by Dr. Robert Bennett

The 10th World Congress on Pain was held in San Diego CA August 17 to 22, 2002. This is a triennial meeting organized by the International Association for the Study of Pain (IASP), the leading world body for pain researchers and clinicians. It was a truly massive and overwhelming meeting with 1788 presentations of one type or another. I do not have a precise number for the attendees, but my estimate is about 3500.

The first day was devoted to refresher courses. I took part in one of these courses devoted to rheumatic pain disorders, giving a one-hour talk on fibromyalgia (FM). The other two speakers were from the UK; Professor Michael Doherty spoke on osteoarthritis and Professor Bruce Kidd spoke on rheumatoid arthritis. I was gratified to learn that at least some UK rheumatologists are focusing their attention on pain mechanisms—but as in many countries this continues to be an uphill battle. There were many sessions devoted to the basic mechanisms underlying chronic pain states such as FM. Indeed, FM was frequently referred to in many of these presentations as being the classical example of a "central pain state". By this is meant that peripheral tissue causes of pain cannot be readily identified in most FM patients and that most of the action is at the level of the spinal cord and above. The neurophysiological and biochemical basis of central sensitization is now being unraveled in minute detail. Much of this work relates to neurochemicals and their interaction with specific receptors. This is the basis of the transmission of sensory impulses from one nerve cell to another. In order to make advances in this field one must devote a large chunk of a research career to just one very specialized topic. Needless to say, the arcane nature of this work makes it very difficult to understand unless one is an "insider". However, understanding the detailed mechanisms of neurochemical receptor interactions will be pivotal in the creation of designer drugs for treating chronic pain, while minimizing the unwanted side effects that plague many of the currently available medications.

Glial Cells Lecture

A state-of-the-art lecture, by Professor Linda Watkins from the University of Colorado in Boulder was particularly noteworthy. For the past 10 years or so, she has studied glial cells. Until fairly recently glial cells were considered boring, as their only known role was to provide a skeletal type support for nerve cells of the brain and spinal cord. Prof. Watkins discovered that glial cells can be activated by infections and other stresses, and they then interact with nerve cells to produce chronic pain states via the secretion of small proinflammatory molecules called cytokines. For instance, 90 percent of patients with HIV infection have chronic pain. Prof. Watkins has shown that one component of the HIV virus (gp 120) interacts with glial cells to induce a chronic pain syndrome. This of course may be of relevant to FM patients who trace the onset of their problem to an antecedent flu-like illness. Furthermore she has recently shown to that the introduction of a cytokine called interleukin-10 into the nervous system of mice with an experimentally induced chronic pain syndrome, attenuates their pain. Interestingly, interleukin-10 inhibits the actions of the pro-inflammatory cytokines. This is obviously exciting and important work which may eventually have a relevance to FM patients—stay tuned.

Fibromyalgia and CFS

There was an interesting symposium entitled "The Biopsychosocial Approach to Fibromyalgia and Chronic Fatigue Syndrome". It featured researchers with differing views as to the nature of FM and CFS. Dr. Milton Cohen, from Australia, asserted that two fundamental errors have been perpetuated in contemporary research on the clinical phenomenon of widespread pain and fatigue. The first is the failure to distinguish a clinical feature from a disease process, without a unifying concept. The second major error is the failure to focus on the neurobiology of the defining clinical finding—i.e. increased pain sensitivity.

Dr. Lawrence Bradley from Birmingham AL contested Dr. Cohen's statement regarding the lack of research on the neurobiology of FM and presented impressive evidence for abnormal pain processing and dysregulation of neuroendocrine function in FM. He noted that disorders such as FM, CFS and irritable bowel syndrome (IBS) had a large degree of overlap. But he also noted that not all persons with CFS showed the abnormal pain sensitivity of typical FM patients. Dr. Bradley concluded that a better understanding of the natural history of these overlap syndromes, looking at genetic contributions, developmental stressors and triggering events, will be essential in unraveling the relationships of these common disorders.

Fibromyalgia Posters

There were 27 individual poster presentations devoted to the topic of FM. Here I review the 9 that I consider to be most relevant and understandable for patients.

1—A study from France explored the efficacy of subcutaneous ketamine on improving pain in FM patients. Ketamine is a class of drugs known as NMDA receptor antagonists. In high doses it is used as an anesthetic. Activation of the NMDA receptor is a critical event in the biochemistry of chronic pain states. Fifty patients received subcutaneous ketamine (up to 50 mg daily) for ten days via an infusion pump similar to that used by diabetic patients. There was a significant improvement in pain scores in 78 percent of the subjects. At six months after discontinuation of the ketamine, 45 percent of the patients still showed improvement. This is an intriguing study but suffered from lack of a control group using a placebo.

2—There was a fascinating study from a New York group exploring the effects of the September 11th World Trade Center disaster on symptoms of FM. In a study prior to September 11 th, this group had screened a population of 9000 women in metropolitan New York and New Jersey for FM symptomatology and psychiatric symptoms. In February and March of 2002 they re-contacted 1000 of the same women to determine whether existing symptoms had changed. Interestingly they did not find any major changes in FM like symptomatology, although there was a minor increased in anxiety-related symptomatology. Interestingly, there was a significant reduction in the number of doctor visits. I asked the author of this study for her interpretation of the reduced doctor's visits. She conjectured it was due to a changed perspective of their problems in the light of the devastation wreaked upon so many others.

3-—There is an ongoing question as to whether FM may be set off by whiplash injuries resulting from motor vehicle accidents. A study from Switzerland applied an objective measure of increased central nervous system sensitization (the nociceptive withdrawal reflex) to 3 groups of subjects; one group with whiplash, another group with FM and a group of healthy controls. The FM and whiplash patients, but not the healthy controls, showed unequivocal evidence of increased central nervous system sensitization. This is an important study that brings some objectivity to this issue.

4—On the same subject, a group from Seattle looked at the onset of FM following whiplash injury. This is an ongoing NIH funded study which aims to eventually enter 400 whiplash subjects. To date 25 subjects have been studied and 20 percent have developed widespread pain, and 80 percent met the tender point criteria for a diagnosis of FM. The authors concluded that some of the findings of FM are common in women 2 to 3 months following whiplash injury. They suggest that part of this increased prevalence may be due to a clustering of tender points in the neck region —as expected in the soft tissue trauma following hyperextension/flexion injuries to the neck. But they also noted that the high prevalence of FM symptomatology is probably not entirely artifactual, as 68 percent of the whiplash subjects also demonstrated tender points in other parts of the body.

5—A psychophysical research study from Gainesville Florida studied FM patients and healthy controls with an objective measure of central sensitization called "temporal summation." They asked the question as to whether central sensitization could be modified by the placebo response, fentanyl (a long acting opioid drug) or naloxone (a drug that antagonizes the analgesic actions of opioids and the placebo response). They found that FM patients had increased levels of central sensitization compared to healthy controls. Temporal summation was attenuated by both placebo and fentanyl to a similar degree and was not influenced by naloxone. It was concluded that central sensitization, which is thought to be a critical component of increased pain sensitivity in FM, can be centrally modulated by both endogenous (i.e. placebo) and exogenous (i.e. fentanyl) manipulations. There is increasing evidence that one's own endogenous pain modulating apparatus, modulated by endorphins, involves the same neural pathways as opioid analgesics. Thus strategies aimed at activating a patient's own endorphin system, such as exercise, adopting positive coping strategies and having an optimistic outlook, are important tools in the effective management of FM.

6—Most physicians who specialize in managing FM patients believe that a multidisciplinary approach to treatment is an essential prerequisite for success. A Canadian group developed a ten-week program for FM patients which included education, group support, coping skills training, physical exercise in a pool, goal setting and daily activity diaries. Patients were seen in groups of 10 to 15. Overall 395 patients had been analyzed at the time this study was reported. Highly significant improvements were seen in the Fibromyalgia Impact Questionnaire (FIQ), a widely used outcome measure in FM studies. Women showed greater improvements than men, and women under 40 showed the most improvement.

7—A study from Brazil reported on the effects of acupuncture on pain and quality of life in patients with FM. Forty-eight women with FM were randomly allocated into 2 treatment groups. Group 1 received amitriptyline plus twice-weekly acupuncture sessions for 3 months. Group 2 received amitriptyline plus stretching and relaxation exercises twice a week. There was a significant reduction of pain intensity and improved function in both groups, but the acupuncture group had significantly better response than the other group. The authors concluded that acupuncture is an effective tool for treatment of FM patients.

8—A study from Salt Lake City attempted to evaluate whether FM patients would be more susceptible to pain experience during mammography and Pap smears. A questionnaire was sent out to 100 women who were randomly selected from a database of FM patients. Fifty- nine patients agreed to take part in the survey. They rated pain and anxiety during their last mammography and Pap smear on a scale of 0 to 10. The mean pain score was 4.32 for mammography and 2.45 for Pap smears. Mean anxiety scores were 2.33 during mammography and 2.2 to during Pap smears. It was concluded that women with FM experience a moderate amount of pain during mammography, and rate mammography as significantly more painful

than Pap smears. Anxiety levels were comparable between the two procedures. As pain is a deterrent to women for undergoing mammography, the authors suggested that more effective pain management during this procedure should be considered for those women susceptible to discomfort during mammography, such as FM patients.

9—A study from the UK evaluated the use of a new antidepressant drug called Reboxitine in a study of patients with FM and neuropathic pain. Reboxitine is a class of drugs that selectively inhibits the reuptake of noradrenaline. Thus its mode of action is somewhat similar to fluoxetine (Prozac) but it inhibits noradrenaline reuptake rather than serotonin reuptake. One of the mechanisms whereby the brain can control the relay of pain impulses upwards from the spinal cord is via a descending pathway from the midbrain which uses noradrenaline as a neurotransmitter. Thus it was conjectured that Reboxitine would modulate pain via this descending noradrenaline system. Twenty-five women with FM and 14 with neuropathic pain (nerve pain arising from conditions such as diabetes or shingles) were included in the study. Eight (32%) of the FM patients had a very significant reduction in pain intensity and 6 elected to continue with Reboxitine after the trial ended. Six (43%) patients in the neuropathic pain group reported significant pain reduction but only one wished to continue using Reboxitine after the study ended. The reason for not continuing with the medication after the end of the study was the side effects of insomnia and agitation. However, in some patients the sense of agitation was interpreted as a feeling of increased energy, which was particularly welcome in some FM patients. This study did not contain a placebo control group and thus the specificity of the Reboxitine effect cannot be assessed.

Summary

Overall the 10th World Congress on Pain was a stimulating and somewhat exhausting experience. As is often the case with large international conferences one was subjected to intense information overload. However, I came away with a sense of awe at the magnitude and quality of the research which is being done worldwide to reduce the burden of chronic pain. As an FM researcher, I was gratified to see that the diagnostic term "fibromyalgia" is being used increasingly by pain researchers who often refer to it as a "classical example of central sensitization." As a rheumatologist, I am increasingly impressed that FM is primarily a neurological disorder which presents as a musculoskeletal pain syndrome. Having said that, I believe that rheumatologists will continue to be the major specialty who treat FM, as the correct diagnosis of musculoskeletal pain is complex, and furthermore there is often an overlap of FM with chronic rheumatic problems such as osteoarthritis, lupus, and rheumatoid arthritis. Interestingly, neurologists seem to be one of the last standouts in accepting the FM concept.

Dr. Bennett is an internationally known FM specialist, Professor of Medicine at Oregon Health Sciences University (OHSU), and Chairman of Arthritis and Rheumatic Diseases Division.

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