-Selitto) seems more efficient than von Frey hairs (15g) in diagnosing paclitaxel-induced hyperalgesia.

Poster No. I-08

The absence impact of estrus cycle in the development of spread mechanical hypersensitivity after infraorbital nerve injury in rats

Gao T, Li L, Hao J-X, Xu X-J & Wiesenfeld-Hallin Z; Dept. of Physiology and Pharmacology, Karolinska Institutet, Sweden

Abstract
Sex difference in pain has been increasingly recognized. Our previous results showed a marked sex difference after ischemic infraorbital nerve injury with female developing more spread hypersensitivity. The present study was to examine if the oestrous phase at the time of irradiation has an impact on the development of spread hypersensitivity and whether the spread hypersensitivity varies across the cycle by using the same model. The female rats showed a significant lower baseline response threshold at the face and upper flank region, whereas the baseline did not change across the oestrous cycle. Female rat were irradiated on preoestrous, oestrous and dioestrous at the time of injury. A

significant sex difference in the facial ares and upper flank region were found when combined the females. The developments of spread mechanical hypersensitivity were similar among the females that were irradiated on different oestrous phase. During week 13-15 after irradiation, spread hypersensitivity was assessed for three cycles consecutively. However, the spread mechanical hypersensitivity did not change within the cycle. The results showed that there is a significant sex difference in the development of spread hypersensitivity in rats after infraortibal nerve injury. However, the baseline threshold was not related to oestrous phase. Such difference was not due to the impact of oestrous cycle on the amount of injury at the irradiation. Oestrous phases were not associated with the severity of the spread mechanical hypersensitivity.

Key words: oestrous cycle, female, male, hypersensitivity, infraorbital nerve injury, sex difference

Poster No. I-09

Cancelled

Poster No. I-10

Sortilin is involved in the down-regulation of K+/Cl- –co-transporter 2 (KCC2) in the spinal nerve ligation model for neuropathic pain

Neustrup S, Møllgaard P, Bjerregaard CV*, Nykjær A* & Bjerrum OJ; Department of Pharmacology and Pharmacotherapy, University of Copenhagen, Denmark, *Department of Medical Biochemistry, University of Aarhus, Denmark

The chronic condition neuropathic pain represents a major clinical burden. The pathogenesis is complex and not fully elucidated. Previous studies establish that nerve injury causes increased release of brain-derived neurotrophic factor (BDNF) in the spinal dorsal horn leading to down-regulation of K^+/Cl^--co-transporter 2 (KCC2) and hence to development of neuropathic pain. Based on the departments' original observation that the neuronal protein sortilin may be an important component in the pathogenesis of neuropathic pain we put forward the hypothesis: *"Sortilin is involved in the down-regulation of KCC2 leading to neuropathic pain"*.

A comparative study of the behavioural and biochemical changes after nerve injury in sortilin knockout (KO) and wild-type C57Bl/6 mice was conducted. Symptoms correlating the clinical manifestations seen in neuropathic pain in humans were induced by the Spinal Nerve Ligation (SNL) model. von Frey (mechanical allodynia) and Hargreaves (thermal hyperalgesia) test showed significant signs of hypersensitivity in WT mice in contrast to KO mice. Immunoblotting of L1-L3 spinal segments showed that after SNL surgery KCC2 was down-regulated in WT but not in KO mice. The hypothesis was confirmed by coincided results demonstrating that SNL KO mice did not develop symptoms of neuropathic pain and had a stable level of KCC2 after SNL, as opposed to WT mice. In conclusion, our studies establish that sortilin constitutes an important element in the pathophysiology of neuropathic pain.

Poster No. I-11

The Place Escape/Avoidance Paradigm as an outcome measure for Central Pain following experimental Spinal Cord Injury

Baastrup C, Finnerup N & Jensen TS; Danish Pain Research Center, Aarhus University Hospital, Denmark

Introduction: The place escape/avoidance paradigm (PEAP) is designed to measure the affective motivational component of pain and is suggested to better predict clinical efficacy and identify clinically relevant doses than traditional withdrawal responses. PEAP has been characterized in models of peripheral nerve injury and acute inflammatory injury, but it has never been used in a model of central neuropathic pain.
Objectives: To modify and test the PEAP in a model of central neuropathic pain and investigate if the response can be pharmacologically modulated.
Methods: Rats with severe or moderate spinal cord contusion (SCC) at T13 and sham animals. The PEAP box, with one black (preference) and one white side (avoidance). Mechanical stimulation was repeatedly applied to the suspected painful thorax (black side) or the neutral head (white side). Time spent in the white side subsequently served as primary outcome. Animals with moderate injury were pre-treated with saline or 30 mg/kg pregabalin.
Results: SCC Animals spend significantly more time in the white side of the PEAP than sham animals ($p=0.018$, severe; $p=0.000$, mild), while pregabalin reversed the PEAP behaviour ($p=0.000$). Together this indicates at-level mechanical hypersensitivity and supports the face validity of the method.

Poster No. I-12

Differential effect of the $P2X_7$ receptor in cancer pain compared to other pain states

Hansen RR[1], Nasser A[1], Nielsen CK[1], Pham Y[1], Schulenberg C[1], Ding M[3], Syberg S[2], Jorgensen NR[2], Stojilkovic S[4] & Heegaard A-M[1]; [1]Department of Pharmacology and Pharmacotherapy, University of Copenhagen, Denmark, [2]Dept. of Geriatrics, Research Centre of Ageing and Osteoporosis in Glostrup, Denmark, [3]Odense University Hospital, University of Southern Denmark, Denmark, [4]NICHD, NIH, USA.

Pain is a common and debilitating complication to metastatic bone cancer. Recent studies indicate that the mechanisms underlying bone cancer pain are distinct from those of neuropathic and inflammatory pain. The purinergic receptor $P2X_7$ has been implicated in chronic inflammatory and neuropathic pain. However, the recent discovery that the $P2X_7$ receptor knockout mice used for these studies express a splice variant of the $P2X_7$ receptor complicates the interpretation of the results. The aim of this study was to investigate the role of the $P2X_7$ receptor in a mouse model of bone cancer pain, and the expression of the P2X7(k) receptor splice variant in relevant tissues. Wild type (WT) and P2rx7 KO mice were subjected to either bone cancer pain or neuropathic pain and pain related behaviour assessed. Furthermore, the effect of the $P2X_7$ receptor antagonist, A438079, was investigated in bone cancer and formalin induced pain. Expression of the P2rx7(k) splice variant receptor in WT and P2rx7 KO mice were investigated in osteoclasts and spinal cord by RT-PCR and western blot. P2rx7 KO mice with bone cancer suffered from reduced limb use and reduced right hind limb weight bearing comparable to that of the cancer operated wild type mice. As expected no mechanical allodynia developed in the SNI operated P2rx7 KO mice. Treatment with A438079 did not affect the pain related behaviours in the bone cancer bearing BALB/cJ mice, but a significant effect was

seen in both phases of the formalin induced pain. The $P2X_7$(k) splice variant receptor was expressed in both osteoclasts and spinal cord of WT and P2rx7 KO mice. Together the results indicate that the $P2X_7$ receptor is not involved in the development of pain in the mouse model of bone cancer pain and lack of the $P2X_7$ receptor might even exasperate the pain related behaviour thus supporting the hypothesis that cancer pain is distinct from other pain states. However the role of the $P2X_7$(k) splice variant receptor still needs to be elucidated. Also, the degree of astrocyte activation varies among different mouse models of bone cancer pain and the role of the $P2X_7$ receptor might depend on the model.

BENZON SYMPOSIUM No. 57

ACUTE PAIN - PATHOPHYSIOLOGY AND RISK FACTORS FOR CHRONIFICATION

OCTOBER 4-7, 2010, COPENHAGEN, DENMARK

Organizing committee:
Henrik Kehlet (Copenhagen), Troels Staehelin Jensen (Aarhus), Arne Svejgaard (Copenhagen) & Povl Krogsgaard-Larsen (Copenhagen)

Abstracts - TUESDAY, October 5, 2010

Persistent Pain as a Sequel of Acute Pain: Epidemiology

Raja SN; Division of Pain Medicine, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, USA

Surgery and trauma are the most common and predictable source of acute pain. A significant proportion of patients still suffer from inadequate pain control following surgery and trauma. The incidence of persistent pain after different surgeries varies from 5-85%, and is more common after amputation, mastectomy, thoracotomy, herniorrhaphy, and cardiac surgery.[1] Similarly, about 40% of patients are reported to have clinically significant persistent pain after limb-threatening lower extremity injury and spinal cord injury. Persistent pelvic pain was also reported in 64% of patients more than 4 years after pelvic and acetabular fractures.

There has been a paradigm shift in recent years from documenting incidence of persistent postoperative pain to studying the risk factors and investigating preventive strategies. Preoperative pain is a consistent risk factor for persistent postoperative pain after limb amputation, breast surgery, hysterectomy, thoracotomy and hernia repair.[2] on In a recent review of the literature on predictive factors for postoperative pain, Werner and colleagues[3] conclude that quantitative sensory testing (QST) of pain perception may predict about half of the variance in postoperative pain experience.[4] Identifying patients who may need aggressive management of their perioperative pain may help decrease the incidence of persistent pain. Analysis of the multiple preoperative parameters predictive of increased incidence of persistent pain will help identify the subset of high-risk patients and develop strategies to minimize persistent postoperative pain following specific surgical procedures.

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The Clinical Presentation of Persistent Pain and Relation to Acute Pain

Jensen TS; Danish Pain Research Center, Aarhus University Hospital, Denmark

Persistent pain has previously been classified according to disease categories, but such classification rarely helps in identifying a rational treatment. Other classifications divide pain into the pain originating tissue, the underlying pathology, or even the simpler one: acute and chronic pain. Acute and chronic pains are fundamentally different in their clinical presentation. The former clearly signals tissue damage and provides strategies to escape from and protect against further injury. Chronic pain on the other hand is not associated with injury and serves no purpose and is accompanied by a series of comorbidities. Despite differences in clinical presentation signs of neuronal hyperexcitability seem to be a key feature in acute and chronic pain irrespective of underlying pathology.
The nervous system changes after noxious stimulation or injury and this change in responsiveness appear to be partly time and intensity dependent and partly dependent on cause of injury. While relative short-lasting and moderate noxious input leads to reversible plastic changes, more intense and long-lasting noxious stimulation implies a risk for persistent and more profound changes in transmitters, receptors, ion channels and in neuronal connectivity. It is still unclear why the same injuries in some patients give rise to long-lasting pain and other types of handicap while other patients rapidly return to normal function. The transition phase from acute to chronic is interesting because it assist in identifying risk factors. The identification of risk factors and the transition from acute to chronic will be illustrated by studies carried out in patients that have been exposed to a forced flexion and extension trauma of the cervical spine (whiplash injury).

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The Role of Quantitative Sensory Testing in Pain Classification ?

Baron R; Division of Neurological Pain Research and Therapy, Department of Neurology, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany

A new hypothetical concept was proposed in which pain is analyzed on the basis of underlying mechanisms rather than on the basis of the etiology. If a precise phenotypic characterization is combined with a selection of drugs acting at those particular mechanisms, it should ultimately be possible to design optimal treatments for the individual patient. Such research can only be performed in large cohorts of patients, ideally on a Research Network level. The German Research Network on Neuropathic Pain established a large data-base that includes epidemiological, clinical and history data as well as a standardized quantitative sensory testing (QST). Up to now more than 2000 patients with different neuropathic pain states have been examined. Furthermore, epidemiological and clinical data on the symptomatology of 2100 patients with painful diabetic neuropathy (DPN) and postherpetic neuralgia (PHN) from a cross sectional survey (pain*DETECT*) are available.

In several entities such as postherpetic neuralgia and painful diabetic neuropathy different sensory profiles could be analyzed which occur in different frequencies. The second step to be solved is the question whether an individual somatosensory phenotype really mirrors distinct pain mechanisms? For this purpose the technique of somatosensory pattern recognition was used and first results have been achieved. This approach uses the somatosensory patterns that are specific for human surrogate models of pain in which the underlying mechanisms are relatively well understood. The last and decisive question is whether these different phenotypes (which are presumably related to different mechanisms) are really associated with different treatment outcomes. In patients with focal neuropathic pain the somatosensory patterns were compared with the response to cutaneous lidocaine treatment. Another study analyzed the response of neuropathic pain patients to systemic opioids. The results of such multi-center network trials will ultimately substantiate the mechanism based treatment concept in neuropathic pain.

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Assessment of Sensitisation in Persistent Pain

Magerl W; Center of Biomedicine and Medical Technology Mannheim, Ruprecht-Karls-University Heidelberg, Germany

Sensitization is a key operating mechanism of the nociceptive system. It occurs on the level of nociceptive primary afferents (peripheral sensitization, e.g. in inflammatory diseases) or on the level of central nociceptive neurons (central sensitization). It is hypothesized that the latter is an important pathomechanism in persistent pain of various origins (postsurgical, neuropathic etc.). The central concept is that persistent or even short-lived vigorous input can drive central nociceptive neurons (spinal, or higher central) into a hyperresponsive state. This concept is derived from animal research (mostly inflicting damage to nociceptive pathways) and from mechanistic analysis in human surrogate models of pain plasticity (mostly inflicting or mimicking tissue injury, like burning, freezing, capsaicin injection, high frequency electrical stimulation; Klein et al. 2005). From both lines of research we have derived that there are two forms of central sensitization, namely an increase in synaptic efficacy in the excited pathway (homosynaptic) and in anatomically adjacent pathways (heterosynaptic, secondary hyperalgesia). Surrogate models have led to a revival of quantitative sensory testing and a considerable refinement of assessment techniques. In turn, the pattern of sensory changes now provides the basis for mechanistic reasoning (mechanism-based diagnosis). Specific sensory changes are interpreted to indicate possible pathological mechanisms. Homosynaptic sensitization occurs primarily to C-fiber input and is adequately assessed by thermal testing in superficial tissue (for cold and/or heat hyperalgesia) and blunt pressure in deep tissue (pressure algometry). Heterosynaptic sensitization is based on facilitation of A-fiber input and is adequately assessed by stimulation with sharp objects (pin

prick hyperalgesia; static) or light stroking tactile stimuli (allodynia; dynamic). Thus, the outcome of specific testing may guide the delineation of mechanisms. This may then lay the ground for future mechanism-based treatment of pain irrespective of the inciting event or disease.

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Structural and Functional Neuronal Changes in Chronic Pain Patients

Schmelz M; Dept Anesthesiology - Mannheim, University of Heidelberg, Germany

Neuropathic pain is caused by lesions to the central or peripheral nervous system. While neuropathic lesions must not be generally linked to pain, key symptoms include reduced sensory and motor function. The mechanisms that determine whether neuropathy is leading to a pure loss of function or a chronic painful condition are unclear. In attempts to clarify these mechanisms structural and functional patterns of small fiber function in neuropathic pain patients have been investigated using quantitative sensory testing, quantification of axon reflex responses and skin biopsies. Although intraepidermal fiber density was an objective marker of small fiber neuropathy no obvious correlation of nerve fiber density and pain was detected. We therefore clinically investigated patients with neuropathic pain and neuropathy patients without pain, assessed functional (quantitative sensory testing, axon reflex erythema) and structural parameters (skin biopsy) and tried to differentiate painful from non-painful neuropathy and correlate structural and functional parameters to pain intensity.
Epidermal innervation density correlated to temperature detection thresholds and dermal innervation density correlated to the area of electrically induced axon reflex erythema in the neuropathy patients. Neuropathy patients also showed significantly reduced innervation densities and impaired temperature detection. However, we did not identify structural differences between painful and non-painful traumatic neuropathy neither could find significant correlations of structural or functional parameters to pain intensity in polyneuropathy patients.
We conclude that the neuropathy leads to characteristic structural and functional impairment of thin nerve fibers. However, it is still unclear which mechanisms lead to painful neuropathy as compared to a pure loss of function without pain. Investigations of mechanisms in neuropathic pain therefore need to include neuropathy patients without pain to differentiate those factors that are inherent to neuropathy as compared to those specifically leading to pain.

Imaging Pathophysiological and Psychological Changes Underpinning the Transition of Acute to Chronic Pain

Tracey I; Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), University of Oxford, United Kingdom

Until recently it has been difficult to obtain reliable objective information from normal subjects and patients regarding their subjective pain experience. Relating specific neurophysiologic markers to perceptual changes induced by peripheral or central sensitisation, behavioural, psychological or pharmacological mechanisms and identifying their site of action within the CNS has been a major goal for

scientists, clinicians and the pharmaceutical industry. Identifying non-invasively where plasticity, sensitisation and other amplification processes might occur along the pain neuraxis for an *individual* and relating this to their specific pain experience or measure of pain relief has considerable value and potential diagnostic value. With the advent of functional neuroimaging methods, such as functional magnetic resonance imaging (FMRI), positron emission tomography (PET), electroencephalography (EEG) and magnetoencephalography (MEG) this has been made feasible. This activation, often considered an "objective" readout of the subjective phenomenon, can be related to what the subject describes, allowing issues such as how anxiety, depression, attention, central sensitization, etc., alter the pain experience to be better understood at a neuroanatomical level. Over the past ten years, we have performed several experiments that have specifically isolated areas of cortex and brainstem central to these processes; particularly those involved in the transition from the acute to chronic state. More recently, pharmacological functional magnetic resonance imaging (phMRI) has been developed and applied to the field of pain research within our laboratory. Again, many advances have been made that illustrate the neural correlates of analgesia in the human brain. New thoughts related to how pain and pleasure interact force us to broaden our understanding of relief mechanisms and wellbeing, results from which shall be discussed. Combined these data provide evidence that neuroimaging tools will play an increasing role in clinical decision making and analgesic drug development in the coming decade.

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Unraveling Temporomandibular Disorders and Related Conditions

Maixner W; Center for Neurosensory Disorders, University of North Carolina, School of Dentistry, USA

Temporomandibular and related sensory disorders (eg, fibromyalgia, IBS, headache conditons) are mosaics of intermediate phenotypes associated with peripheral and central nervous system dynamics, stress responsiveness and inflammatory states. As complex and common conditions they are influenced by polygenetic factors and shaped by environmental pressures (Figure 1). Emerging concepts of the contribution of phenotypic traits and genetic variants to the risk of TMD and related conditions from recently completed[3,4] and ongoing (see www.oppera.org) cross-sectional and prospective studies will be presented. Dr Maixner will also discuss emerging technologies that can be used to unraveling genetic networks in subpopulation of patients with persistent pain conditions.

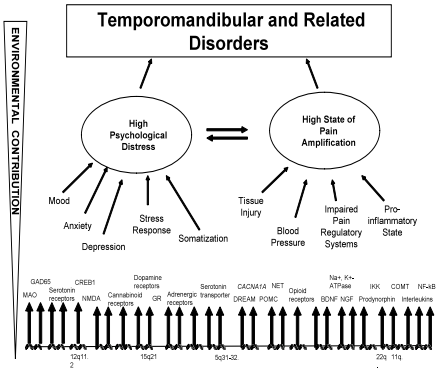

Figure 1: TMD and related conditions - genetic and environmental influences[1]

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Generalized Persistent Pain Syndromes

Mayer EA, Naliboff BD, Labus J & Tillisch K; Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at UCLA, USA

Generalized persistent pain syndromes (GPPS) refers to a number of syndromes currently defined by subspeciality specific symptom criteria in which symptoms of pain and discomfort are referred to visceral (irritable bowel syndrome [IBS], functional dyspepsia [FD], functional abdominal pain syndrome [FAPS], painful bladder syndrome/interstitial cystitis [PBS/IC], chronic pelvic pain, CPP) or to somatic structures (fibromyalgia [FMS], temporomandibular disorders [TMD], back pain [LBP]). GPPS affect up to 15% of the population world wide. Despite the high prevalence, the considerable impairment of disease related quality of life (QoL), and the associated burden of illness, the development of effective treatments for PPDs has generally been disappointing. Available pharmacologic therapies only work in a subset of patients, and are often associated with intolerable side effects. While much scientific interest is still focused in identifying peripheral, organ-based pathologies to explain the clinical manifestation of individual syndromes, there has been a growing appreciation of the shared epidemiological and pathophysiological features, suggesting a common underlying abnormality in brain body interactions. These shared features include vulnerability factors (female sex, early life trauma, and genetics), comorbidity of syndromes and transition from one syndrome to

another in the same patients, comorbidity with disorders of mood and affect, and responsiveness to centrally targeted pharmacological and non-pharmacological therapies. More recently, abnormalities of sympathetic nervous system activity and central pain amplification have been proposed as a shared pathophysiological mechanism. Brain imaging techniques have identified alterations in brain circuits concerned with emotional arousal, prefrontal limbic pontine inhibition and homeostatic afferent processing.

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Poster No. II-01

Preoperative chronic pain and the development of acute and chronic postoperative pain

Gerbershagen HJ[1], Aduckathil S[2], Rothaug J[3] & Meissner W[3]; [1]Department of Anesthesiology, University Medical Center Utrecht, Netherlands, [2]Department of Anesthesiology, University of Cologne, Germany, [3]Department of Anesthesiology, Friedrich-Schiller-University Jena, Germany

Introduction: Acute postoperative pain intensity is reported to be the most consistent risk factor for the development of CPSP (chronic postsurgical pain). Most studies with improved acute postoperative pain therapy failed to reduce the frequency and intensity of CPSP. Our studies in urology patients did indicate a relationship between preoperative chronic pain and acute as well as chronic postoperative pain. Thus, undertreatment of chronic pain patients in the acute postoperative period may contribute to the development of CPSP. A large, multicenter sample was analyzed to determine possible insufficient postoperative pain treatment in chronic pain patients.

Methods: From the QUIPS ("Quality in Postoperative Pain Therapy") project, 4,167 patients undergoing genital and urinary-tract surgery in 44 German hospitals were assigned to 60 surgical procedures. Patients were asked if they had any chronic pain before surgery, and 24h after surgery they were asked to report whether they would have liked to have received additional analgesics since surgery. The worst pain intensity during the first postoperative day was recorded and compared between chronic and non-chronic pain patients. In order to study larger sample sizes, surgical procedures were included if the procedure sample had more than 20 patients.

Results: A total of 21 surgical procedures in 2,906 patients were analyzed. Patients with preoperative chronic pain (17.6%) reported significantly higher worst postoperative pain intensities (NRS 3.9 vs. 4.7; $P < 0.001$). The number of patients who wished to have received more analgesics during the first 24h after surgery was comparable in both groups (10% vs. 8.8%). In 15 of the 21 surgical procedures chronic pain patients scored higher pain intensities without reporting more often, and sometimes reporting less often, the wish to have received additional analgesics.

Conclusion: While this study confirmed that patients with chronic preoperative pain report higher pain intensities after surgery, this patient sample did not indicate insufficient pain management. The chronic pain patients did not wish additional pain medication more often than patients without preoperative chronic pain. Many studies have failed to reduce the incidence and intensity of CPSP by reducing acute postoperative pain intensity. This finding may be explained by subgroups of chronic pain patients who report both higher pain intensities and adequate postoperative pain relief.

Poster No. II-02

Psychological predictors of chronic post operative pain and suboptimal recovery

Peters ML[1], Marcus ME[2] & van Kleef M[2]; [1]Department of Clinical Psychological Science, Maastricht University, The Netherlands, [2]Department of Anaesthesiology, Maastricht University Hospital, The Netherlands

Recent studies indicated that psychological factors may contribute to acute post-operative pain intensity, but little is known about psychological risk factors for persistent post-operative pain. Our team conducts longitudinal prospective studies to identify predictors of chronic post-operative pain and unfavourable recovery in patients undergoing various types of surgery. In addition to demographic, medical, and intervention-related variables we assess psychological state and trait factors of patients pre-operatively.
Our first study involved 401 patients undergoing various elective surgical procedures that were followed up at 6 and 12 months after the operation. The main outcome was a change in the SF-36 quality of life score from pre-operation to follow-up. Most patients showed improvements in health-related quality of life after the operation, but a considerable proportion of patients ($\pm$15%) showed an increase in pain and a deterioration of physical and emotional functioning. The most important predictors of adverse long-term outcome were acute post-operative pain, duration of the operation and physical co-morbidity. Psychological factors affecting outcome were surgical anxiety and optimism. Currently we are conducting a similar study in day surgery patients. More than 1000 patients have already been included and at the symposium the preliminary results of the 1-year follow-up assessment will be presented (N> 500).
Our third and most recent study involves women undergoing hysterectomy. The design of this study will be presented. In addition to the previously identified predictors this study also includes genetic factors. Of major interest is the genotype x psychological trait interaction in the prediction of long-term pain, and the possible epigenetic contribution.

Poster No. II-03

Predicting Post-Operative Pain with a Multi-Mechanistic Model

Hastie BA[1], Stavropoulos MF[2], Frye RF[3], Riley JL III[1] & Wallace M[4]; [1]Community Dentistry & Behavioral Science, [2]Oral & Maxillofacial Surgery, University of Florida College of Dentistry; [3]Department of Pharmacotherapy & Translational Research, University of Florida College of Pharmacy, [4]Molecular Genetics & Microbiology, University of Florida College of Medicine; USA

Understanding influences of acute pain experience and identifying risk factors for chronic pain development may lend insight into pre-emptive care for invasive procedures, improved acute post-operative care, and eventually thwart transition to chronic pain. Little is known about these factors individually, much less collectively. This study sought to test the validity of a predictive model which included multiple domains: (1) Baseline Preoperative Psychophysical Measures; (2) Psychological Measures (e.g. baseline, immediate pre-operative, post-operative); (3) Acute Pain Ratings (day of surgery; timed ratings several days post-operatively); (4) Genetic Markers; (5) Pharmacokinetic/Pharmacodynamic (PK/PD) measures of opioid efficacy and metabolism. From an acute surgical sample of young adults (n=84, mean age=22), we tested the most salient factors within each domain independently and then collectively tested a full

model using the most significant predictors from each domain. Items from individual domains that were at $p<0.10$ were retained and incorporated into the full model. R^2 for individual domain tests included psychophysical measures R^2=0.19-0.23, genetic R^2=0.10-0.32, PK/PD R^2=0.26-0.47, and psychological domain R^2=0.29-0.43. The overall model was far more predictive than individual domain models (R^2 range=0.59-0.73). The strength of certain predictors varied in acute post-operative phase, suggesting important influences on biological processes (i.e. pain, inflammation) that might change over time and alter recovery. These considerations may prove significant in acute pain management and in transition to chronic pain. This population was comprised of healthy young adults with short-term acute pain. However, very recent data from a thoracic surgery model including longer-term follow-up reveals similar predictive strength. These findings illuminate potential pathways of clinical relevance and how collectively they might influence pain trajectory. This underscores the significance of considering multiple domains that comprise the pain continuum as well as potentially salient risk factors in the transition from acute to chronic pain.

Poster No. II-04
CANCELLED

Poster No. II-05
The Acute Pain Trajectory: A New Tool for Assessing the Risk of Postoperative Pain Chronification

Chapman CR, Donaldson G, Davis J & Bradshaw D; Department of Anesthesiology, The University of Utah, USA

Poorly controlled acute postoperative pain increases the risk of chronic postoperative pain. Definitive quantification of the course of acute postoperative pain is an essential step in identifying who incurs risk for chronification. We have examined six-day postoperative pain trajectories in 502 patients undergoing elective surgery at the University of Utah. A pain trajectory is a linear fit of an individual's pain ratings over six days on a standard 11-point scale. It yields two measures: 1) Intercept, or initial pain level immediately following surgery; and 2) Slope, or rate of pain resolution over the six days. Study of the pain trajectory slope is unprecedented and may provide clues about risk for chronification. The average patient had an intercept of 5.6 and a slope of .31, indicating that postoperative pain resolved by about one-third unit per day.

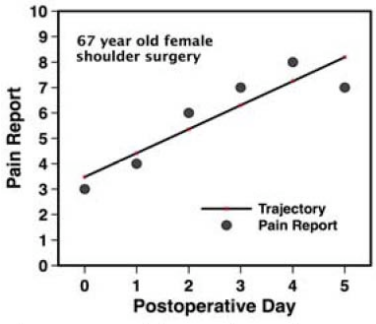

Fig. 1. A Positive Pain Trajectory. Intercept = 3.5, Slope = .94.

However, further examination of the slopes revealed three patient subgroups:
1) Those with negative slopes who resolved their pain;
2) Those with flat slopes whose pain was constant over six days; and
3) Those with positive slopes whose pain worsened steadily over the six days.
Of the 502 patients, only 63% demonstrated the expected negative slopes while 25% had flat slopes and 12% had positive slopes like the patient depicted in Figure 1. The 37% of patients whose pain did not resolve or even worsened over six days may risk pain chronification. The pain trajectory offers new measures for

characterizing and quantifying the course of postoperative pain that may prove useful as risk factors for pain chronification following surgery.

Poster No. II-06

The Antwerp Personalised Pain Initiative (APPI): prevention of chronic post-surgical pain through an individualized and targeted analgesic treatment after day care surgery

Hans G[1,2], Sermeus L[1,2], Leys J[3] & Vercauteren M[1,2]; [1]Department of Anesthesiology, [2]Multidisciplinary Pain Center, [3]Department of Pharmacy, Antwerp University Hospital, Belgium

Chronification of pain after a surgical procedure is a recognised medical problem. However, little is known concerning the development of chronic pain after *day care surgery*. These patients quickly leave the hospital, receiving only minimal amounts of weak analgesics and lacking any medical follow-up in the following days/weeks (until next follow-up with the surgeon). In this period pathological processes of sensitization and wind-up can develop, setting the base for chronic pain states. To respond to this serious shortcoming, the Antwerp Personalised Pain Initiative was established. In a first phase of the project, incidence and intensity of postoperative pain was identified for diverse day care surgical procedures (total of 250 patients). It became evident that certain surgical procedures (e.g. laparoscopy, inguinal hernia repair) induce severe pain in up to 70% of patients, while other surgical procedures almost never induce moderate to severe pain. Additionally, an analysis of patient characteristics that negatively influence the risk of serious and/or prolonged postoperative pain was carried out. After identifying the "high risk" surgical procedures and patient groups, an individualized approach to postoperative pain management was implemented in our hospital. Based on the personal characteristics of the patient (e.g. previous surgery, existing pain, use of analgesics and medical history) and the type of surgery that the patient is scheduled for, a patient-specific "risk-score" is completed before surgery. Based on this score an individualized pain management schedule is started immediately after the surgical procedure. Such treatment may consist of (or a combination of) class 1 or class 2 analgesics. Upon discharge, the patient receives an "analgesic kit" (9 different kits were composed) containing a treatment for 3 up to 7 days (dependent on the total risk-score of the patient), accompanied by a clear instruction form. Moreover, the patient has the possibility to invoke specialist advice in case of continuing pain via a dedicated telephone number which is manned 6 days a week.

Poster No. II-07

The use of premedication in Danish anaesthesiological departments

Hansen HM; Multidisciplinary Pain Center, University of Copenhagen, Rigshospitalet, Denmark

Tissue damage as surgery causes central sensitization which seems to be inhibited by gabapentin, pregabalin and ketamin (1). Within the last 10 years more than 30 papers indicate that gabapentin is useful to prevent and treat postoperative pain (2,3).
So far there are no available data on premedication or how and in which dosage gabapentin and pregabalin are used to prevent and treat postoperative pain in Denmark.

Premedication in Denmark is elucidated based on questionnaire Spring 2010.

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Poster No. II-08

Cancelled

Poster No. II-09

Dysfunction of capsaicin-sensitive C-fibers in Complex Regional Pain Syndrome

Terkelsen AJ[1], Gierthmühlen J[2], Finnerup NB[1], Højlund AP[3] & Jensen TS[1]; [1]Danish Pain Research Center and Dept. of Neurology, Aarhus University Hospital, Denmark, [2]Division of Neurological Pain Research and Therapy, Dept. of Neurology, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany, [3]Dept. of Orthopaedic Surgery, Odense University Hospital, Denmark

Background/Aim: Complex Regional Pain Syndrome type I (CRPS-I) is a pain condition with regional sensory and autonomic abnormalities in the affected limb. Over time the pain may spread to involve all extremities, which may bee due to a small fiber neuropathy [1]. The primary aim was to examine the function of small unmyelinated capsaicin-sensitive C-fibers in CRPS-I on the affected and non-affected hand.
Material: Twenty CRPS-I patients with distally localized pain in the upper arm, diagnosed according to the CRPS research diagnostic criteria [2], and twenty age-, gender-, and BMI-matched controls participated.
Methods: Topical capsaicin 5% was applied to the back of the affected and non-affected hand in patients and of both hands in controls for 30 min during which pain intensity ratings were assessed by means of a computerized visual analogue scale (VAS, 0-100). The pain was expressed as the area under the curve of pain (AUC) and the maximum VAS score. A laser Doppler perfusion imager scanner (LDI–2, Moor instruments Ltd) was used to estimate the capsaicin-induced flare.
Results: Capsaicin-induced pain and flare did not differ between the hands in both groups. Patients had increased capsaicin-induced pain and reduced capsaicin-induced flare on both hands compared with healthy controls.
Conclusion: The present findings suggest a dysfunction of capsaicin-sensitive fibers in CRPS-I that may reflect a small-fiber neuropathy with abnormal hypersensitivity of the remaining intact fibers (irritable nociceptors) [3].

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Poster No. II-10

Sleep disturbance associated with postoperative pain

Quinlan J[1,2], Warnaby K[1,3], Wulff K[4] & Tracey I[1,3]; [1]Nuffield Department of Anaesthetics, University of Oxford, [2]John Radcliffe Hospital, Oxford, [3]Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), University of Oxford, [4]Nuffield Laboratory of Ophthalmology, University of Oxford, United Kingdom

Aims of investigation: We are conducting a prospective, longitudinal study to investigate the influence of multiple factors upon the development of persisting postoperative pain.
Method: We are studying patients undergoing surgery for hernia repair and collecting data on pre-, peri- and postoperative variables to identify predictive factors for persisting postoperative pain. Detailed psychological questionnaires applied pre- and postoperatively also capture information about pain and sleep. Data regarding the surgical, anaesthetic and analgesic management of the patient is collected, along with postoperative telephone interviews to obtain further information on pain and sleep. This abstract investigates the interaction of sleep (both pre- and postoperatively) and postoperative pain.
Results: Preoperative scores from the Pittsburgh Sleep Quality Index (PSQI) enable us to divide our patients into good and poor sleepers, with a global score >5 indicating poor sleep quality. Our first 12 patients have scores ranging from 2 to 8, with an even split between the two groups. Initial results show a positive correlation between preoperative anxiety and preoperative daytime sleep disturbance, indicating poor sleep efficiency; and a further positive correlation between preoperative anxiety and increased pain on waking in the post-operative care unit, despite the presence of a local anaesthetic block.
Conclusions: Our early findings show that anxious patients may have disrupted sleeping patterns, possibly reducing their ability to cope with pain postoperatively. This may then increase their risk of developing long-term pain. The study design employed allows us to disentangle how pain and sleep interact to affect pain coping.

Poster No. II-11
Cancelled

Poster No. II-12
Chronic Tennis Elbow – Assessment of NK1-receptors by positron emission tomography (PET)
Peterson M[1], Butler S[2], Gordh T[2] & Svardsudd K[1]; [1]Department of Public Health and Caring Sciences, Family Medicine and Clinical Epidemiology Section, Uppsala University; [2]Department of Anesthesiology, Akademiska Hospital, Uppsala, Sweden

Musculoskeletal pain (MSP) is a common problem with an estimated cost of 2.9% of gross domestic product (GDP) in the US [1]. Chronic tendinitis (tendinosis) is a subgroup of MSP. The pain starts as an acute inflammatory process due to microtrauma as a result of excessive loading [2]. Most cases of acute tendinitis will heal spontaneously and only a portion will transit into a chronic stage. Sensitization of the central nervous system is a widely accepted explanation for chronic pain but in chronic tendinitis there are also findings suggesting peripheral sensitization [3, 4]. In a study utilizing positron emission tomography (PET) in chronic tennis elbow (TE) we saw increased uptake of an NK1-receptor antagonist in the painful elbow region. This may be interpreted as a sign of local upregulation of NK1-receptors as part of local sensitization.

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Poster No. II-13

Repeated stress may induce a hypo-serotonergic state with increased vulnerability to pain

Naesh O; Dept. of Anaesthesia & Intensive Care, Helsingborgs Lasarett, Sweden

Serotonin (5-HT) is involved in the modulation of pain transmission in the raphe nucleus and in the descending inhibitory system of the dorsal horn. The CNS concentration of serotonin is depending on the dietary supply of tryptophan. Free plasma 5-HT is metabolized and excreted as 5-HIAA [1]. Platelet 5-HT kinetics is widely accepted as a model for variations in 5-HT in the CNS [2].

There is a definite link between mental depression and vulnerability to stress and pain [3]. The mainstay of antidepressant therapy is to enhance serotonergic function and antidepressants are effective in the treatment of certain forms of chronic pain.

Various stress modalities (e.g. surgery, exercise, mental stress) are accompanied by an acute peak followed by a prolonged increase in the concentration of 5-HT in plasma paralleled by an intraplatelet decrease in 5-HT [4]. We have recently shown this to be an effect of a post-stress platelet 5-HT re-uptake block [5].

With an insufficient supply of tryptophan and ongoing stressful stimuli (i.e. pre- and postoperatively), it may be assumed that the concentration of 5-HT in serotonergic pathways will further decline. After several stress-events the system may eventually end up in a hyposerotonergic state with low levels of 5-HT in crucial areas of the CNS and an altered pain processing.

Such a hypo-serotonergic state may be of importance in chronification of pain following repetitive surgical procedures and intensive care. Perioperative use of antidepressants could hypothetically interfere with this process.

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Poster No. II-14

A delta and C fiber components of contact heat evoked potentials (CHEPs) in capsaicin induced heat hyperalgesia

Madsen CS[1], Finnerup NB[1], Johnsen B[2], Fuglsang-Frederiksen A[2] & Jensen TS[1]; [1]Danish Pain Research Center, Aarhus University Hospital, Denmark, [2]Department of Clinical neurophysiology, Aarhus University Hospital, Denmark

Introduction: There is limited knowledge about the contribution of C and A delta fibers in capsaicin induced heat hyperalgesia. We wanted to examine whether 1) contact heat can evoke reproducible C fiber responses following selective A fiber nerve blockade alone or in combination with application of topical capsaicin and 2) the effect of capsaicin on the A delta response.

Methods: Twenty heat stimuli of 51°C were delivered using the contact heat evoked potential stimulator (CHEPS), and heat hyperalgesia was induced by topical application of 200 µl capsaicin (5%) on the dorsum of both hands. At the

left wrist, a selective A delta nerve fiber block was performed by superficial radial nerve compression before capsaicin application, and on the right arm evoked potentials were recorded with and without capsaicin.
Results: On the right arm, capsaicin yielded a decrease in N2 latency from mean 345.2 (37.2) ms 310.5 (38.5) ms recorded from the vertex (Cz) position ($p=0.003$, paired *t*-test). On the left arm, when only the sensations of warmth remained unaffected of the pressure blockade (after 89.5 ± 5.9 min), 3 subjects showed ultra-late responses 1014-1242 ms (1111 ± 117.7 ms). After the subsequent capsaicin application, ultra-late responses were recorded in 11 subjects (N2 latency 1222.2 ± 75.2 ms).
Conclusions: Our findings suggest that capsaicin facilitates both A delta and C fiber mediated responses to heat.
Contact heat evoked ultra-late responses corresponding to C fiber activity were seen in a few subjects during the compression blockade, with increasing responses following capsaicin application.

Poster No. II-15

Evaluation of the antihyperalgesic effect of ketamine in elective Cesarean Delivery using dynamic quantitative sensory testing

Lavand'homme P & Roelants F; Anesthesiology, St Luc Hospital UCL Medical School, Belgium

Background: Perioperative treatments are aimed to decrease acute pain and to prevent pain-related pathologic modulation of the central nervous system which may lead to persistent postsurgical pain. Individual differences in endogenous pain modulation place individuals at risk to develop severe pain (Edwards R. Neurology 2005). Temporal summation (TS) which relies on NMDA receptors activation is an indirect method to evaluate CNS sensitization and nociceptive system hyperexcitability (Granot M, Curr Opin Anaesthesiol 2009; Eide PK, Eur J Pain 2000). We here assessed the effect of an antihyperalgesic dose of ketamine (KET) after elective caesarean delivery (CD) according the presence of a preoperative TS.
Methods: All patients underwent preoperative evaluation of TS on volar forearm and were then randomly allocated to receive either IV KET 0.15 mg/kg or saline before surgical incision. Surgery was realized under spinal anaesthesia and postoperative analgesia was provided by PCA morphine and systemic diclofenac. At 24 h and 48h, postoperative pain scores were recorded. At 48h, TS was tested again, pain scores and area of mechanical hyperalgesia (MH) surrounding the wound measured. Persistent postoperative pain was questioned at 2 months. For data analysis, patients were classified into 4 groups according to the presence (TS+) or not (TS-) of a preoperative TS.

	TS+ (n=19)	KET TS+(n=21)	TS- (n=42)	KET TS- (n=45)
Preoperative TS+ 48h postop TS+	100% 61%	100% 47%	0% 26% *†	0% 7% *† ¥
Presence of wound MH at 48h	58%	45%	25% *	24% *
Scar pain at 2 months	25%	26%	0% *†	5% †

* P<0.05 with TS+ group; † P<0.05 with KET TS+ group; ¥ P<0.05 with TS- group

Results: At 24 h, TS+ patients displayed higher pain scores at movement than TS- patients and than KET TS+ patients. At 48h, there was no difference in pain scores and area of MH. A positive correlation was found between: preoperative

TS value and area of MH (0.47; p=0.03), area of MH and postsurgical pain duration (0.50; p=0.03), preoperative TS value and 48h postoperative TS value (0.46; p=0.000).
Discussion: The use of dynamic quantitative sensory testing may help to better understand the variability of individual response to perioperative treatments.

Poster No. II-16

Smoking as a Risk Factor for Severe Postoperative Pain after Ambulatory Surgery

Shi YY[1], Durieux M[2], Turan A[3], Kovac A[4] & Apfel CC[1]; [1]Department of Anaesthesia and Perioperative Care, UCSF, [2]Department of Anaesthesia, University of Virginia, [3]Department of Outcomes Research, The Cleveland Clinic Foundation, [4]Department of Anesthesiology, Kansas University Medical Center, USA

Today, severe postoperative pain still affects one out of every four surgical patients. In addition to patient suffering and associated health care cost, poorly managed post-surgical pain may contribute to the development of chronic pain. Identifying patients at risk for severe post-surgical pain could afford clinicians the opportunity to adopt a proactive and personalized approach to post-surgical pain management. Unfortunately, previous studies were rather limited in size or outcomes were only collected in the immediate postoperative period. Thus, we prospectively collected pre-, intra-, and postoperative data from 2157 adults who underwent elective ambulatory surgery under general anaesthesia from 12 US hospitals. The primary endpoint for this analysis was the incidence of severe acute postoperative pain (≥7 out of 10) at the end of anaesthesia until the second postop day.
Patient characteristics were: age 49.5±15.4 years, 64.6% females, 28.3±6.9 BMI, and 15.2% smokers. Overall, 24.5% of patients experienced severe postoperative pain in the PACU which grew to 33.6% of patients by 48 hours post discharge. In the PACU, 22.0% of non-smokers and 38.5% of smokers reported severe pain. By 48 hours postdischarge, 54.1% of smokers but only 29.9% of nonsmokers reported severe postoperative pain. In addition, smokers reported a significantly ($p<0.001$) higher average pain score (95%CI) than non-smokers in the PACU, 4.94 (4.59-5.28) vs. 3.74 (3.60-3.88), and again at 48hr post-discharge, 6.35 (6.02-6.68) vs. 4.60 (4.47-4.74). Logistic regression analyses identified age <40 years, BMI >30, preoperative anticipation, surgery time >1 hr and current smoking status as a significant independent predictor for severe postoperative pain. The odds ratios for smoking were 1.74 (95%CI 1.26-2.41) in the PACU and 2.25 (95%CI 1.64-3.09) ($p>0.001$) at 48 hours postop. In conclusion, smoking turned out to be an independent predictor for severe post-surgical pain.

Poster No. II-17

No evidence for generalized increased post-operative pain responsiveness: a combined behavioral and serial FMRI study

Kupers R[1,2], Schneider F[3], Naert A[2], Husted H[4] & Kehlet H[2]; [1]Institute of Neuroscience & Pharmacology, University of Copenhagen, Denmark; [2]Dept. Surgical Pathophysiology, Rigshospitalet, University of Copenhagen, Denmark; [3]Dept. Radiology, University Hospital, Saint Etienne, France; [4]Dept. Orthopedic Surgery, Hvidovre Hospital, University of Copenhagen, Denmark

Although it is generally accepted that increased pain responsiveness and central

sensitization develop following major tissue injury, this claim has not been tested using brain imaging methods in a clinical pain setting. We therefore tested this hypothesis using a post-operative pain model, in conjunction with serial fMRI.
We studied brain and pain responses to innocuous and noxious heat in seven patients before and after total knee arthroplasty. Noxious and innocuous thermal stimuli were applied to the upper leg, proximal to the surgical area and to the lower forearm, a site remote from the surgical area. A group of eight age -and sex-matched control subjects underwent the same two-test procedure except that they were not submitted to an orthopaedic surgical intervention.
Subjective pain and brain responses to innocuous and noxious stimulation were not increased post-operatively. Actually, responses in primary and secondary somatosensory cortex for stimulation of the operated leg were significantly smaller following surgery. Brain responses in the control group did not differ significantly across the two sessions.
These data argue against the development of an overall increased pain responsiveness following a major surgical trauma. The data are in contrast with results from animal studies and from brain imaging studies using surrogate models of clinical pain which have shown increased central responsiveness in the area around the insult, thereby calling into question the clinical implications of acute postinjury sensitization.

Poster No. II-18

Failure of inhibitory pain modulation may underlie hemilateral hyperalgesia in complex regional pain syndrome

Knudsen L[1], Finch PM[1,2] & Drummond PD[1]; [1]School of Psychology, Murdoch University, Western Australia, [2]Perth Pain Management Centre, Perth, Western Australia

Complex regional pain syndrome (CRPS) is characterized by sensory disturbances that spread hemilaterally from the affected limb [1]. Central inhibitory pain control is disrupted and pain is facilitated in the CRPS-limb [2]. Hemilateral antinociception emanates from locus coeruleus during hindpaw inflammation in the rat [3]. The aim was to determine whether a dysfunction in inhibitory pain control to stimulation on the ipsilateral side of the body contributes to hemilateral hyperalgesia in CRPS. In 22 CRPS patients, sharpness sensations and pressure-pain thresholds were assessed on each side of the forehead before and after immersion of each limb in painfully-cold water for 1 min (the cold pressor task). Immersion of the healthy limb produced weak ($p = 0.06$) bilateral forehead analgesia to pressure. In contrast, sensitivity to pressure increased in the forehead after immersion of the CRPS-limb, especially in the ipsilateral forehead. The findings suggest that nociceptive stimulation of the CRPS-limb fails to evoke inhibitory pain control processes. Disruption of such processes may contribute to uncontrolled sensitization to incoming stimuli from the ipsilateral side of the body, and may account for hemilateral hyperalgesia ipsilateral to the affected limb in CRPS.

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Poster No. II-19

Persistent postoperative pain is associated with sensory abnormalities

Johansen A[1], Romundstad L[2], Nielsen CS[3], Schirmer H[4], Eggen AE[5] & Stubhaug A[2]; [1]Dept. of Anesthesiology, University Hospital of Northern Norway, [2]Division of Emergency Medicine, Oslo University Hospital, [3]Dept. of Mental Health, Norwegian Institute of Public Health, [4]Dept. of Cardiology, University Hospital of Northern Norway, [5]Inst. of Community Medicine, University of Tromsø, Norway

Aim: The aim of this study was 1) to assess the prevalence of persistent postoperative pain among individuals operated during the last 3 years in a general population and 2) to describe factors associated with chronic postoperative pain.
Material and methods: As part of a cross-sectional health survey in the municipality of Tromsø, North Norway, all participants answered questions on surgery, persisting pain and sensory abnormalities in the area of surgery. N = 12,984. Age 30-87 years, median 59. 53,4% women. Logistic regression was used to reveal any associations between pain and self-reported hyposensitivity, hypersensitivity and allodynia.
Results: 2,316 individuals (17.8%) had surgery between 3 months and 3 years prior to the survey. 826 (40.4%)of the 2044 who answered a questionnaire on postsurgical pain, reported having some degree of pain in the area of surgery. Of these 826 individuals, 45.2% had pain, when at worst, of moderate or severe intensity, i.e. 4 or higher on 0-10 NRS. The areas of surgery carrying the strongest association with persistent pain were(in descending order of frequency): 1) Shoulder/upper arm [74,5% (108/145)], 2) back [73.9% (65/88)], 3) lungs [66,7% (8/12)], 4) knee/lower leg [63,7% (179/281)], 5) hand [58,8%,(90/153)]. 6) hip/thigh [58,3% (74/127)] and 7) ankle/foot [58,7 % (84/143)]. 18,3% (413) reported reduced sensitivity in the area near the surgical scar, while 10,6% (240) reported hypersensitivity and 5.6% (127) allodynia. For those reporting hypoesthesia, the odds ratio (OR) for having pain was 2.71 (95% confidence interval 2.08 -3.53), for those reporting hyperesthesia, OR was 4.82 (3.24 – 7.18) and for those with allodynia 5.83 (3.12 – 10.90).
Conclusions: 3-36 months after surgery, 40% reported having pain in the area of surgery. There is a strong association between persistent pain and the presence of hyposensitivity, hypersensitivity and allodynia.

Poster No. II-20

Development and validation of a screening-instrument for the prediction of chronic postsurgical pain (CPPS)

Neugebauer EAM; Institute for Research in Operative Medicine, Witten/Herdecke University, Germany

The incidence of chronic postsurgical pain (CPSP) after various common operations is 10% to 50%. Identification of patients at risk of developing chronic pain, and the management and prevention of CPSP remains inadequate. We have developed and validated an easily applicable screening instrument for the detection of high risk patients that takes into account the multifactorial aetiology of CPSP.
Two hundred forty five patients who underwent different types of surgery were prospectively included in the study. Follow-up data were collected six months after baseline assessment in 199 patients. To validate the developed screening

instrument according to the criterion CPSP, we subjected the data of 150 patients to logistic regression analyses.
Six months after surgery, 43.3% of the patients reported CPSP. Five predictors multivariately contributed to the prediction of CPSP: Capacity overload, preoperative pain in the operating field, other chronic preoperative pain, post surgical acute pain, and co-morbid stress symptoms (Nagelkerke's R^2 = .33, ROC area = .77, 95% CI: .70 - .84). The remaining five items, each assessed by yes-no responses, constituted an ordinal scale ranging from 0 to 5 (number of risk factors). The number of patients reporting CPSP increased linearly with every additional risk factor, i.e. the screener is sensitive across the full range of the scale.
These results suggest that several easily assessable pre- and peri-operative patient characteristics can predict a patient's risk of developing CPSP. The CPPS may help care givers to tailor individual pain management and to assist high-risk patients with pain coping.

BENZON SYMPOSIUM No. 57

ACUTE PAIN - PATHOPHYSIOLOGY AND RISK FACTORS FOR CHRONIFICATION

OCTOBER 4-7, 2010, COPENHAGEN, DENMARK

Organizing committee:
Henrik Kehlet (Copenhagen), Troels Staehelin Jensen (Aarhus), Arne Svejgaard (Copenhagen) & Povl Krogsgaard-Larsen (Copenhagen)

Abstracts - WEDNESDAY, October 6, 2010

Breast Surgery

Kalso E; Pain Clinic, Helsinki University Hospital, Finland

Breast surgery is an important component in the treatment of breast cancer usually preceding adjuvant treatments such as chemotherapy, radiotherapy and hormonal therapy. The treatment of breast cancer has developed significant over the last years and consequently most women survive. Thus, the treatment should cause as little complications as possible as these may have a significant impact on the quality of life of the breast cancer survivors.
Pain following breast surgery is an important topic to study as breast cancer is the most common form of cancer in the women of the Western world. Persistent pain following breast surgery offers excellent possibilities for research as nearly all patients are women (no gender differences as confounding factors) who are usually highly motivated to participate in clinical research. Also, tissue and nerve injuries are easier to study (e.g. with quantitative sensory testing) compared with post-surgical pains that have a visceral component. Also, preoperative pain in the area of surgery is rare compared with many other types of surgery (inguinal hernia, hysteractomies). Studying factors that are related to a higher risk for persistent pain following breast surgery is, however, also challenging as adjuvant treatments (chemotherapy, radiotherapy, and hormonal therapy) have effects of the recovery of tissue and nerve injury, and mood.
The study of risk factors for persistent pain following breast surgery could be divided into factors that are general for pain persistence (e.g. mood, stress, endogenous pain control, recovery of tissue and nerve injury, and genetic factors related to these), and factors that are specific for this type of surgery (different surgical techniques used, cancer, and factors related to female gender and hormonal effects).

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Persistent Postherniotomy Pain

Aasvang EK; Section of Surgical Pathophysiology, University of Copenhagen, Rigshospitalet, Denmark

Persistent pain has for more than a decade been recognized as a serious adverse outcome after groin hernia surgery (1) with approximately 5% of patients reporting persistent postoperative pain affecting everyday activities.
Several factors, surgical and patient related has been suggested to be related to the risk for development of persistent postherniotomy pain (PPP), whereof the most important include:
Preoperative pain: The intensity of preoperative pain has in several studies been shown to correlate to the risk for development of PPP (2).
Nerve injury: A nerve injury is a necessary but insufficient factor for PPP. This conclusion is supported by the finding that in PPP patients sensory disturbances reveal a heterogeneous pattern with most patients having significant cutaneous and/or deep tissue hyperalgesia, but about 20% have sensory function within the normal spectrum seen in pain-free postherniotomy control patients (3).
Acute pain: have been found to correlate to development of PPP. However, recent studies on groin hernia repair suggest that at least part of this may be due to more severe nerve injury in high acute pain patients, rather than the suggested mechanism where high acute pain leads to persistent neuroplastic changes and pain (4).
Inflammation: Other than the inflammation surrounding a directly injured nerve groin hernia repair may itself initiate inflammation due to the reaction to the inserted mesh. However studies have yet to show that this in itself is a factor for PPP.
Genetics: Studies have yet to identify the role of a genetic predisposition to PPP.
Recently a multifactorial prospective study in 450 patients undergoing elective groin hernia repair, investigated the relative role of several factors in the risk for development of PPP, showing that preoperative pain, response to a preoperative heat stimulus and severity of nerve injury was independent factors for predicting PPP. Furthermore, laparoscopic surgery significantly reduced the risk for PPP especially in high risk pain patients (4).

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Thoracotomy

Kehlet H; Section of Surgical Pathophysiology, University of Copenhagen, Rigshospitalet, Denmark

Chronic pain complaints after thoracic surgery have been reported as a clinical problem in 25-60 % of patients and include multiple pathogenic mechanisms that include pre-, intra- and postoperative factors. Due to inconsistencies in collection of these perioperative data precise conclusions for preventive and treatment strategies is somewhat hindered. However, intercostal nerve injury seems to be the most important pathogenic factor. Potential nerve sparing techniques include thoracoscopic approaches with reduced port size, and closure techniques without

compression of the intercostal nerve. A protocol for better design of prospective studies will be presented.

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Obstetric and Gynecologic Surgery

Eisenach J[1], Pan P[1], Smiley R[2], Liu B[1] & Boada D[1]; [1]Department of Anesthesiology, Wake Forest University, USA, [2]Department of Anesthesiology, Columbia University, USA

Hysterectomy, one of the most common major surgical procedures performed world wide, is often utilized to test novel analgesics for drug approval and, more recently, for examination of risk factors for chronic pain after surgery. As regards the latter, somewhat paradoxical observations have been observed. For one, hysterectomy is commonly performed in patients with preexisting pelvic pain, and is curative of pain in a majority of women. Indeed, although the overall incidence of chronic pain after hysterectomy in recent studies is moderately high (19%), the vast majority of these women had chronic pain before their surgery, and the incidence of new onset pain is remarkably low (2.9%). For another, it has been assumed by some that chronic pain after surgery reflects either the degree of surgical nerve trauma or chronic inflammation induced by surgical injury, yet there is no difference in the incidence of chronic pain after hysterectomy when the surgery, and likely resultant inflammation, are grossly different – open abdominal exposure versus vaginal resection versus laparoscopic surgery. One could conclude that, although the acute pain response following hysterectomy might be useful for postoperative analgesic drug development, there are several unique features of this population or surgery which do not fit into to current hypotheses regarding the etiology and mechanisms of chronic pain after physical injury.

Yet more confusing is the incidence of chronic pain after childbirth, which ranges from 0 to nearly 30% of women. Our clinical and laboratory studies suggest that the incidence is very low (< 1% following cesarean delivery) and that this reflects a protective effect of the pueperium rather than pregnancy per se. Certainly, back pain and headache are common in the months following delivery, but we speculate that tissue trauma during vaginal delivery or surgical and nerve trauma from cesarean delivery, is unlikely to cause chronic pain.

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How to prevent postherpetic neuralgia?

Haanpää M; Department of Neurosurgery, Helsinki University Central Hospital, Finland

Herpes zoster (HZ) is caused by the reactivation of varicella zoster virus (VZV), which has remained dormant in the sensory ganglia since the primary infection, varicella. The risk for HZ increases with age, paralleling the concomitant waning of cell-mediated immunity to the VZV. About 12% of zoster patients develop at least one complication, of which postherpetic neuralgia (PHN), i.e., prolonged pain after HZ, is the most common. The effect of HZ and PHN on the quality of life is serious in many older people. Prevention of PHN remains one of the top priorities in the field of pain medicine, because once established PHN is virtually impossible to cure, and even its symptom control is difficult. Older age and the severity of the acute pain are the most obvious risk factors for PHN. Therefore, elderly patients, especially those with severe pain, should be treated with antiviral drugs, which decrease the tissue damage caused by the virus. However, the effect of antivirals on preventing PHN is limited. Adequate acute pain relief prevents the development of sensitization of the nervous system, and hence early use of analgesics in HZ is reasonable. One study suggests that early treatment with amitriptyline may help to prevent PHN, and tricyclics are suggested as a part of the clinical treatment of HZ in elderly patients[1]. Psychosocial aspects should be taken into account in the treatment of zoster, because they may contribute to the development of PHN[2].

The best way to prevent PHN is to prevent zoster itself. The Shingles Prevention Study indicates that zoster vaccine reduces the risk of HZ in healthy older adults[3]. The vaccine was associated with a 51% reduction in the incidence of HZ, a 67% reduction in the incidence of PHN, and a 61% reduction in the burden of illness caused by HZ in vaccine recipients compared with placebo recipients. The vaccine effect declined with increasing age. The vaccine was safe and well tolerated causing only mild local reactions at the injection site. Currently the reimbursement policy limits its broad use.

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Chronification of Headache Disorders

Olesen J & Jensen R; Danish Headache Center, Dept. Neurology, Glostrup Hospital & University of Copenhagen, Faculty of Health, Denmark

Migraine and tension-type headache are episodic primary headache disorders though present for decades. Chronic means that they become very frequent or daily. Chronic in secondary headaches means that they persist for more than 3 month, similar to the definition of other chronic pains. Chronic post-traumatic headache is the most common type. Factors predicting chronification are for migraine and tension-type headache a high frequency of attacks, female sex and overuse of drugs for acute attacks. The chronification of post-traumatic headache is inversely related to the severity of trauma i.e. more frequent with mild head trauma than with severe trauma. This may partly be due to the much more common occurrence of mild trauma. Thus, only a small fraction with post-

concussional symptoms becomes chronic. Seemingly, there may be an element of post-traumatic stress involved, for example reflected in a high frequency with combat injury but little research on this has been done.
Chronification of migraine and tension-type headache is not irreversible. Many revert spontaneously back to the episodic form. Others revert after discontinuation of medication overuse but others do not and continue to pose a therapeutic problem. A highly structured therapeutic program has been developed for patients with medication overuse and successful discontinuation is possible in almost all patients. Unfortunately, recurrence of the problem is not uncommon and prevention is therefore much to prefer. Patients should in time receive prophylactic medication so as to keep attack frequency at 6 days per month permitting liberal use of acute medication for each attack.
Chronic post-traumatic headache poses a difficult therapeutic problem. In fact we have been able to help only those with medication overuse. Pharmacological prophylactic treatment, psychological- behavioral treatment and physiotherapy, individually or in combination, have proven fruitless in our hands. New therapeutic regimens have been developed and are currently being tested.

Psychosocial Contributions to the Chronicity of Pain

Haythornthwaite JA; Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, USA

Pain at the time of injury or surgery is one of the primary factors associated with persistence of pain. A number of psychosocial factors are associated with both the experience of acute pain and the persistence of pain following acute injury or surgery. These factors include socioeconomic parameters, anxiety and depression, stress, catastrophizing, and sleep disturbance. The evidence supporting the association of each of these factors with acute pain and persistence of pain following injury/surgery will be reviewed, and recent data identifying possible mechanisms linking these factors to the persistence of pain will be discussed.

Individual Differences in Pain Sensitivity as a Risk Factor for Chronic Pain

Fillingim RB; Gainesville VA Medical Center, University of Florida, College of Dentistry, USA

Responses to painful stimuli are characterized by robust inter-individual variability, which is mediated by interactions among numerous biopsychosocial factors, including genetic influences, sex/gender, race/ethnicity, and multiple psychological variables (3). The clinical relevance of individual differences in experimental pain sensitivity has garnered increasing attention in recent years. For example, heightened sensitivity to experimentally-induced pain has been documented in multiple chronic pain conditions, and experimental pain sensitivity has been associated with the severity of clinical pain in multiple populations (1). However, most of this evidence derives from case-control studies and the absence of prospective studies makes it difficult to determine whether enhanced pain sensitivity represents a risk factor for versus a consequence of chronic pain. Additional findings demonstrate that pre-operative pain sensitivity predicts acute post-operative pain (2), and a recent study reported that a measure of endogenous pain inhibition predicted risk of developing chronic pain following thoracotomy (4). Thus, increasing research points to the possibility that

experimental pain sensitivity may be a risk factor for chronic pain. This presentation will briefly discuss methodological issues of importance when investigating experimental pain sensitivity and endogenous pain modulation. Then, the available literature regarding pain sensitivity and incidence of chronic pain will be reviewed, and model will be presented for conceptualizing individual differences in pain sensitivity as a risk factor for development of chronic pain.

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Poster No. III-01

A prospective study of risk factors for chronic post-surgical pain in women undergoing hysterectomy for benign disorders

Pinto PR[1], McIntyre T[1,2], Araújo-Soares V[3] & Almeida A[4]; [1] School of Psychology, University of Minho, Portugal, [2] Department of Psychology, University of Houston, USA, [3] Institute of Health and Society, Newcastle University, UK, [4] School of Health Sciences, University of Minho, Portugal

Aim: To determine the incidence of chronic post-surgical pain after hysterectomy and to examine the role of clinical and psychosocial risk factors in a Portuguese sample. Method: This prospective study included data collection at four time points: 24 H before surgery, 48 H, 4 and 9 months after surgery. The study is ongoing and 79 women have completed the first three assessments. The instruments used were standardized measures of pain (e.g. BPI, DN4, CSQ-R) and psychosocial variables (e.g. HADS, LOT-R, IPQ-R, SIP), and analgesic use was recorded post-surgery. Results: Preliminary results (n=79; Age: *M*=51.4, *SD*=8.7) showed that 4 months after hysterectomy 45.6% of the women reported pain. Pain was located primarily in the pelvic region or in the abdominal scar. The worst pain intensity was 4 on a 0–10 numeric rating scale and analgesics for this pain were used by 22% of women. The majority (61.1%) had pain daily and 50% reported some daily interference from their pain. There were no significant differences between women with pain and those without pain when comparing surgical, anaesthetic and analgesic characteristics. Risk factors for pain 4 months after hysterectomy were pre-surgical pain (OR, 3.10; 95%CI, 1.09–8.85), pre-surgical depression (OR, 1.38; 95%CI, 1.08–1.75) and post-surgical rescue analgesics consumption (OR, 3.20; 95%CI, 1.12–9.15). Pre-surgical depression and post-surgical analgesics consumption were the strongest contributors to the model. Discussion: Data suggest that both clinical (e.g. pre-surgical pain) and psychosocial factors (e.g. depression) should be considered in the development of chronic pain after surgery.

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Poster No. III-02

Chronic pain after breast augmentation is associated with peripheral nerve injury and central changes

Kaasa T, Myhre M, Romundstad L & Stubhaug A; Department for Pain Treatment, Oslo University Hospital - Rikshospitalet, Norway

Background: 116 women, who answered a questionnaire in a four years follow-up study of pain, sensory changes and quality of life after cosmetic breast augmentation surgery, were invited to participate in a psychophysical study. Twenty women answered the request, and 12 of these women finally met for examination.
Six of the 12 women had pain in the area of surgery, three were pain-free, but reported sensory changes and three reported no pain or sensory disturbances. We performed a detailed quantitative sensory examination, with a protocol adapted from Rollke et al. [1]

Table 1. Number in each group (subjects with pain vs. subjects without pain) showing presence of sensory characteristics		Pain (N=6)	No pain (N=6)
Question-naire	Hypoesthesia	5	3
	Hyperesthesia	6	3
Examination	Hypoesthesia (tactile, heat, cold)	6	6
	Hypersensitivity detected	4	1
	Hyperpathia to heat	5	5
	Paradoxical heat sensation during cold stimulation	4	0
	Allodynia, cotton	0	0
	Allodynia, brush	0	1
	Cold allodynia	5	1
	Abnormal temporal summation	5	1
	Deep pain after algometry	4	0

While only 3/6 patients in the pain-free group reported hypoesthesia, an area of hypoesthesia to tactile-, heat- and cold stimuli was identified in all subjects when examined. The most striking difference between the group reporting pain and those not reporting pain was the presence of paradoxical heat sensation, the presence of abnormal temporal summation, and the presence of deep pain during/after pressure pain threshold testing with the algometer.

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Poster No. III-03

A Systematic Review and Meta-analysis of Persistent Pain Following Sentinel Bode Biopsy Compared to Axillary Node Dissection

Perkins FM, Rosenkranz KM & Sorensen-Franklin J; Departments of Anesthesiology and Surgery, Dartmouth Medical School, USA, and the Veterans Administration Hospital, USA

We performed a systematic review of the world literature (Index Medicus, Cochrane Database) of studies comparing pain and quality of life following sentinel node biopsy and axillary dissection. All clinical trials involving the search criteria were obtained and translated where necessary. The find similar function in OVID was used to obtain additional articles, and all cited references were reviewed to try to achieve a complete database. The papers were reviewed by

the three authors (an anaesthesiologist, a surgeon, and a pain physician) and categorized as not appropriate for the meta-analysis or appropriate. The appropriate papers were then divided into randomized controlled studies or case series. If the papers indicate that the data needed for the meta-analysis was obtained, but not presented in a form that the investigators could use, an attempt was made to contact the lead author of the article to obtain the desired data. Data sets that were published more than once were only included as a single trial. The odds ratio for the parameter of interest was then calculated for each article and for the group of articles.

From cases series data (9 trials) the odds ration (95% CI) of persistent pain is 0.31 (0.26 – 0.37). For the randomized controlled trails (4 trials) the odds ration is 0.53 (0.42 – 0.66). We attribute the apparently greater effect size seen in the case control studies to systematic exclusion of patients with tumour positive axillary nodes. These patients receive less intensive radiation and chemotherapy and have a lower risk of persistent pain.

Poster No. III-04

Effects of Perioperative Gabapentin Administration on Transition to Chronic Pain after Joint Arthroplasty Surgery

Clarke H & Katz J; Department of Anaesthesia and Pain Management, Toronto General Hospital, Canada

This presentation will briefly review some of the known predictors of chronic postsurgical pain. Data will be presented with respect to multimodal analgesia and orthopaedic surgery. Specifically, we will review data from a recent study that failed to find a significant opioid sparing effect, a reduction in acute pain, or a treatment related difference in long term pain following a single perioperative dose of gabapentin in patients undergoing hip arthroplasty. We will also present data on the use of the $\alpha 2\delta$ voltage-dependent calcium channel blockers (gabapentin and pregabalin) as a treatment modality to facilitate functional recovery after joint arthroplasty surgery and to examine their efficacy in reducing chronic post arthroplasty pain.

Poster No. III-05

Gender and chronic pain 6 months after thoracotomy

Hetmann F[1], Kongsgaard, UE[2] & Schou-Bredal I[3]; [1]Department of Anaesthesia, [2]Department of Research and Development, [3]Department of Breast and Endocrine Surgery, Oslo University Hospital, Norway

Background: Chronic pain after a thoracotomy is a well known complication. Research indicates that women are at particular risk of developing chronic pain after surgery.
Aim: To investigate the prevalence of pain 6 months after thoracotomy and to explore the association between preoperative pain, age, gender and pain at 6 months.
Patients and methods: 57 consecutive patients (25 females/32 men) completed a questionnaire to assess any pain prior to surgery and at 6 months after surgery. Any pain was answered by yes or no, and pain sites were marked on a body figure. The most common sites of pain reported before surgery were lower back, neck, shoulders and hips, and this pain was not associated with the patients' current diagnosis. At 6 months patients reported their pain to origin

from the site of surgery, in addition to their previous pain. A logistic regression model was used to determine the association between pain at 6 months, age, gender and pain prior to surgery.
Results: The prevalence of chronic pain prior to surgery and at 6 months was 40% and 50%, respectively. Age was not associated with postoperative pain (p=0.75). However, there was a statistically significance when pain at 6 months was adjusted for gender (p=0.019) and pain prior to surgery (p=0.017). The data analysis did not reveal any additive effect between gender and prior pain.
Conclusion: Gender and prior pain seem to be important predictors for chronic pain. In this small sample, women and patients with pain prior to surgery had an increased risk of developing chronic pain 6 months after a thoracotomy.

Poster No. III-06

From Acute to Chronic Postoperative Pain

Eckhardt MR[1], Ørding H[1], Licht P[2], Andersen C[3] & Toft P[3]; [1]Department of Anaesthesia, Vejle Hospital, [2]Department of Thoracic Surgery, Odense University Hospital, [3]Department of Anaesthesia and Intensive Care, Odense University Hospital, Denmark

Introduction: Chronic pain is present in 10-40% of patients one year after cholecystectomy. So far the pathogenesis for the pain has not been uncovered, as have only few of the risk factors. High intensity of acute pain in the first week after cholecystectomy and – to a lesser extent – psychic vulnerability has been shown to predispose to chronic postcholecystektomy pain though.
Postcholecystectomy pain has never been classified systematically in relation to neuropathic, inflammatory or other components, but several individuals have shown hyperalgesia in the referred pain area.
Objective: To uncover risk factors for postcholecystectomy pain and classify postcholecystectomy pain by QST.
To further examine the significance of different acute pain patterns for the development of chronic postcholecystektomy pain.
Method: 100 patients scheduled for laparoscopic cholecystectomy will be examined with QST (Quantative Sensory Testing), and psychological tests before surgery. Intensity of pain and type of pain will be recorded for the first postoperative week. After 3 months, patients with pain will undergo a follow-up examination programme. Those patients where no explanation for the pain can be found and who still has pain, will be examined after 6 and 12 months with QST and psychological tests.
Results: So far 6 patients have been included. More results will be presented at the conference.

Poster No. III-07

Pain-Out: An International Registry for Acute Postoperative Pain and a Platform for Studying Acute to Chronic Pain Transition

Zaslansky R[1], Fletcher D[2], Pogatzki-Zahn E[3], Chapman CR[4], Rothaug J[1] & Meissner W[1]; [1]Depts. of Anesthesiology & Intensive Care, Friedrich-Schiller University Hospital, Germany, [2]Hôpital Raymond-Poincarré, France, [3]Westfaelische Wilhelms-Universitaet, Germany, [4]University of Utah, USA

Risk factors for the progression of acute pain after surgery to Chronic Post Surgical Pain (CPSP) are inherently multi-factorial. Pre- existing pain and severe post-operative pain are known vulnerabilities, but many others exist. To date, most studies report data from single institutions, focus on a single type of surgery, and have a modest sample size. Comprehensive, multi-factorial

investigation of CPSP should, ideally, draw upon a large-scale, continuously growing, database that is comprehensive, multi-center, and international. An acute pain registry can make this possible.
Pain-Out, funded by the EU's 7th Framework Program, models on the German post-operative Pain Registry (QUIPS), with oversight by an IASP Working Group. It tracks post-operative outcomes, processes and structures, forming an International Registry of Acute Pain. In 2008 we studied feasibility of collecting such data internationally in 13 countries and 14 medical centres, with data from 688 adult patients after orthopaedic and general surgery. Patients reported pre-existing chronic pain and the worst pain 24 hrs after surgery. Frequency of pre-existing pain ranged from 27% - 79% across sites with orthopaedic patients having significantly higher frequency (62%) than general surgery (42%) patients. 'Pain at its worst' was slightly but significantly higher for patients reporting pre-existing pain. One of us (DF) is leading an application to study CPSP in Pain-Out collaborating centres and additional centres wishing to join. This study will follow patients 24 hrs after surgery and after one year. The Registry will provide a platform for studying CPSP on an international basis following patients after a large variety of surgeries, further defining risk factors for CPSP.

Poster No. III-08

Identifying pre-operative risk factors for chronic post surgical pain in day case patients; a project proposal

Rockett M; Pain Clinic, Derriford Hospital, United Kingdom

To date, there has been only one well designed prospective trial of CPSP following laparoscopic cholcystectomy, which measured an incidence of 10% for significant chronic pain at 1 year but did not identify any pre-operative risk factors. The aim of the current study is to identify novel pre-operative risk factors associated with the presence of significant chronic pain (VAS >41mm) at 6 months. These data would allow targeting of preventative treatment to high risk patients in a subsequent interventional trial. As a secondary endpoint, the nature of the patients' pain will be characterised in greater detail than previously attempted. Anaesthesia, analgesia and surgery will be standardised. **Primary endpoint:** The presence of significant pain (VAS >41mm in last week) at 6 months. **Secondary endpoints:** *Preoperative*: pain interference (BPI), severity (frequency and worst pain), coping (catastrophising subscale of the Coping Strategies Questionnaire), self efficacy (SES questionnaire), affect (HAD questionnaire), baseline neuropathic characteristics (Pain Detect Questionnaire). Baseline limited quantitative sensory testing (QST) over gallbladder versus control side – skin fine touch and pain threshold and muscle pain threshold. Baseline pain drawing for total area and location of pain. *Intra-operative variables include:* duration of surgery, grade of surgeon, non standard surgery (e.g.: bile duct exploration) and bile spillage. *Acute post-operative variables:* VAS in recovery, use of strong opioids in recovery, opioid related side effects and complications in recovery. *Measures of pain in first post operative week via questionnaire:* mean daily VAS on activity, use of analgesics at home, complications. *Follow up telephone questionnaire at six months:* ongoing pain yes/no. Patients with VAS>41mm related to CPSP in the last week will be invited for assessment with repeated questionnaires, pain drawing and QST as above. There will also be a surgical assessment following the model suggested by Kehlet 2005, in order to identify the ~50% of patients likely to have pain due to organic pathology. **Analysis:** The primary aim of the study will be to determine an

association between preoperative factors and the presence of significant CPSP. Multiple regression analysis will be applied to determine whether preoperative variables are associated with significant pain at 6 months. Pre-operative pain analysis may also allow identification of patients with pain due to other pathology who do not require surgery.

Poster No. III-09

Implementation of quality management program improves postoperative pain treatment – a prospective pre/post-intervention questionnaire study

Usichenko T[1], Röttenbacher I[1], Kohlmann T[2], Julich A[1], Adler S[1] & Wendt M[1]; [1]Department of Anesthesiology and Intensive Care Medicine and [2]Institute of Community Medicine, University of Greifswald, Germany

Background: Organizational approach is proposed as an immediate solution to improve postoperative pain (POP) management (1). The aim was to evaluate the clinical effectiveness of quality management program (QMP), introduced at the university hospital.

Methods: QMP included: i) structured patient information about POP treatment; ii) procedure-specific, multimodal analgesic protocols, modified to meet the individual patients' requirements; iii) protocols for treatment of analgesia-related adverse affects; iv) nurse-based acute pain service; v) multidisciplinary task-force in surgical departments; vi) education of the staff; vii) quality assurance measures.

Patients from orthopaedics, gynaecology, visceral and trauma surgery departments were involved in 2 prospective surveys. Survey 1 (296 questionnaires distributed) was performed at baseline; survey 2 (294 questionnaires) was performed after the implementation of QMP with an interval of 1 year.

The patients were asked to report: i) pain intensity on Numerical Rating Scale (NRS-11, from 0=no pain to 10=intolerable pain; minimal and maximal; at rest and on movement); ii) incidence of analgesia-related side effects; iii) incidence of pain interference with daily activities; iv) patient satisfaction with treatment of POP using NRS-5 (1=very good to 5=bad).

Results: The questionnaire was returned by 91% of patients from survey 1 and by 85% from survey 2. Demographics and type of surgery were comparable in patients from both surveys. Patients from survey 2 reported less pain than patients from survey 1 in all categories and time-points of measurement. Clinically significant was the reduction of maximal POP intensity on the day of surgery from 6 (4-8) to 4 (3-6) and pain intensity on movement from 5 (3-7) to 3 (2-5); median (interquartile range); $p<0.001$. Nausea was reported by 35% of patients from survey 1 vs. 14% from survey 2, vomiting - by 21% vs. 9% of patients and fatigue by 66% in survey 1 vs. 25% from survey 2 ($p<0.001$). Patients' life quality and satisfaction also improved in survey 2 vs. survey 1 ($p<0.001$).

Conclusion: The implementation of QMP allowed reducing POP intensity with simultaneous decrease of analgesia-related side effects, which led to an increased quality of life and patients' satisfaction.

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Poster No. III-10

Mechanosensitivity before and after hysterectomy: A prospective study on the prediction of acute and chronic postoperative pain

Nikolajsen L[1], Brandsborg B[1], Dueholm M[2], Kehlet H[3] & Jensen TS[1]; [1]Danish Pain Research Center and [2]Department of Obstetrics and Gynaecology, Aarhus University Hospital, Denmark, [3]Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University, Denmark

Background: The incidence of chronic pain after hysterectomy is reported to be up to 30%. This study aimed to assess the predictive value of preoperative abdominal and vaginal mechanosensitivity for the subsequent development of acute and chronic pain after hysterectomy.
Methods: Ninety women undergoing hysterectomy for benign conditions were studied. Experimental testing was carried out on the day before hysterectomy, on the first postoperative day, and after 4 months. Abdominal testing included brush-evoked allodynia, pinprick hyperalgesia, wind-up-like pain, and pressure pain thresholds. Vaginal testing included pressure pain thresholds. The intensity of pelvic pain was recorded on a numerical rating scale before hysterectomy, daily in the first postoperative week, and after 4 months.
Results: The incidence of pelvic pain was 51% before hysterectomy and 17% after 4 months. Preoperative brush-evoked allodynia, pinprick hyperalgesia and vaginal pressure pain threshold were associated with the intensity of acute postoperative pain (P = 0.04, <0.01 and <0.01, respectively). Preoperative brush-evoked allodynia was also associated with pelvic pain after 4 months (P < 0.01).
Conclusions: Preoperative pain sensitization as reflected by cutaneous and vaginal hypersensitivity is associated with acute pain after hysterectomy, but less so with persistent pain.

Poster No. III-11

Surgical management of inguinal neuralgia after a low transverse Pfannenstiel incision

Roumen RMH, Loos MJA & Scheltinga MRM; Dept of Surgery, Máxima Medical Center, The Netherlands

Background: The low transverse Pfannenstiel incision has been associated with chronic lower abdominal pain because of nerve entrapment (2%–4%). Treatment options include peripheral nerve blocks or a neurectomy of neighbouring nerves. Knowledge on adequate (surgical) management is scarce. The authors assessed the long-term pain relief after local nerve blocks or neurectomy in patients suffering from chronic pain because of Pfannenstiel-induced nerve entrapment.
Methods: Patients treated for iliohypogastric and/or ilioinguinal neuralgia after a Pfannenstiel incision received a questionnaire assessing current pain intensity (by 5-point verbal rating scale), complications, and overall satisfaction.
Results: Twenty-seven women with Pfannenstiel-related neuralgia were identified between 2000 and 2007. A single diagnostic nerve block provided long-term pain relief in 5 patients. Satisfaction in women undergoing neurectomy (n = 22) was good to excellent in 73%, moderate in 14%, and poor in 13% (median follow-up, 2 years). Complications were rare. Successful treatment improved intercourse-related pain in most patients. Co-morbidities (endometriosis, lumbosacral radicular syndrome) and earlier pain treatment were identified as risk factors for surgical failure.

Conclusions: Peripheral nerve blocking provides long-term pain reduction in some individuals. An iliohypogastric or ilioinguinal nerve neurectomy is a safe and effective procedure in most remaining patients.

Poster No. III-12

A pilot study assessing pain and health-related quality of life in women after cAesarean section

Subocz EG, Harrison MB & VanDenKerkhof E; Department of Anesthesiology & Nursing, Queen's University, Canada

Background: Little is known about the incidence and risk factors for chronic post-surgical pain (CPSP) after caesarean section (CS). This pilot study assessed the feasibility of conducting a prospective, cohort study to identify predictors of pain and decreased health-related quality of life (HRQOL) in women undergoing CS.
Method: A convenience sample was recruited from Kingston General Hospital two hours prior to their scheduled CS. Preoperative questionnaires were self-completed on pain (Brief Pain Inventory [BPI]), HRQOL (Short Form – 36 Health Survey [SF-36]), depressive mood (Centre for Epidemiological Studies – Depression Scale), anxiety (State Trait Anxiety Inventory), somatization (Seven Symptom Screen Test), and demographic and healthcare use details. Follow-up questionnaires were completed at 6 weeks and 6 months postoperatively.
Results: Forty (RR=84%) women consented to participate. Preoperatively, 18 (44%) women reported pain in the past week, moderate to severe pain was reported by 9 (27%) in the recovery room and 33 (88%) on the ward. Twenty-three percent reported pain at 6 weeks, 8% reported pain at 6 months and 13% reported pain interference at 6 months. Pain following CS was associated with tubal ligation, moderate to severe pain expectancy, severe acute postoperative pain, somatization and pain interference preoperatively (bivariate analysis; $p<.05$). The SF-36 physical component scores were lower than population norms both pre- and post-operatively. Mental component scores were higher than population norms preoperatively, and similar to population norms postoperatively. Preoperatively, 24% had depressive symptoms, 22% high state anxiety, and 7.5% high trait anxiety; however, there was no association with postoperative pain. Six weeks postoperatively, over 30% had sought a healthcare professional for pain and 15% were still using pain medication.
Conclusion: Post-caesarean pain may continue to affect some women during the weeks and months after surgery. Further research is needed to explore long-term pain after c-section and its possible impact on the individual and the healthcare system.

Poster No. III-13

Low dose ropivacaine for preventing brachial artery spasm (BAS) during trans radial PCR procedure

Yevstratov E[1] & Krupskaya N[2]; [1]Anaesthesiology dep., St. Katherine Hospital of Cardiology, [2]Anaesthesiology, Odessa Regional Hospital, Ukraine

The radial artery approach for coronary angiography and angioplasty has been shown to be a safe alternative to the femoral approach. Although this technique is increasingly preferred, brachial artery spasm (BAS), a potential complication, limits its widespread use. BAS may be resistant to vasodilator medications, which

are usually useful in this situation, and may cause serious complications. We performed coronary artery angiography by 5Fr catheters.
Regional anaesthesia for an ambulatory practice in this category of patients requires local anaesthetics with a clear profile: fast onset, well-defined duration an early recovery from paralysis but with long analgesia for pain free discharge. Nearly any regional anaesthesia technique is suitable; however, the new local anaesthetics ropivacaine and levobupivacaine are long acting agents and differ concerning the differential blockade. In all our cases was performed a single shot technique under ultrasonography guidance by the same anaesthesiologist during procedure.
Brachial plexus block (BPB): single shot techniques in adults, 15ml 0.250% solution of ropivacaine with 5ml 2% Lidocaine can be used to provide this technique with selective nerve stimulation, leads to short-acting blockade of the nerve and long-acting sensitive blockade[1].This technique allows reducing volumes and the risk of systemic toxicity. Commonly we're used a both approaches anterior interscalenius block with stellate ganglion block, and posterior access of BPB anterior access the neck slightly flexed, keep the nerve stimulator output constant between 0.5 and 1.5 mA under ultrasonography guiduance8-11MHz[2]. The posterior approach provides less motor block than the anterior approach. Patients on anticoagulants who undergo (BPB) should be managed with the precautions and require accuracy and professional skills from an anaesthesiologist. Ultrasonography guidance will be helpful to perform BPB avoid blood vessel puncture.

Poster No. III-14

Psychophysical characterisation of persistent pain after video assisted thoracic surgery

Wildgaard K[1], Ringsted TK[1], Hansen HJ[2] & Kehlet H[1]; [1]Section for Surgical Pathophysiology and [2]Department of Thoracic Surgery, University of Copenhagen, Rigshospitalet, Denmark

Summary: Introduction of video assisted thoracic surgery (VATS) is believed to reduce the incidence of post- thoracotomy pain syndrome (PTPS). Though nerve damage during VATS has been suggested as an important component for the development of PTPS (1), no detailed psychophysical characterisation has been presented.
Design: Psychophysical follow-up on a cohort 34 ± 13 months after VATS.
Methods: 13 patients (median NRS = 5) with PTPS and 32 patients without PTPS underwent a detailed quantitative sensory test protocol in order to assess sensory dysfunction. Sensory dysfunction on the ipsilateral underarm was compared between pain and non-pain patients and the operated side of the thorax with the control side in pain and non-pain patients. Finally we also compared side-to-side differences between pain and pain free patients.
Results: Pain patients did not show signs of general pain hypersensitivity when compared to pain-free patients, as assessed by QST on the ipsilateral underarm. Both pain ($p=0.009$) and pain-free patients ($p=0.032$) had increased tactile detection threshold on the operated side when compared to the control side. Furthermore both groups showed reduced pressure pain tolerance threshold on the operated side ($p<0.001$) compared to the control side. Cold detection threshold was increased on the operated side compared to the control side, but only in pain-free patients ($p=0.008$). When comparing +/- PTPS in regards to side-to-side differences, tactile detection threshold was raised in the PTPS group ($p=0.011$).

Conclusion: These findings suggest that nerve damage is present after VATS surgery, but other factors may contribute to PTPS. Overall sensory dysfunction seems less than we found in thoracotomy.

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Poster No. III-15

Neurophysiological characterization of persistent pain after laparoscopic inguinal hernia repair

Linderoth G[1,2], Werner MU[3], Kehlet H[1] & Aasvang EK[1]; [1]Section of Surgical Pathophysiology, [2]Section of Acute Pain Management and Palliative Medicine, and [3]Multidisciplinary Pain Center, University of Copenhagen, Rigshospitalet, Denmark

Background: Approximately 5% of patients undergoing laparoscopic inguinal repair experience persistent pain influencing everyday activities. However, compared with persistent pain after open repair, the clinical and neurophysiologic characteristics have not been described in detail. Thus, the aim of our study was to describe and classify patients with severe persistent pain after laparoscopic herniorrhaphy.
Methods: Eleven patients with severe persistent pain following laparoscopic inguinal herniorrhaphy were assessed in detail by medical history, questionnaires (impairments of daily activities, pain description, psychological parameters, and socioeconomic status), physical examination, sensory mapping and quantitative sensory testing.
Results: Median years since operation were 2 (range 1-14). The patients could be divided into three groups according to the pain localization and the QST-findings. Group I (n = 2) had inguinal pain without cutaneous hyperalgesia, group II (n = 5) had inguinal pain with cutaneous hyperalgesia and group III (n = 4) had pain outside the inguinal region with 3 patients demonstrating cutaneous hyperalgesia for mechanical or cold stimulation. Four patients experienced dysejaculation. Seven patients were unemployed or retired due to the post-herniorraphy pain.
Conclusions: These results suggest that patients with severe persistent pain after laparoscopic inguinal herniorrhaphy present with varying degrees of neuropathic and inflammatory pain, in different anatomical locations, thus demarcating it from persistent pain following open groin hernia repair. A classification based on larger materials is required in order to define mechanism-based treatment strategies.

Poster No. III-16

Chronic post-traumatic oro-facial pain (PTDFP) and non-painful complaints. Case report

Sevastjanova M[1] & Kirznere J[2]; [1]Oral and Maxillofacial Surgery and [2] Stomatologic Institute, Riga Stradins University, Latvia

Craniofacial contributions to long-term persistent PTOFP are admitted as a result of convergence between trigeminal and upper cervical spinal nerves. Lack of early detectable pathology or similarity with other pain disorders makes difficult clinical diagnosis.
Case report: A 43 years aged woman suffered about 15 years from recurrent unilaterally pain in the right submandibular region irradiated to eye and face.

Last 7 years patient reported non-painful problems with swallowing and feeling of „fish-bone" in right side of throat.
Without objective organic and neurologic findings patients condition was interpreted as developing chronic PTOFP after blunt head-neck injuries (fall back) in ages 12 and 18 years, last with damage of trachea and cervical emphysema. Treatment options include neurological symptomatically, psychiatric, tonsilectomia at least.
Last CT re-examination reveals loss of physiological cervical lordosis, degenerative changes in atlantoaxial joint and calcific degenerative changes of hyoid bone. Rhteumatoid and mineral metabolism diseases are excluded.
Summary: Seemingly more sufficiently applied knowledge of craniocervical dysfunctions helps to recognize possible pathophysiological mechanisms of complaints. Although, remains questionable preventive treatment approach.

Poster No. III-17

Can peroperative, subcutaneous injection of bupivacaine-adrenaline close to the fascia decrease the need of opiates after caesarean section?

Niklasson B[1], Börjesson A[1], Carmnes U-B[1], Segerdahl M[2], Georgsson Öhman S[3] & Blanck A[1]; [1]Department of Obstetrics and Gynaecology and [2]Department of Anesthesiology, Karolinska University Hospital, Sweden, [3]Sophiahemmet University College, Stockholm, Sweden

Background: A central difference between patients undergoing caesarean section and patients undergoing abdominal surgery for other reasons is that the first category is supposed to immediately take care of a newborn baby. Active pain management will improve interaction between mother and child, improve breastfeeding, enhance mobilization after surgery and decrease complications. The risk for persistent pain has been shown to increase with ineffective pain management. **Objective:** The aim of the present study was to investigate if the local anaesthesia would decrease the need of postoperative opioids and to evaluate the effect on pain at three, six and twelve month after the caesarean section.
Design: Randomized, controlled, double-blind study.
Participants: 266 patients (general anaesthesia (n=6), spinal anaesthesia (n=260)) undergoing planned caesarean section at the Karolinska University Hospital, Huddinge.
Interventions: Women were allocated to one of two pain management groups, i.e. subcutaneous injection of 40 ml bupivacaine-adrenaline (0.25% and 5 mg/ml) or 40 ml 0.9 % saline solution, close to the fascia.
Results: Single injection with bupivacaine-adrenaline decreases the need of opiates the first twelve hours after caesarean section. Using follow-up questionnaires at three, six and twelve months after the operation a number of women reported pain but no significant differences between the groups were found. At three months 83 women reported pain, mostly around the surgical site. At six months 61 women reported pain and in the last questionnaire 43 women still reported pain, mostly in the neck, shoulder and back.
Conclusion: Local anaesthesia with bupivacaine-adrenaline is a simple and safe strategy to decrease the need for postoperative opioids during the first 12 hours after caesarean section.

Poster No. III-18

Postoperative pain assessment following general and orthopedic surgery

Marchertiene I, Kaciuriniene V, Macas A, Mikalauskas A & Teberaite Z; Clinic of Anaesthesiology, Kaunas Medical University, Lithuania

The aim of this study was to evaluate the pain intensity according to type of the surgery, method of the postoperative pain management and gender. METHODS: A prospective trial of 200 patients scheduled for elective major and orthopaedic surgery. Pain and the overall patient satisfaction with pain treatment were assessed on 5-point verbal rating scales on arrival to the postoperative ward and every next hour up to 5 hours after operation and daily thereafter up to the 4th postoperative day(POD). The pain treatment was controlled by nurses and included NSAIDs with opiates as needed after major surgery and continuous epidural infusion (local anaesthetics and opiates) after orthopaedic surgery. 91 of the patients were interviewed by the telephone on the 7th day after discharge from hospital. RESULTS: 156 (78%) of the patients reported experiencing pain on the 1st POD: 38%- suffered moderate pain, 20.5% - severe pain and 2.5% – very severe pain. 22% of the patients reported no pain on the 1 POD. Women suffered more pain than men (p=0.02). The pain occurred only on awakening after general anaesthesia (77.5%) and within 1-4 hours after operation with combined (both regional and general) anaesthesia. Compared with patients who underwent orthopaedic surgery, those who underwent major surgery reported more pain (63.4% vs. 89.3%) on the 1st POD. The majority of patients reported the pain gradually decreasing during 2-3-4 POD. Severe pain was felt in 10.5% of the patients on POD 2, in 2.3% -on POD 3, and in 1.7% on POD 4. Moderate pain was reported in 45%, 32.7% and 12.4%, mild pain- 34.5%, 47.1% and 44.2% of the patients on POD 2, POD 3 and POD 4 respectively. 38.5% of the patients suffered pain on 7 day after discharge from the hospital: 16% of the patients felt mild pain after major surgery and 28%- moderate pain after orthopaedic surgery. More than 90% of the patients were satisfied with the pain management during study period. CONCLUSION: Patients perceive significant postoperative pain under standardized pain treatment. Assessment of postoperative pain in surgical recovery wards by staff members is fairly limited. The patient satisfaction with analgesia as an optimal quality outcome of postoperative pain management may be questioned.

Poster No. III-19

Chronic pain following thoracic surgery in patients with pulmonary malignancies

Grosen K[1], Petersen GL[2], Pfeiffer-Jensen M[3] & Pilegaard HK[1]; [1]Department of Cardiothoracic and Vascular Surgery, [2]Danish Pain Research Center and [3]Department of Rheumatology, Aarhus University Hospital, Denmark

Previous studies have shown that chronic pain is a frequent and serious complication following thoracic surgery. However, the prevalence of chronic pain following both thoracoscopy and anterior thoracotomy in patients with pulmonary malignancies is poorly characterized and the impact of this pain on patients' lives remains unclear. Thus, this study aims to investigate the prevalence of chronic pain following thoracoscopy or anterior thoracotomy, and the severity and impact of persistent post-surgical pain on daily life.
A questionnaire was sent to 702 patients who had undergone thoracic surgery for pulmonary malignancies between 4 months and 10 years ago at the Department

of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Skejby, Denmark. The questionnaire included questions on the presence of chronic pain, chronic pain duration, localization, severity, characteristics, neuropathic symptoms and the impact of this pain on patients' lives. Patient characteristics, information on surgical procedures and continuity of care will be retrieved from both medical records and from the National Danish Lung Cancer Registry.
We are currently recruiting participants for the study. At present, 552 patients (78.6%) have accepted to participate in the study. We expect to find a lower prevalence of chronic pain following anterior thoracotomy compared with previous studies of chronic pain following posterolateral thoracotomy, and that this pain affects health related quality of life. Results will be ready for presentation at the symposium in October 2010.

Poster No. III-20

A Very Early Phantom Limb Pain (PLP) after Lower Extremity Amputation. A Case Presentation

Cadavid AM & Mayungo T; Anesthesiology, University of Antioquia and Hospital San Vicente de Paúl, Colombia

A 19 year old male patient was admitted to our hospital after a complex trauma in his left lower limb. Had a series of reconstructive surgeries in an effort to save the limb, with postoperative pain (POP) treated with IV opioids. He needed several interventions and debridement of dead tissue on his leg that failed to control infection, and patient had a below the knee amputation two months later. The acute pain service was consulted because this patient developed a severe PLP 18 hours after surgery, described as "pressure" pain, excruciating, in the absent foot that respond poorly to an IV PCA with morphine and NSAIDs. The second day we added a ketamine infusion, decreasing his pain level to 3/10 on VRS. He continued to have episodes of moderate to severe stump and phantom limb pain requiring multimodal analgesia for neuropathic pain on his follow-up.
Discussion: PLP usually starts between the third weeks to the first year after surgery. It has been reported to occur as early as 1 week after amputation (1). Our patient developed severe PLP in a very short postoperative period, refractory to opioids. Although there is a positive correlation between intensity of preamputation pain and incidence of PLP (2) we support the hypothesis that duration of pain, inflammation and/or opioid use before amputation constitutes an additional factor for developing a faster and more severe PLP. These phenomena may occur after intense cortical and spinal sensitization, in this case demonstrated by a good response of patient to ketamine treatment, an NMDA antagonist compound, with central action instead of peripheral effect (3).

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Poster No. III-21

A systematic review of risk factors for persistent pain after breast cancer treatment

Andersen KG; Section for Surgical Pathophysiology, University of Copenhagen, Rigshospitalet, Denmark

Chronic pain is a considerable clinical problem after breast cancer treatment, affecting 25-60% of the patients. Development of chronic pain identified in other surgical procedures and in breast cancer, indicates a complex pathophysiology that involves pre-, intra- and postoperative factors. This review is a systematic analysis on methodology and systematics in research on the Post Mastectomy Pain Syndrome (PMPS) and persistent pain after breast cancer treatment in the period 1995-2010. The purpose was to clarify the significance and relative role of potential risk factors. Literature was identified by a search in PubMed and OVID, as well as obtaining relevant studies from a systematic review of reference lists. Studies were included and analyzed according to protocol. 60 studies were identified of which most were retrospective or questionnaires [1,2]. Only 3 studies included QST and only 26 studies were prospective. Furthermore, many did not respond modern principles of surgical and adjuvant therapy. The data show inconsistencies in definition of PMPS, treatment groups, as well as collection of pre- intra and postoperative data, precluding clear conclusions with regard to pathophysiologic mechanisms as well as rational strategies for prevention and treatment. A proposal for design of future prospective studies will be presented[1,2].

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Poster No. III-22

Predictors of chronic pain after vaginal hysterectomy

Kaciuriniene V, Ciudere J, Marchertiene I & Macas A; Clinic of Anaesthesiology, Kaunas Medical University, Lithuania

The aim of the study was to identify risk factors for chronic postsurgical pain after spinal anaesthesia for elective vaginal hysterectomy for benign conditions. METHODS: Retrospective study reviewed the clinical data, surgical procedure and consumption of postoperative analgesics from patient charts in 174 women who underwent vaginal hysterectomy performed under spinal anaesthesia. A standardized telephone survey was conducted by a blinded independent investigator after 6-16 months after surgery to evaluate pain (numeric rating scale 0-10) and functional outcome. Questions were about pain location, intensity, frequency, medical treatment and impact on daily living before hysterectomy and at the time of the study. Data were analyzed with the chi2 test and logistic regression ($p<0.05$ statistically significant). RESULTS: 102 women were reached by telephone after surgery. 36 (32.4%) patients reported pelvic pain within the last 3 months and the mean pain score was 4.41 (SD=3.42). In 34 (33.3%) women the pain in the pelvic region was before hysterectomy (OR=5.71; 95% CI 2.32, 14.02). Pelvic pain after surgery was associated with back pain before hysterectomy (OR=6.4; CI 1.22, 33.59) and back pain at the time of survey (OR=3.26; CI 1.33, 7.98), whereas back pain after hysterectomy was not significantly associated with back pain before surgery ($p=0.17$). Previous pelvic surgery was another independent risk factor for chronic pelvic pain (OR=3.26; CI 1.05, 7.86). There was no difference in the prevalence of chronic

pelvic pain between women who had received spinal morphine for anaesthesia (47 of 102, 43.1%) and those who had not, but spinal morphine was associated with less back pain after surgery (OR=0.26, CI 0.09, 0.69). Tendency toward chronic postsurgical pain was seen for additional analgesics on the first postoperative day (p=0.074; OR=4.4) and the type of plastic surgery (p=0.073; OR=0.29). CONCLUSION: Pain persisting after vaginal hysterectomy performed under spinal anaesthesia is most often related to preoperative factors. We recommend prospective study including neurological assessment for patients with high risk for chronic postsurgical pain to explore in more detail the issues surrounding back pain history and chronic pelvic pain.

BENZON SYMPOSIUM No. 57

ACUTE PAIN - PATHOPHYSIOLOGY AND RISK FACTORS FOR CHRONIFICATION

OCTOBER 4-7, 2010, COPENHAGEN, DENMARK

Organizing committee:

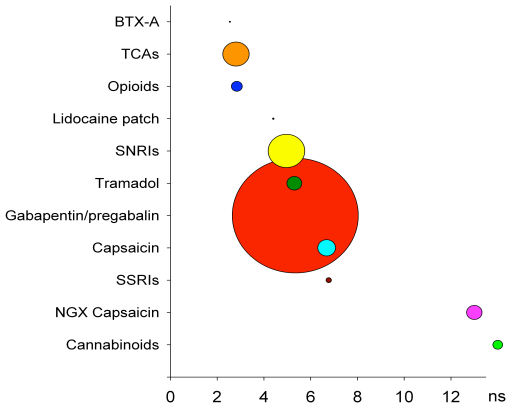
Henrik Kehlet (Copenhagen), Troels Staehelin Jensen (Aarhus), Arne Svejgaard (Copenhagen) & Povl Krogsgaard-Larsen (Copenhagen)

Abstracts - THURSDAY, October 7, 2010

Update on Existing Pharmacological Treatment in Neuropathic Pain

Finnerup NB[1], Sindrup SH[2] & Jensen TS[1]; [1]Danish Pain Research Center, Aarhus University, Denmark, [2]Department of Neurology, Odense University Hospital, Denmark

Over 170 randomized controlled studies have evaluated the effect of pharmacological agents for neuropathic pain conditions, including postherpetic neuralgia, painful polyneuropathy, peripheral nerve injury, and central pain [1]. Tricyclic antidepressants (TCAs), serotonin noradrenaline reuptake inhibitors (SNRIs), the anticonvulsants gabapentin and pregabalin, lidocaine patch, and opioids are recommended as first- or second- line treatment of neuropathic pain [2].



NNT (numbers needed to treat) for more than 50% pain relief

Other drug classes seem to relieve neuropathic pain in subgroups of patients, but more trials are needed to evaluate the overall effect and predictors of efficacy of these drugs, which include lamotrigine, oxcarbazepine, carbamazepine, valproate, and lacosamide. Topical treatments with botulinum toxin A and high-dose capsaicin are new treatment modalities which seem to have an effect on peripheral neuropathic pain.

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Potential new Targets in Persistent Pain: One or Multiple Mechanisms?

Dickenson A; Neuroscience, Physiology and Pharmacology, University College London, United Kingdom

The mechanisms of pain and analgesia exhibit plasticity in different pain states in that the signaling mechanisms change following physiopathological events. Understanding this plasticity has lead to improved understanding and therapies for the two broad major types of pain, neuropathic and inflammatory pain.

However, despite its prevalence, chronic pain continuing long after a peripheral trauma has received much less attention. Tissue heals with time whereas nerves have very limited capacity for recovery after damage. Thus, post-traumatic pain is highly likely to be neuropathic in nature.
Tissue damage leads to ongoing chemical activation of pain sensors whereas nerve trauma induces alterations in the function and levels of ion channels in peripheral nerve fibers and this altered sodium channel function can produce abnormal impulse propagation towards the spinal cord. Familial pain disorders point to the importance of changes in sodium, TRP and other channels. Next, impulses arrive in the central terminals of afferent fibers where altered calcium channel function is precipitated by the peripheral damage, leading to more transmitter release, favoring central spinal hypersensitivity. NMDA receptor activation in persistent pain states, in concert with other systems, generates wind-up and long term potentiation, plausible mechanisms for enhanced and prolonged pain states. Memory related genes are also activated. In patients, the intensity of the post-traumatic surgical pain is a predicator of chronicity and these spinal changes are likely to be intimately linked to the prolongation of the pain state.
Centers of the brain important in emotional and aversive responses to pain now join in. These centers in the brain will be activated not only by pain but also by "top-down" processes such as fear, anxiety and other life-events. These pathways, many of which are monoamine, can then descend to facilitate spinal mechanisms of pain showing the key interplay between sensory and psychological events in pain processing. Thus there are clearly multiple mechanisms.

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Preemptive Analgesia: Fact or Fiction?

Brennan TJ; Department of Anesthesia, University of Iowa Hospitals and Clinics, USA

Persistent pain causes long-term distress, suffering, and disability with considerable associated health care costs. Frequently, acute injury or disease results in acute pain that subsequently develops into a chronic pain syndrome. In many cases, the timing and incident injury are not known and preemptive or preventative strategies may not applicable. An example of this is a whiplash associated disorder. In other cases, like surgery, timing of the injurious event in elective cases is known and preventative strategies should be implemented.
The perioperative period is ideal for translating concepts of pain memory, plasticity and preemptive treatments because of the nature of injury, its onset, duration and degree are generally known. Furthermore, predisposing factors can be identified.[1] Many studies using various analgesic techniques have not been able to consistently document a clinically meaningful relationship between the reduction of acute postoperative pain and the prevention of persistent pain.[2] Although it is agreed that persistent postsurgical pain represents an important clinical problem, much research is needed before we have a clear answer to its pathogenesis and as well as its prevention and treatment. Importantly, evaluation of predisposing factors is critical for developing potential preventative strategies.

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Predictors of Persistent Pain after Acute Injury

Raja SN; Anesthesiology & Critical Care Medicine & Neurology, Johns Hopkins University, USA

An increased knowledge of chronic pain that persists after an acute injury has led to a shift in paradigm- from treating chronic pain to preventing its development. Developing strategies to prevent chronic pain after surgery or acute trauma requires a better understanding of the risk factors and predictors of acute pain persisting as chronic pain. For example, the incidence of chronic pain years after surgery for breast cancer varies from 20-60%.[1] Mastectomy with reconstruction (49%) results in a higher incidence of persistent pain versus mastectomy without reconstruction (31%). Reconstruction that included breast implants had a greater prevalence of pain (53%) than reconstruction without implants (30%).
A cross-sectional nationwide survey of Danish women suggested that factors associated with persistent pain include young age, adjuvant radiotherapy but not chemotherapy, and axillary lymph node dissection.[1] Patients with pain complaints in other parts of the body had a higher prevalence of pain in the surgical area.[1,3] Other risk factors identified include psychosocial status, preoperative breast pain, and acute postoperative pain intensity.
Preoperative pain represents a consistent risk factor for development of persistent postoperative pain for a series of surgical conditions such as limb amputation, breast surgery, hysterectomy, thoracotomy and hernia repair. A better understanding of the predictors of post-surgical pain will help identify the subset of patients who are likely to require additional care to optimize their peri-operative pain management. Werner and colleagues critically reviewed the literature on the predictive factors for postoperative pain based on preoperative quantitative testing of a patient's basal pain perception and concluded that quantitative testing of pain perception predicted nearly half of the variance in postoperative pain experience.[4] This finding highlights the individual differences in pain perception and response to tissue injury.

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Strategies for Future Study Designs in Chronic Pain

Gilron I; Departments of Anesthesiology, Pharmacology & Toxicology, Queen's University, Canada

Chronic pain after surgery is a relatively frequent and devastating problem which can occur following at least one-third to sometimes more than one-half of certain surgical procedures (e.g. limb amputation, thoracotomy, mastectomy and herniorrhaphy). Since avoidance of surgery (e.g. primary prevention) is often

impossible and palliation of established chronic postsurgical pain (e.g. tertiary prevention) is often unsuccessful, much effort is being devoted to the development of secondary prevention measures, e.g. interventions administered before, during and after surgery with the intention of preventing transition to chronic pain. In order to optimally design future clinical trials of preventive interventions, several crucial issues must be considered. These include use of a procedure-specific approach and standardization and/or stratified treatment randomization with respect to surgical technique, predefined risk factors for transition and coexisting pre-surgical pain. Outcome measurement methods and definition of primary trial outcomes are equally critical to the design, analysis and interpretation of such trials. Using published examples of previous prevention studies, these and other issues will be discussed with the ultimate goal of optimizing clinical trial designs for the prevention of chronic pain after surgery.

Poster No. IV-01

Prevention of Phantom Limb Pain in a Routine Clinical Setting

Schug SA & Gillespie G; Pharmacology and Anaesthesiology Unit, University of Western Australia and Royal Perth Hospital, Australia

There continues to be disagreement on the best way to prevent post-amputation pain syndromes. A retrospective review was undertaken to identify if anaesthetic/analgesic techniques have an influence on development of such syndromes after below knee amputations (BKA) in a routine hospital setting.
This is a retrospective review of 53 patients who underwent BKA at Royal Perth Hospital over a two-year period. Patients were followed-up by a telephone questionnaire around 12 months post amputation. Patients were very specifically asked to differentiate phantom sensations from stump pain and phantom limb pain. Pain intensity was assessed on a numerical rating scale (0-10/10) and NRS>6 was defined as severe pain.
The overall incidence of phantom sensation was 94%, of stump pain 35% (mean NRS 5.8) and of phantom limb pain 56% (mean NRS 6.4). Severe phantom limb pain occurred in 58% of all phantom limb pain sufferers; 29 % of these patients had seen a doctor about this. While there was no effect of anaesthetic and analgesic techniques on the occurrence of phantom sensation, spinal anaesthesia (31%) and epidural anaesthesia/analgesia (12%) reduced the incidence of severe phantom limb pain compared with general anaesthesia/systemic analgesia (55%), despite frequent use of ketamine in the latter group.
Phantom sensations after BKA seem universal, but even stump and phantom limb pain are common. This pain is often severe and requires medical attention. Neuraxial blockade and in particular epidural anaesthesia/analgesia seems to be an effective way to prevent phantom limb pain in a routine clinical setting.

Poster No. IV-02

Risk Factors and Mechanisms for Persistent Postsurgical Pain after Total Knee Replacement

Buvanendran A; Anesthesiology, Rush University Medical Center, USA

Introduction: Total knee replacement (TKR) is regarded as a safe, cost-effective treatment for osteoarthritis providing substantial improvements in functional status and quality of life. However, for the 15% of patients dissatisfied after TKR, persistent postsurgical pain (PPP) of the operated knee is their most frequent complaint.

Methods: In 31 patients undergoing primary TKR, we evaluated PPP at 6 months after surgery, in addition to pre- and postsurgical SF-36 and KOOS questionnaires. Patients were evaluated at 1, 3 and 6 months after TKR to determine level of functionality and knee pain. PPP was defined as "pain in the operated knee at six months after TKR, with other causes of pain excluded and reported intensity on 0-10 NRS scale of ≥4".
Results: Preoperative total SF-36 score is an *independent risk factor* for the development of PPP. The preoperative SF-36 total score was predictive of PPP at 6-months (P=0.0185) with an odds ratio of 0.859 (95% confidence interval: 0.757, 0.975), indicating that a lower SF-36 total score (indicating poorer functional and psychosocial state) can lead to PPP. The preoperative scores on the KOOS activity of daily living (ADL) and KOOS quality of life (QOL) were not significantly different between the patients with PPP versus those without PPP at 6 months (P= 0.5819 for KOOS ADL and P=0.7008 for KOOS QOL). In addition, higher acute postoperative NRS pain intensity *independently* predicts increased incidence of PPP. The acute postoperative NRS pain intensity is significantly higher, by 1.3 NRS, for the PPP than the non-PPP group (repeated measures test, P=0.0358) and the predictive model trended towards significance (logistic regression, P=0.064) with an odds ratio of 1.86 (95% CI: 0.97, 3.58). Finally, we found that preoperative SF-36 total score was a predictor of 6 month KOOS ADL scores (P < 0.0001), specifically that high values of SF-36 predict high values of KOOS ADL (high functioning) at 6 months. Preoperative SF-36 total score also predicted KOOS QOL (P=0.0075), again with a positive relationship.
Discussion: The results indicate that broadly defined mental and physical functioning at preop (SF-36 scores) predict the development of persistent knee pain and predict the levels of ADL function and QOL at 6 months post TKR surgery. A full prospective study with at least 300 patients is needed to explore all of the risk factors and mechanisms, including importance (weighting) and interactions.

Poster No. IV-03

Tailored neurectomy for treatment of postherniorrhaphy inguinal neuralgia

Loos MJA, Scheltinga MRM & Roumen RMH; Dept of Surgery, Máxima Medical Center, The Netherlands

Background: Groin hernia repair occasionally leads to severe chronic pain associated with entrapped or damaged nerves. Conservative treatment is often unsuccessful. Selective neurectomy may be effective, but long-term results are scarce. The authors assessed the long-term efficacy of surgical neurectomy for chronic, postherniorrhaphy groin neuralgia.
Methods: A registry of patients with postherniorrhaphy groin pain treated by neurectomy was analyzed. Patients received a questionnaire evaluating the current pain intensity, overall treatment results, and effects on sexual intercourse-related pain. The risk factors for failure and presence of a learning curve were investigated.
Results: Fifty-four patients underwent a neurectomy over a 5-year time period, 49 of whom responded to the questionnaire (response rate, 91%). After a median follow-up period of 1.5 years, 52% claimed to be pain-free or almost pain-free (good to excellent), 24% reported some relief but still felt pain at a regular basis (moderate), and 24% did not benefit (poor or worse). Sexual intercourse-related pain responded favourably to neurectomy in two thirds of

patients. There seemed to be a steep learning curve, and poor treatment results depended on previously received pain regimens (P = .021).
Conclusion: A selective operative neurectomy for postherniorrhaphy groin neuralgia provides good long-term pain relief in most patients. Hernia surgeons should feel responsible for this iatrogenic complication and should consider incorporating selective neurectomy in their surgical armamentarium.

Poster No. IV-04

Development of a framework to establish core risk factor and outcome domains for chronic postsurgical pain studies

Bruce J[1], Peters M[2] & VanDenKerkhof EG[3]; [1]Epidemiology Group, Section of Population Health, University of Aberdeen, United Kingdom; [2]Department of Clinical Psychological Science, Maastricht University, The Netherlands; [3]Dept of Anesthesiology & School of Nursing, Queen's University, Canada

Objective: To propose development a core set of risk factor and outcome domains that would facilitate more complete reporting of potential risk factors and outcomes for chronic post-surgical pain (CPSP) at the population level.
Methods: Based on the best available evidence[1-2], we propose the use of standardized measurement tools for recording core risk factor and outcome domains for studies of CPSP, and the establishment of an electronic, secure and internationally accessible CPSP data repository.
Results: core risk factor and outcome domains were identified based on current literature. The proposed list of core risk factor domains include: pain, physical functioning, emotional/psychological functioning, perioperative factors and healthcare resource use. The core outcome domains include: pain, physical functioning, emotional/psychological functioning, global recovery, and healthcare resource use. Proposed standardized measurement tools are presented by domain. Finally, suggestions for possible measures to be included within a minimum dataset are included.
Conclusions: Future CPSP studies should examine core risk factor and outcome domains to facilitate data pooling and comparisons across studies/countries. Depending on the primary focus of a given study, domains may be excluded or others included. We propose a minimum core dataset for future studies of CPSP; this would facilitate more complete reporting and allow merging of datasets from different patient populations.

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2. Macrae WA. *BJA* 2008;101:77-86.