PANEL ON PAIN RESEARCH

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FINAL REPORT

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BACKGROUND

The National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health sponsors research and research training activities in dental, oral and craniofacial disorders and diseases through its intramural and extramural programs. Its research support portfolio includes a strong component in orofacial and other aspects of pain, ranging from the genetic analysis of nociceptor function to experimental therapeutics for acute and chronic pain. The Institute has convened several expert panels in the past year to help it identify long-range research opportunities in a number of science areas central to its mission. As part of this initiative, the Institute convened a Panel on Pain Research on May 13, 2003. This is a summary report of the Panel's deliberations and recommendations.

The Director of NIDCR opened the meeting by thanking the participants for contributing to this important activity. He indicated that many of the Panelists were aware of the history of NIDCR's involvement in pain research, both intramurally and as the leader in the trans-NIH Pain Consortium, which was established in 1996. Recently, NIDCR has worked closely with the NIH Director to revitalize the Consortium in 2003. This effort dovetails, furthermore, with the road map initiatives being developed as trans-NIH programs that identify scientific opportunities to serve as a framework for developing NIH budgets for 2005 and beyond. The road map activity focuses on 3 general themes, the building blocks of biology, multidisciplinary teams for the future, and the reengineering of the clinical research enterprise. Pain research certainly relates to all 3 themes and so the time is ripe to reassess the future of pain research and to move it forward at the NIH and at NIDCR. The Panel was asked to suggest how the Institute could best catalyze the opportunities and its resources to accomplish this. Pain research is a good example of an activity that no one Institute or Center can do on its own, and NIDCR will be looking for leverage through partnerships to enhance this area of research and take advantage of the resources of NIH.

NIDCR supports about 15% of the research related to pain at the NIH, but has 1.4% of the NIH budget. About 85% of NIDCR's funds go to the extramural community and 10% to the intramural programs. Much of what will be discussed today will apply to the external community, but we do have a significant presence on campus in terms of pain research and it is clear that the intramural program will take advantage of the opportunities that are identified.

The Pain Consortium is being restarted and it could be a perfect example of the type of program that transcends individual Institutes and Centers, both extra and intramurally. In addition, NIDCR has issued a Request for Applications (RFA) for a Center program and pain is one of the areas in which we are encouraging applications.

STATE OF THE SCIENCE PRESENTATIONS

Some members of the Panel were asked to make presentations on the "state of the science" in important aspects of pain research and to identify emerging opportunities in those areas. Dr. Jeffrey Mogil presented an overview of the use of genetic techniques in pain research. We have a good idea now of the sub-cortical anatomy and neuro-chemistry associated with pain transmission and pain modulation, and with recent advances in imaging techniques, we are also improving our understanding of what is happening at the cortical level as well. The trend in the last 20 years has been to understand the phenotype and the genes coding for important proteins and their interactions with each other. One type of approach is to define the molecular building blocks (i.e., the proteins) of pain, and it turns out that it is easier to do this by studying the genes rather than the proteins themselves. The second approach is genetics as the study of variability and of inherited individual differences.

There are two types of "pain genes" that can be considered. If a protein is involved in pain, then the gene coding for that protein is a pain gene. Some of these genes are poly-morphic and exist in different allelic forms with some reasonable frequency in the population. These are the ones responsible for individual differences. A number of options are available to identify pain genes. The majority of studies involve picking a gene and knocking it out and see what effects that has on the top-level behavioral phenotype. Another approach is to start with the behavioral phenotype and search for the genes (of the 35,000 present in the genome) that are responsible for that phenotype. Two ways to do this are linkage mapping and gene expression profiling.

A number of genes (approximately 45) have been identified in knockout mice that are associated with altered sensitivity for thermal nociception alone. A lot of these are potential new targets for drugs with better side-effect profiles than the ones available now. But the problem is to determine which of these genes are really critical, and we cannot make global concepts out of such a list. We need to figure out which genes are "cause" versus "effect" and if there are any "master" genes responsible for the differential expression of other genes. We need to know which of these genes are involved specifically in thermal nociception, but not in mechanical or chemical nociception and which are involved in nociception across the board.

A technique that has been used in the Mogil lab is complex trait genetics (linkage mapping). It is well known that humans exhibit great variability in their sensitivity to pain. It is the case, apparently, that less than 15% of people receiving major peripheral nerve injuries go on to develop chronic pain. Chronic pain after injury may be the classic example of gene-environment interaction. So, figuring out if there really are susceptibility or propensity genes for chronic pain might be a key to understanding whether there is a conversion from a nociceptive to a neuropathic pathological state. There is a wide range of heritability estimates for various pain-related traits, but there are problems continuing to plague association and linkage studies in humans. The solution is linkage disequilibrium mapping which combines the best features of both, but is very expensive, though it will happen in the next few years for some diseases.

In the meantime, we need to do genetic studies in animals and the question is, is this okay? Now that the human and mouse genomes have been sequenced, it has been found that only 2-3% of genes in each are species-specific. There are analogs in each genome probably doing the same things. And so, mouse pain genetics should actually work. We have investigated kappa-opioid analgesia in the mouse and formed a linkage to a particular end of chromosome 8 in female (but not male) mice. We picked a candidate gene, the melancortin-1 receptor gene, and obtained and tested spontaneous mutants of this gene. We looked at the human analog, which turns out to be the gene responsible for red hair and found that female redheads had higher pentazocine analgesia than all other groups, a finding directly predicted by the mouse data.

Despite the fact that we are using all these new molecular approaches, it is important to remember that the entire exercise depends on the animal model and that the power of the genotyping is only as strong as the accuracy of the phenotyping. There has been good progress in pre-clinical pain models and we have gone from acute models to chronic models, but most models are still inadequate. The acute models may not be clinically relevant and the chronic models, to a large extent, measures the wrong thing, (hypersensitivity to evoked stimuli, both thermal and mechanical); there remain no models of chronic, spontaneous neuropathic pain itself.

Some Panel members argued that measurements of spontaneous pain are available, but others felt that the core issue is not being addressed by the usual measurements done in animal models. The practicality of doing the right measurements is just not there. Validation is what may be lacking. The same issue regarding the validity of the measures occurs in the behavioral and psychological study of pain because they are not believed by biologists as indices of what is really going on. The future requires that the two universes (behavior and biology) interact and interrogate each other. In a related dimension, there is an easier association between animals and humans in inflammatory pain models. However, there is a real dissociation in neuropathic pain models. In addition, the profusion of models and lack of consensus has prevented the consolidation of findings between models. There are incentives for the proliferation of models, but if a mechanism is going to be translationally valid, it has to be effective in more than one model. There has to be an instrument that everyone accepts and uses to be able to do translational research and to bridge the preclinical and the clinical sides.

Comments were also made about the role of the environment and its influence on the genotype. The problem is that the genotype is quite finite but the environment is infinite, and we may not be able to figure out what the environmental factors are or what can be done about them. There is emerging evidence that early experiences are important in how people respond to later painful situations.

Dr. John Levine (UCSF) indicated that the peripheral nervous system is the site of initiation of the pain in the vast majority of pain syndromes, and that if you block its activity, you eliminate pain in the majority of patients with acute or chronic pain. A great deal has been learned about the transduction mechanisms in the primary afferent sensory neuron for pain (i.e., the nociceptor). Nociceptors transmit information to the CNS but

also release mediators at their peripheral terminals, which can produce or enhance an inflammatory response. Although nociceptors are a functionally heterogeneous group of sensory neurons, we can extract RNA from individual cells and reconstruct the biochemical pathways that are present in them and compare them with other cells to determine what makes a nociceptor, as well as examine changes that occur in these biochemical pathways under pathological conditions. While molecules in nociceptors (i.e., acid-sensing ion channels, vanilloid receptors, etc.) were thought to be unique to pain sensory neurons, they are now known to be part of much larger families and not uniquely found in sensory neurons. Thus, it may well be the interaction between these molecules what is unique to nociceptors. For example, sustained stimulation of nociceptors produces pain sensation, which increases with time, in contrast to other sensory modalities in which intensity of the sensory experience decreases in the presence of sustained stimulation.

Clinical interest in the biology of the nociceptor focuses not so much on the transduction processes (i.e., nociceptive pain) but on the alterations in transduction that occur in the setting of inflammation or nerve injury. With respect to inflammatory pain, the earliest models suggested that many of the pain-producing mediators produce sensitization of the nociceptor and enhanced transduction via a common biochemical mechanism, and the hope was that this pathway could be targeted, providing a whole set of analgesic agents that would work peripherally, never having to get into the central nervous system. It is now clear that multiple pathways, signaling in parallel as well as with cross talk between the pathways, contribute to pain associated with inflammation. The number of ion channels involved in molding the function of the nociceptor has now grown significantly and this needs to be addressed if progress is to be made in terms of clinical relevance. There must be multiple mechanisms in a very complex system and the ability to put this system together, including identification of the molecular isozymes involved, is a major goal in pain research.

There is a growing body of literature, both from animal experiments and clinical studies, that there is a dramatic sexual dimorphism in pain and analgesic mechanisms, at all levels of the neuraxis, including the primary afferent nociceptor. These sex-related differences in nociceptor function are regulated by sex hormone status, especially that of estrogen. This sexual dimorphism in pain mechanisms needs to be understood in terms of the incidence and severity of, for example, inflammatory diseases, most of which are more common and more severe in women.

While there has also been a “maturing” of our understanding of the mechanisms underlying neuropathic pain, currently the most severe and intractable pain syndromes requiring management of their symptoms, there is still a great deal we do not understand in terms of how injury induces changes in nociceptor function and whether injury induced by toxic (e.g., chemotherapy), traumatic (e.g., CRPS-I/RSD), metabolic (e.g., diabetic) or infectious (e.g., AIDS) results cause similar or different changes. Such information is critical to elucidating novel therapies for the various neuropathic pain syndromes. The way that the mechanisms responsible for neuropathic pain can be elucidated is to develop clinically relevant models and to show a more direct correlation

between several levels of analysis, from behavior and physiology, to molecular and cell biology, and genetics.

The complexity of the issues is certainly evident. In addition to a large number of ion channels in individuals nociceptors, there are also multiple isoforms of various enzyme systems and multimerization of these molecules well as various splice variants. There are also issues of functional compartments at the sub cellular level and elucidating them will help in understanding the pathophysiological changes that occur in clinical pain syndromes. The transition from acute to chronic pain involves plasticity at multiple levels, from molecular plasticity to environmental plasticity and these need to be understood if progress is to be made.

Being able to get from the bench to the bedside, and back again to validate concepts more fully, is going to be real test of whether we are likely to be successful in treating patients with intractable pain, or not. As far as is known, the mechanisms underlying pain in the head and neck are the same as elsewhere in the body and the ability to elucidate those mechanisms will impact on multiple aspects of medicine and health care. Interdisciplinary approaches and interdisciplinary-trained physician-scientists are needed to allow us to cross the boundary between bench and bedside.

In the ensuing discussion, it was mentioned that the issues highlighted are those of modern cell biology. The translational and clinical research issues are also evident and more should be done about defining and characterizing chronic pain. The definition of chronic pain as a function of time is a convenience in the clinic. The implications of chronic pain start when there are changes in the functioning of the person, independent of the progression of the pathology. Both temporal and spatial dimensions are needed to define chronic pain and it is important to recognize that chronic pain is a state in which there has been reorganization (i.e., plasticity). Many of the currently used animal models of chronic pain use a time frame (i.e., 7 days) during which this plasticity may not yet have occurred.

The type of pain being discussed is pain as a disease itself. When talking about cardiac pain (angina) a note of caution has to be indicated as blocking it can eliminate the danger signals that it provides, as well as attenuate input to the nervous system that can have negative consequences for the patient. The issue of pain as a signal comes up in any disease and pain itself or its intensity can be considered as an outcome. The issue of engaging other NIH Institutes in pain research was discussed, and Dr. Tabak indicated NIDCR has to take the lead in areas that are related to our core mission and to encourage others through the Pain Consortium to address the many potential opportunities that exist. The Pain Consortium uses resources housed within the participating Institutes and Centers, but there is now a real opportunity to make it a powerful engine of support through the road map initiatives of the NIH Director. The Consortium can be used as the ideal road map initiative in terms of multi disciplinary research, and of other road map guiding principles.

Dr. Michael Iadarola spoke about primary afferent neurons and their work on vanilloid Type I receptors. Pain, or more accurately nociception, can be broken down to 3 steps before it hits the brain: the genesis, the transmission, and the processing in the spinal cord. The primary afferent neuron connects the elements at both ends and is loaded with receptors to modulate signal transduction and potential generation. Most aspects related to individual variability in pain perception occur above the neck and there is a large number of circuits that are activated, some dependent and some independent of the intensity of pain. Below the neck there is a lot of modularity and one of the modules is the vanilloid I receptors. These are membrane receptors and have a six trans-membrane domain with a core loop between domains 5 and 6. The receptor exists as a tetramer in the membrane and can be phosphorylated by PKA and PKC dependent processes. A I EGFP fusion protein of the vanilloid receptor was made and transfected into Cos-7 cells. The protein is expressed well and is highly localized in the endoplasmic reticulum.

Exposure of these cells to Capsaicin or to Resnifertoxin (RTX) activates calcium uptake. The latter drug also activates uptake in the axon, leading to the idea that there is an axonal localization of VR1 and that this may contribute to chronic pain. The VR1 in the ER can be activated independently and calcium release and uptake is very important, particularly the calcium-induced calcium release from the ER. The vanilloid receptor can desensitize under many different conditions and release of VR1 through the plasma membrane has deleterious effects on the cell. The calcium-induced calcium release preserves the function of nerve endings in prolonged pain states and provides a controlled source of intracellular calcium. Dehidroexphenylglycine blocks the desensitization. So, this G-protein coupled receptor modulates the activity of an important depolarizing ion channel in the pain-sensing cell. And there are a lot of activators and sensitizers, including glutamate, bradykinin, NGF, protons and metabalites.

When RTX is added to both the ER and the mitochondria, the cell dies and microinjection of the trigeminal ganglion produces a denervation on one side of the face and removes pain-sensing cells in the ganglion. There is also loss of other sensibilities (hyper-algesia and thermal sensations to some extent). RTX could be given in the intrathecal CSF space. The concept was further explored in a different model, dogs with advance osteosarcomas or arthritis. They were injected intracisternally with RTX. The animals improved significantly and were essentially pain-free after 9 months. Panel members suggested that this needs to be approached with caution since neurolytic injections have unintended effects due to spread and may affect motor function (such as bowel and bladder functions). There were no problems observed with the animals in this regard, and they retained their pinch sensation and probably warm and cold sensations. This model introduces sub selective neurolytic therapy. For terminal cancer patients celiac block has been shown to be efficacious by rigorous meta analysis.

This offers an opportunity to try specialized procedure-based medicine, as there is a great need for true tailor-made treatments in pain. The goal of basic science is to find something interesting, while that of translational research is to find something useful and

practical. Translational research is costly and one has to comply with FDA regulations to do a clinical toxicology study. A question is how to handle the ethics of this type of study, as placebo and traditional therapy do not resemble the intervention being used.

A mouse library can be created for the molecular labeling of pain circuits, pain cells and pain molecules and study them in vivo. Subtypes of neurons and their interactions can be studied and be very useful in future research. The transcriptome in the dorsal ganglion suggests that there are 44,187 sequencing reactions, a number ten-fold lower than those of the spleen and mammary glands.

Imaging should be done as well. An important question is where in the brain, spinal cord or peripheral nervous system, is the physiological variability found. This may be associated with different areas of the brain.

Additional discussion focused on the specificity of the findings and their applicability to other species. For example, the rat VRI may be different from the dog and human receptor. It would be useful to develop therapies that worked equally well against dog and human enzymes, but unfortunately this often turns out not to be the case. The work shown by Dr. Iadarola involves the entire cell, or cell populations, rather than single molecules.

Dr. Kenneth Hargreaves spoke about the role of translational research. Orofacial pain is the most common form of craniofacial pain in the U.S. and is reported by 22% of the population or 39 million people. The major complaint is toothache and chronic or persistent types of pain are actually less than half as common. Surveys across the country indicate that 25-29% of respondents are highly fearful of dental treatment and this contributes to the avoidance of care. There is a parallel problem for clinicians in that with acute pain there is an eight-fold increase in local anesthetic failure. Central sensitization can play a role as well as changes (up regulation) of sodium channels. The acute pain problem is relatively homogenous in different populations and this facilitates research with less variance than those seen in chronic pain conditions.

Management of this highly prevalent pain is not highly successful and poorly managed acute pain is a risk factor for chronic pain. In terms of preclinical research, it can be said that preclinical models are actually pretty good but also have significant limitations. Animal research does not incorporate the biopsychosocial and environmental interactions that represent major components of the patient's pain complaints and response to treatment. There is a poor track record in terms of animal pharmacology. The NK receptor antagonists work extremely well in animal models but are largely ineffective in clinical trials. And there are issues in terms of SNPs and polymorphisms (that do not translate between animal SNPs and human SNPs). There is, therefore, a number of limitations that prevent routine translation between preclinical research findings and what actually works in patients. In transgenic animals, the expression levels of the target (e.g., receptor) can alter signal pathways and display a pharmacological profile that is not seen in the human tissue. Similarly, the expression level of receptors in transfected cell lines can dramatically alter their coupling signals and proteins.

An important aspect refers to the demographics of pain. There are pain conditions with clear age risk factors. One is trigeminal neuralgia. This a unique craniofacial neuropathic pain that is not seen anywhere else in the body. Another in post-hepatic neuralgia. The aging population in the U.S. needs to be considered in the research agenda.

The approach in translational research may be to consider information from preclinical studies and to incorporate mechanistic research into clinical trials. An example is genetic research focusing on humans and performing heritability studies. Patients who have congenital insensitivity to pain have almost 100% of their insensitivity due to polymorphisms in the TRK-A receptor. Other conditions (sciatica, migraine, dysmenorrhea) range from 20 to 60% heritability. In the dental field, the Minnesota twin study indicated that there was no evidence of heritability in TMD-related pain. This suggests that not all pain disorders are amenable to the genetic approach.

The other approach is to study polymorphisms. There are 2 hypothesis in this type of study: One is that common forms of a disease result from the most common polymorphisms in the gene; the second is the multiple rare variant hypothesis that there are probably many polymorphisms that serve as risk factors in a certain condition. The latter is probably more common in pain research.

Another example of translational research are studies that focus on central sensitization per se. They suggest that surgical pain may have a component that results from central sensitization. This in turn suggests needed changes in how clinician's use drugs such as local anesthetics for managing surgical pain. We have used a technique of microdyalisis in the surgical wound. Preoperative administration of 125 mg of steroid significantly reduced tissue levels of inflammatory mediators in humans experiencing surgical pain. Another approach is to take surgical biopsies and evaluate under in vitro conditions the pharmacology of peripheral nerve terminals. There is a 2-3 fold elevation in substance P in the affected tissue and pretreatment with receptor agonists blocks the release induced by capsaicin.

Another approach involves psychophysical or quantitative sensory testing. This can give you some mechanistic information in people experiencing acute facial pain and allows you to look at central sensitization or altered nociceptor processing. Imaging studies can give information, but they are usually done in small numbers of patients often involve correlational analysis and are rarely replicated. Thus, caution must be employed in interpreting the results of imaging studies.

General recommendations would include training to increase the pool of clinician scientists trained in translational research. Tissue banks need to be developed and additional support for "bridge" studies needs to be stimulated.

The discussion centered on the need to do interventions first and, if they work, to then do the mechanistic research. Many things are done where we are not sure how they may work or, even more, that they really work. There are successful trials statistically

but with subgroups that do much better than others. The question may be how to make the FDA happy to do the intervention first and how do you justify it without substantiating evidence?

The Panel also discussed the issue of the availability of trained researchers and the disincentives for research careers including accumulated student debt, the regulatory burden, the administrative impact of grant awards, and the upfront costs for enrolling patients in clinical research. The National Pain Care Policy Act of 2003 was introduced in Congress on April 29, 2003, which authorizes a White House Conference on Pain, establishes a National Center for Pain and Palliative Care Research at the NIH, and speaks of 6 regional centers for education and treatment.

Additional discussion was held about the demographics of pain in terms of the age and gender, and of the similarity in both demographics and neurochemical characteristics of some chronic pain syndromes and the major psychiatric disorders.

DISCUSSION AND RECOMMENDATIONS

The discussion following the presentations (summarized above) focused on the following topics:

- There is an array of pharmacological approaches and of behavioral interventions available for the treatment of pain, but there are lots of people who are not making use of these resources. Some of this is due to financial barriers and some to lack of understanding. Behavioral and social scientists are needed to bridge the gap. Current theraputics fail because they are never implemented, because they are implemented ineffectively or because they are ineffective. Issues of cultural background and beliefs about pain have to be considered, as the country gets more diverse. Providers in primary care settings have an unacceptably small understanding of pain evaluation and what is available for its treatment.

- If pain is a disease in its own right, perhaps there should be a pain institute at the NIH. However, because it covers a broad spectrum of diseases and organ systems, this would be in essence to create a second NIH and a better approach may be a coordinating center or office.

- The coverage of pain in the educational curriculum of medical and other health professional schools is not adequate and practicing clinicians and residents are not generally interested in pain management. NIH can support changes in the educational system, perhaps through R25 awards (curriculum development grants) to provide shared, multidisciplinary training modules across the health professions. The culture of medical institutions varies significantly across the country in terms of patient centricity.

■ RESEARCH OPPORTUNITIES

- In terms of research questions, the Panelists highlighted the following:

- We know quite a lot about the role of sodium channels in primary afferent nociceptors, but more needs to be done in terms of the role of these and other channels in the CNS.

- Existing animal models can be utilized to look at the long-term consequences of the injury or of chronic inflammation and neuroplasticity.

- Pain research is already successful in terms of the identification of elements within the pain "matrix" (genes, mediators, proteins). The new opportunities lie in the translation to the every day use of therapeutic combinations. A systems or integrated approach to the study of pain is needed and the opportunity can be framed not so much in the discovery of elements, but in trying to address gaps that may have clinical relevance. Perhaps, mutual, cooperative funding with, for example, AHRQ to try to bridge the interface of basic research and clinical care and to address issues of health services research and cultural and other factors that may have a clinical impact.

- The field of pain research can draw upon existing evidence-based reports (e.g., the Cochrane data base) that clearly indicate where the evidence is good and where it is not. This can fill additional elements in the matrix.

- The diversity of assessment instruments and experimental design approaches has resulted in waste, as it becomes impossible to aggregate studies and their different output measurements and times. The treatment schedules and diagnostic criteria used aren't uniform in studies, for example, of opioids. A benefit of evidence-based medicine is that it shows what the gaps in knowledge are. There is a recent large-scale effort supported by industry to standardize methods and assessment and outcome measures in pain.

- A good mechanistic understanding of the disease process resulting in pain is needed. The answers in neurology are being propelled by genetics (gene identification). It is important to identify all the molecules that are involved in pain transduction using primary afferent neurons. Emphasis should be placed in understanding what comes out of damaged or traumatized tissues and how the

nervous system responds. Imaging and other basic investigative techniques should be used in humans as part of the translational research agenda.

- Targets of bench to bedside application and of bedside to bench impact need to be identified. Both the chronic changes that occur in a setting of persistent pain and the variability in pain perception and response to therapy need to be clearly identified.

- Translational models with an emphasis on comparative physiology and molecular biology would be very valuable.

- Although a great deal of progress has been made with the use of DNA microarrays, we are still missing information about protein modification and protein-protein interactions and how this leads to changes in function.

- The issue of acute pain as a risk factor for chronic pain needs systematic study to identify the medical, pharmacologic and behavioral strategies that can minimize the expression of pain. Also, to elucidate how the brain tracks and influences pain perception and behavior as a function of treatment (the central processing of pain). Then the tailoring of drugs will take on a different meaning. Pain should be assessed for intensity, duration and, in clinical trials, for its impact on functionability and qualify of life.

- High quality epidemiology and defined diagnostic criteria is essential for a company to develop therapies based on novel targets. The infrastructure is not currently in place to even act on the known targets (e.g., sodium channel, VRI, etc.) that exist. Beyond Cox-2 inhibitors, which are essentially an improvement on a known mechanism, a novel mechanism-based therapy has yet to be developed despite considerable progress in basic research. FDA guidelines, which are fairly outdated and have not been substantially revised to reflect progress in basics pain research, may represent a barrier to development of novel therapies. The need for defining standard criteria in the preclinical evaluation of pain was discussed. The risk is that too rigid a standardization isn't the best way to develop innovative scientific ideas and pain research may need a degree of openness now as each form of neuropathy may be a different disease that should be evaluated differently.

- The elements of what are considered high quality clinical trials design should not be suspended because one is trying to do a study

of a mechanism; however, one may have to go with small n's for interventions that will allow you to collect a certain amount of preliminary data to then move in another direction.

- Psychosocial treatments do help patients with disease-related pain. What needs to be done is to elucidate the biological mechanisms that connect to the psychosocial response. The opposite should also be investigated to determine if there are important psychosocial effects that come late with positive outcomes of drug or surgical therapies. Patient beliefs about pain may be related to the phenomenon of chronification. This may also be related to environmental plasticity.

- When people talk about the disconnect between animal models and clinical pain states, the focus is usually on the basic scientists and their failure to come up with models that are appropriate representations of the clinical state. Almost no one tries to go the other way and provide a good definition and classification of clinical states. We do not know what animal models are good surrogates for which clinical pain states. A related problem is the failure of clinical trials (i.e., with NK1 receptor antagonists) and the lack of information about the reason for what went wrong including, for example, the possibility of species differences or the use of the wrong animal model in the basic science phase, or the user of the wrong disease state in the trial.

- Genomics can be used for discovering new genes, but then work has to be done on them with mice again one by one and this will take time. Genomics is not going to absolve us from having to do a lot of slow arduous work, for example, in animal models of clinical pain conditions. We still need to do the phentoyping and the integrative biology.

- Developing classification schemes for clinical states and for preclinical models may be a difficult task at present because we are still in the earlier stages of developing these important tools. But in genetic studies of mice strains using up to 24 pain tests, it was possible to reduce them to simplified categories in terms of variability in pain sensitivity. A mechanistic classification of pain can be a great breakthrough but it may be a long time before this approach can be done clinically to drive treatment. It is not yet clear, however, how far one can generalize from animal genetic studies to clinical pain conditions.

- Focusing on translational research can have a major impact on the field. This can be done in well-characterized acute and chronic

pain models, where the genetic and environmental influences on pain can begin to be sorted out. An example of each type of model where it is relatively easy to have a clear diagnosis can be selected to do mechanistic studies at the biological and psychosocial levels. The same approach used in the Cell Signaling Research Consortium can be used here and a national consortium focusing on these selected models can be created. This can be followed by research on more diffuse or generalized pain states. The general consensus of the Advisory Panel was to give lower priority to the development of patient registries for chronic orofacial pain conditions as likely not to be a cost-effective strategy at present.

■ BARRIERS

- The issue of bureaucratic barriers to translation of preclinical discoveries into clinical care is not a trivial one. The time it takes to get a protocol approved, let alone conducted, is itself enough to discourage people.

- Barriers also exist in terms of the financial, administrative and bureaucratic disincentives in clinical trials research and of societal attitudes (i.e., stigmatization of patients) and undervaluing pain as a symptom.

- Patient-related barriers exist, particularly in minority groups, and they need to be addressed or we will end up with pain management approaches that work in one segment of the population but not across the diverse groups in the U.S.

- The issue of an adequate workforce in pain research was brought up. It is a complex issue that includes a lack of interest in science careers, financial disincentives, etc. and initiatives are needed to enhance the training of new generations of researchers that address these barriers.

■ SPECIFIC APPROACHES

- Revitalizing the trans-NIH Pain Consortium is absolutely critical and resources are needed to increase the scope of the NIDCR's intramural program.

- More support can be provided to GCRCs to have more staff and resources to address these barriers and to become a better used venue for pain research. GCRCs can enhance interactions between investigators and fields of science and foster multidisciplinary

collaborations. They could be a good place where a major initiative in pain research could be developed and implemented.

- New initiatives should be developed in the extramural program to support innovative research activities and collaborations as the ones discussed at this Panel. The visibility of the extramural program staff is very important at national and international meetings.

- Although money is being spent to train more physicians in science, a parallel effort may be to provide basic scientists with the opportunity to understand or at least observe clinical patients to get a good clinical perspective.

- Given the excellent track record of NIDCR in pain research, this may be an opportune moment to publicize and highlight the visibility of its programs, to increase leverage and budgetary resources and to make people aware of what has been done and will be done in the future.