STANFORD UNIVERSITY - Research Consent Form
Protocol Title: DEVELOPMENT OF HYPERALGESIA IN PAIN PATIENTS ON CHRONIC OPIOID THERAPY (Protocol No. 95156)
Protocol Director: Dr. Larry F. Chu, MD, MS
IRB Approval Date: _April 26, 2005____ IRB Expiration Date: April 25, 2006

STANFORD INFORMED CONSENT FORM

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Are you participating in any other research studies? _____ yes _____ no

INFORMED CONSENT

DEVELOPMENT OF HYPERALGESIA IN PAIN PATIENTS ON CHRONIC OPIOID THERAPY

You are invited to participate in a research study examining whether chronic opioid use causes increased sensitivity to pain (hyperalgesia). Recent evidence suggests that the chronic use of opioids (such as morphine) for the treatment of pain somewhat paradoxically may cause a hypersensitivity to pain. In other words, patients who receive opioids for the treatment of their pain may become more sensitive to pain because they are treated with opioids. If this is true it may impact the way opioids will be used for the treatment of chronic pain. We hope to learn if chronic opioids in pain patients causes hypersensitivity to pain. These results may ultimately allow us to treat patients with chronic pain more effectively. You were selected as a possible participant because you are between 18 and 70 years of age and are suffering from chronic non-cancer pain requiring the use of opioids. We will enroll 160 chronic pain patients.

Your participation in this study is entirely voluntary.

Your decision whether or not to participate will not prejudice you or your medical care. If you wish to participate in this study, you must sign this form. If you decide to participate, you are free to withdraw your consent, including your authorization regarding the use and disclosure of your health information, and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify Larry Chu, M.D. at 415-607-1276.

If you decide to participate, the study will be conducted in the manner described below.

1. Prior to enrolling you in the study, you must a) have been evaluated by a pain physician at either the Stanford or Palo Alto Veterans Administration Hospital (medical history, physical exam), b) be found to have chronic non-cancer related pain requiring the use of opioids, and c) be willing to enroll in a study for a total period of 12 months. The actual study itself lasts only one month, but we would like to be able to keep in touch with you and ask questions about your pain up to 12 months from your enrollment date.

2. In order for you to participate in this study you a) are currently not requiring more than 30 mg of morphine per day (or of another opioid equivalent to 30 mg of morphine), b) are not using any anticonvulsant or antidepressant drugs, c) do not have a history of
substance abuse, d) do not have peripheral neuropathy (lesion or malfunction of nerves).

3. If you are a women at a child bearing age you will be asked about the possibility of pregnancy or breast-feeding during the study. A pregnancy test will be performed and a negative result will be required before continuing in this study.

4. If you decide to participate in this study you will receive the opioid morphine for the treatment of your chronic pain condition while you are participating in the study. If you are taking another opioid you will be switched over to a daily dose of morphine that is equivalent to the dose of the opioid that you are currently taking. YOU WILL CONTINUE TO TAKE THIS DOSE OF PAIN MEDICINE DURING THE ONE MONTH DOSING PHASE OF THE STUDY—REGARDLESS OF WHICH DOSING GROUP YOU ARE ASSIGNED.

5. We will then randomly assign (like flipping a coin) you to an “active” group or a “placebo” group. You will be given pills to take that may help your pain control. YOU WILL HAVE APPROXIMATELY 50% CHANCE OF RECEIVING THE STUDY DRUG (MORPHINE). The dose of these pills may be adjusted as frequently as every two days if you find that your current dose is insufficient to treat your pain. If you are assigned to the “active” group you will receive morphine pills. If you are assigned to the “placebo” group you will receive sugar pills.

6. During the 1–month study period you will be asked to participate in 4 separate test sessions (2 before starting the dosing phase and 2 afterwards). A test session takes place at the Pain Clinic of Stanford or the VA Hospital and lasts about 2.5 to 3.5 hours.

7. The night prior to each study session fasting will be required. A study session usually starts at about 8:00 in the morning. We will ask you to omit your regular dose of morphine on the morning of a test session.

8. At the beginning of a test session a) a small plastic tube will be inserted in a vein of your arm and b) blood will be collected (2 teaspoons) to measure the concentration of morphine.

   After the research study is finished, your blood samples will be destroyed.

9. During a test session we will measure your sensitivity to pain in two different ways. First, you will be asked to place your hand and part of your forearm in a container of ice-cold water and to indicate the onset of pain as well as the time that pain becomes intolerable. Second, we will place a small metal probe (about a third of a square inch) on your forearm. Initially, the probe will be at a comfortable temperature and will then be heated up at a rate of 1.8 degrees Fahrenheit per second. You will be asked to push a button when the pain induced by heating the probe becomes intolerable. Once you push the button the probe will immediately cool down and the maximum probe temperature tolerated will be recorded. For your safety, i.e. to prevent burn injuries, the probe can only be heated to a maximum temperature of 126 degrees Fahrenheit. Assessing your pain sensitivity with outlined two tests will take about 10-15 min.

10. Pain sensitivity will be tested three times before an infusion containing remifentanil or saline will be started. Remifentanil, an opioid like morphine, will be administered through the small plastic tube inserted into your vein. Three different doses of remifentanil will be administered during the drug infusion. Your pain sensitivity will
be assessed for each of the three doses, and once more after the infusion of remifentanil has been stopped. Therefore, your pain sensitivity will be assessed seven times during a test session.

11. Throughout the study an electrical tracing of the heartbeat (ECG), measurement of your blood pressure, counting of your respiratory rate and measuring the amount of oxygen your blood is carrying will be performed.

12. You will be asked to have someone drive you home at the end of the session.

Assessment of your pain sensitivity will cause brief periods of pain. Any assessment will be stopped immediately upon your request. Specifically, assessments will be stopped immediately when the pain becomes intolerable.

The risks of participating in this study include potential side effects of the remifentanil infusion such as lightheadedness, nausea, vomiting, sweating and feeling sad. Less common reactions include weakness, headache, agitation and muscle rigidity. High doses can significantly affect your breathing, heartbeat, blood pressure and cause loss of consciousness. We do not expect you to suffer from these side effects since the doses given to you have been proven to be safe in previous studies conducted by the investigators.

**Remifentanil is known to have a significant potential for addiction in some individuals. You should NOT participate in this study if you have any history of addiction to a drug or to alcohol.**

PLEASE CHECK THIS BOX INDICATING THAT YOU DO NOT HAVE A HISTORY OF ADDICTION TO A DRUG OR ALCOHOL.

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**Personnel with direct physical access to and routine handling of addicting drugs in the regular course of their work duties should not participate in this study.**

PLEASE CHECK THIS BOX INDICATING THAT YOU DO NOT HAVE ACCESS TO ADDICTING DRUGS OUTSIDE PARTICIPATION IN THIS STUDY.

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Since there is always the possibility of unexpected adverse reactions you will be monitored continuously during study sessions by trained and experience medical personnel. Drugs reversing any of the mentioned side effects will be readily available.

The risks associated with the insertion of a small plastic tube into one of your veins include bruising, local inflammation, and pain during insertion.
You will not receive any direct benefit by participating in this study.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY.

You will be told if any new information is learned which may affect your condition or influence your willingness to continue participation in this study.

While participating in this study, you should not take part in any other research project without approval from all of the investigators. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

The alternative to participating in this study is not to participate and be treated with opioids according to the standard practices.

Any data that may be published in scientific journals will not reveal the identity of the subjects. Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The responses to questions concerning illegal drug use could be self-incriminating and harmful to you if they became known outside the study. As explained in the confidentiality statement on page 3 of the consent, we do not intend to disclose this information.

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of a reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from this study.
You will be paid $200 completing this study. You will receive $50 for the first session, $50 for the second and $100 for the third and final session. This will compensate you for your travel expenses (e.g. taxi home) and other arrangements that are necessary due to your participation in this study. Legally, you can be paid only if you are a US citizen, a legal resident alien (i.e., possess a "green" card), or have a work eligible visa sponsored by the paying institution.

The sponsor will pay for all costs associated with sensory testing and conducting this study. You or your insurance company will be responsible for your medical care and your pain medications. You or your insurance company will be responsible for the cost of all drugs and medications, with the exception of medications administered by the investigators during study sessions which will be paid by the investigators.

The National Institutes of Health is providing financial support and/or material for this study.

At the discretion of the protocol director subjects may be taken out of this study due to unanticipated circumstances.

Some possible reasons for withdrawing a subject from the study are.

- failure to follow instructions
- failure to complete all six testing sessions
- failure to comply with pain medication dosing
- the investigator decides that continuation could be harmful to you
- you need treatment not allowed in the study
- the study is canceled
- other administrative reasons

If you have any questions, we expect you to ask us. If you have any additional questions later, Dr. Larry Chu at 415-607-1276 will be happy to answer them.

If you think you have experienced a research related injury, call Dr. Larry Chu at 415-607-1276 (voice) or 650-723-8222 X14201 (pager).

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

By signing this form, you are authorizing the use and disclosure of your health information collected in connection with your participation in this research study. Your information will only be used in accordance with the provisions of this consent form and applicable law. If you decide to terminate your participation in the study, or if you are removed from the study by the protocol director, you may revoke your authorization, except to the extent that the law allows us to continue using your information.

What Information Will Be Used or Disclosed?
Your health information related to this study, specifically your blood samples (morphine plasma and metabolite levels) and physical examinations, clinical exam findings, pain testing results, may be used or disclosed in connection with this research study.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:
The Protocol Director Larry Chu, MD
The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
Dr. Martin Angst and the Research team

Who May Receive / Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- National Institutes of Health
- Sang Park, Ph. D., Analytical Facility, Department of Anesthesiology, University of Washington School of Medicine

*Your information may be redisclosed if the recipients described above are not required by law to protect the privacy of the information.

Expiration
Your authorization for the use and/or disclosure of your health information will continue until 1/1/2105.

When Access to Your Information May Be Limited
You may not be allowed to see or copy certain information in your medical records collected in connection with your participation in this research study while the research is in progress.

All forms of medical diagnosis and treatment -- whether routine or experimental -- involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment but this study does not provide financial assistance for additional medical or other costs. Additionally, Stanford is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form. For further information, please call (650) 723-5244 or write the Administrative Panel on Human Subjects in Medical Research, Administrative Panels Office, Stanford University, Stanford, CA 94305-5401. In addition, if you are not satisfied with the manner in which this study is being conducted or if you have any questions concerning your rights as a research study subject, please contact the Human Subjects Office at the same address and telephone number.
As a human subject you have the following rights. These rights include but are not limited to the subject's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should rise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form;
- and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PERSON OBTAINING CONSENT, THAT YOU HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

________________________________ ______________
Signature of Participant Date

Social Security #

Person Obtaining Consent
I attest that the requirements for informed consent for the medical research project described in this form have been satisfied – that the participant has been provided with the Experimental Subject’s Bill of Rights, if appropriate, that I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

________________________________ ________________  ______________________
Signature of Person Obtaining Consent      Date