INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 00-CH-0093 PRINCIPAL INVESTIGATOR: Karel Pacak, M.D., Ph.D., D.Sc.

STUDY TITLE: Diagnosis, Pathophysiology, and Molecular Biology of Pheochromocytoma

Continuing Review Approved by the IRB on 11/15/06
Amendment Approved by the IRB on 11/15/06 (EE)
Adult

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

OVERVIEW OF THE STUDY

We are inviting you to participate in this study because we believe that you may have pheochromocytoma, a tumor located in the adrenal gland or outside the adrenal gland. Pheochromocytomas are a surgically correctable cause of chronic high blood pressure. The clinical features and consequences of pheochromocytoma result from release of biochemicals called catecholamines (epinephrine and norepinephrine) by the tumor. We wish to know whether various biochemical and scanning methods will improve our ability to diagnose and localize a pheochromocytoma. In addition, we wish to find out if there are any specific genetic or other markers to predict the course, malignant potential, and recurrence of pheochromocytoma. Some of this testing is not available elsewhere and so may benefit you.

If diagnostic tests indicate that you have a pheochromocytoma, you will be offered surgery at the NIH. You may benefit from detection and removal of previously unrecognized tumor. If the tumor cannot be found, you may be offered medical treatment, and we will continue to look for the tumor in follow-up evaluations. If surgery is not indicated (e.g., if you have multiple tumors that cannot be removed), then you may have follow-up evaluations to assess the size or number of tumors.

You will not be paid for your participation in this study. However, all protocol-related tests, procedures, and hospitalization at the NIH are without cost to you.

Pheochromocytoma can occur as part of diseases that run in families. If you have an inherited disease that is associated with an increased risk of developing a pheochromocytoma, we will discuss with you the chances of developing this tumor. If appropriate, we will arrange counseling by a genetic counselor.

The main goal of this study is to develop new tests to diagnose and find a pheochromocytoma. If a pheochromocytoma is undetected, situations that normally would not pose a hazard, such as surgery, childbirth, or general anesthesia, can evoke catecholamine release by the tumor, with catastrophic results, such as stroke, heart attack, or sudden death. Both the detection of pheochromocytoma and finding where the tumor is can be difficult. Commonly used diagnostic imaging methods such as computed tomography (CT scanning) and magnetic resonance imaging (MRI scanning) are very good at locating a mass. Metaiodobenzylguanidine (MIBG), fluorodeoxyglucose positron emission tomography scanning, bone and octreotide scans are types of nuclear medicine scanning that are useful in identifying a mass as a pheochromocytoma but are not very sensitive and can miss a tumor that really is there.

This protocol focuses on a new blood test and a new imaging approach, called fluorodopamine and fluorodopa positron emission tomographic (PET) scanning. The paragraphs below explain how PET scanning works.

You will be admitted to the Clinical Center of the NIH for standard medical and imaging tests, to assess whether you have pheochromocytoma. These tests include taking blood through an intravenous (i.v.) tube or collecting urine. You may also stay in a local hotel or guest house during most of this time and return to the Clinical Center for the tests. You must refrain from smoking and from consumption of alcohol or caffeinated or decaffeinated beverages for 18 hours and Tylenol™ (generic name acetaminophen) in any form for 5 days before blood testing. Water is permissible.

You are free to withdraw from the study at any time. Should you do so, we will not continue further diagnostic tests, and we will not perform surgery at the NIH. Any information obtained up to that time would be made available to you and your physician.

BLOOD TESTS FOR PHEOCHROMOCYTOMA

We have found so far that measurements of levels of catecholamines and their breakdown products, called metanephrines, provide an extremely sensitive way to detect pheochromocytomas. If the blood tests are negative, then you do not have the tumor. We don't know, however, whether a positive test necessarily means that you do have the tumor. This project considers this problem.

For blood tests you should remain in the supine position for at least 20 minutes before and during collection of the blood sample (10 cc). The sample is drawn without a tourniquet, through an indwelling i.v. (normal saline infused at a slow rate to keep the line open) for at least 20 minutes before the sample is drawn.

You may receive two drugs, glucagon and clonidine, which are used in standard medical evaluation of pheochromocytoma. At least 20 minutes before the test, two i.v. catheters are inserted into your arm veins, and you rest in the lying position.

GLUCAGON STIMULATION TEST (FDA APPROVED)

This test is to determine if a suspected pheochromocytoma can be stimulated to produce diagnostic increases in plasma catecholamine levels. You receive 1.0 mg glucagon i.v. over 30 seconds. Blood pressure and heart rate are measured every minute for at least 5 minutes before and for at least 15 minutes after glucagon is given. Five blood samples (10 cc, about 2 teaspoons) are obtained through the i.v., for levels of catecholamines and metanephrines at intervals 0, 1, 2, 3, and 5 minutes after glucagon is given. In patients with pheochromocytoma, blood pressure and heart rate can increase within 30-60 seconds and last for several minutes after glucagon is given. Severe allergic reactions are very rare, but increased sweatiness, nausea, sometimes vomiting, as well as a feeling of a need to urinate may occur after glucagon administration. A physician will administer glucagon and be present during the entire test. An antidote drug will be immediately available if there is a prolonged, excessive increase in blood pressure.

CLONIDINE SUPPRESSION TEST (FDA APPROVED)

This test is to determine if you have high levels of plasma catecholamines from a pheochromocytoma. You receive 0.3 mg clonidine/70 kg by mouth. Blood pressure and heart rate are monitored every 5 minutes for 20 minutes before and every 15 minutes for 3 hours after administration of clonidine. Blood is drawn via an i.v. for levels of catecholamines and metanephrines before and at 3 hours after clonidine is given. Normally, plasma levels of catecholamines decrease after clonidine, but in patients with pheochromocytoma, the levels usually do not decrease. Thus, the failure of response is actually positive test result. Clonidine often causes drowsiness and a fall in blood pressure, regardless of the presence of pheochromocytoma. These effects can last several hours, and so you will not be allowed to drive or operate machinery until the next day.

REGIONAL VENOUS SAMPLING

In some unusual cases pheochromocytomas may not be located by typical imaging studies. In other cases one or more masses may be found that are suspicious but not identified as pheochromocytomas. In these situations it may be appropriate to do a test called selective vena caval sampling. This is a clinically indicated, not a research, procedure. The testing involves inserting a long intravenous tube into a major blood vessel returning blood to the heart (i.e., the inferior vena cava) to sample blood from veins draining organs in the neck, chest, abdomen, or pelvis. The blood is assayed for levels of catecholamines and metanephrines. Because of the clinical indication for selective vena caval sampling, radiation exposure related to the procedure is not included in the dosimetric estimates for use of radioactivity for research purposes.

TESTS BASED ON IMAGING

Clinically indicated imaging tests used in the evaluation of pheochromocytoma will include computed tomography (CT scanning), magnetic resonance imaging (MRI), sonography, bone and octreotide scans, [^{123}I]- or [^{131}I]-MIBG scintigraphy, and fluorodeoxyglucose PET scanning. You may undergo imaging studies before and after surgical treatment of pheochromocytoma. Fluorodopamine and fluorodopa PET scanning is considered a research procedure.

[^{123}I]-MIBG SCINTIGRAPHY

You may be provided with [^{123}I]-MIBG from GE Healthcare Ltd. to perform [^{123}I]-MIBG scintigraphy. In such a situation you will need to sign separate consent and discharge forms provided to you by GE Healthcare. You will also undergo a limited physical examination before, shortly after and 24 hours after [^{123}I]-MIBG administration. An electrocardiogram will be recorded upon your admission, a few minutes before and about 5 min, 30 min, and 24 hours after [^{123}I]-MIBG administration. A one time measurement of blood oxygen using pulse oximetry will be performed 5 min after [^{123}I]-MIBG administration. The imaging procedure is the same regardless of who is providing [^{123}I]-MIBG to perform [^{123}I]-MIBG scintigraphy. This study could benefit you and future patients to allow better localization of pheochromocytoma that could result in its early detection and treatment. It may also help investigators to find out how successful this imaging technique is compared to others currently available for the localization of pheochromocytoma. You may be eligible to be reimbursed for travel expenses for up to $ 225.00. In case you decide not to receive [^{123}I]-MIBG from GE Healthcare Ltd., you will receive [^{123}I]-MIBG provided by NIH from a different source.

There is no financial interest by the Principal Investigator or other Investigators and their family members in GE Healthcare Ltd. To carry out the study, GE Healthcare Ltd. will disburse funds to the NICHD. The NICHD Pheochromocytoma Research Program will use funds to promote pheochromocytoma research.

FLUORODOPAMINE AND FLUORODOPA PET SCANNING

The basis for visualization of pheochromocytoma in this study is PET scanning after injection of a synthetic, radioactive catecholamine called fluorodopamine and a synthetic radioactive catecholamine precursor called fluorodopa. Both radiopharmaceuticals fluorodopamine and fluorodopa offer promise for improved detection and localization of pheochromocytoma.

After injection of radioactive fluorodopamine, fluorodopamine enters pheochromocytoma cells and these cells become radioactive, allowing us to see the tumors on the PET scan. Most cells in the body do not become radioactive after fluorodopamine injection. This means that if we see that a mass takes up the radioactivity and concentrates it, it is likely to be a pheochromocytoma.

Another PET agent that can be used in the localization of pheochromocytoma is fluorodopa. The compound dopa is an amino acid. Amino acids are present in our body and are used for building proteins and transmit signals. Fluorodopa enters pheochromocytoma cells, they become radioactive and PET scanner detects them. Also most cells in the body do not become radioactive after fluorodopa injection. Some of you may receive a single oral administration of 200 mg of carbidopa 60 minutes prior to fluorodopa injection. The rationale for this procedure is to increase the amount of fluorodopa in tumor. Carbidopa is a drug that is often used in the treatment of Parkinson disease. Up to 20 patients will be participating in the fluorodopa imaging portion of this study. If you are one of them, you will have two fluorodopa PET scans approximately one week apart. The first fluorodopa PET scanning will be performed without carbidopa; the second one will be performed one hour after the administration of 200 mg of carbidopa. This will allow us to determine whether to use carbidopa to obtain the most accurate localization of pheochromocytoma.

You will not be permitted to eat anything for at least 6 hours before the test is started, but will be allowed to drink as much water as you wish. If possible you should drink 2 to 3 glasses of water before the test.

The PET scanning is done in the PET or Nuclear Medicine Department of the NIH Clinical Center. The PET scanner is shaped like a doughnut, and the part of your body being scanned is in the hole. You are placed in the PET scanner, with the head, neck, chest, abdomen, pelvis, or extremities in the field of view. Initial scanning called transmission scanning is done for the computer to correct the imaging data for the density of different organs. The transmission scans can be done using a source of radioactivity inside the PET scanner or using a CT scan. The transmission scan using a CT scan also helps localize where fluorodopamine and fluorodopa abnormalities are located. A plastic catheter is inserted into an arm vein for injection of drugs (fluorodopamine and fluorodopa). Fluorodopamine and fluorodopa are tested by a quality control facility just prior to use. The injection of fluorodopamine and fluorodopa lasts 3 minutes. During the injection you should feel nothing unusual. The PET scanning can last up to about 3 hours. For the fluorodopa PET scan you will be asked to get up and empty your bladder approximately 2 hours after the start of the PET scan. Throughout the PET scanning, you are monitored by a physician or Research Nurse. You may be repositioned in the scanner in order to increase the field of view.

After the scan is finished, you will be asked to empty your bladder every 90 minutes for the next 6 hours to remove the radioactive compound in the urine.

Fluorodopamine and fluorodopa PET scanning is are research tests. We, therefore, do not know whether the results of the PET scanning will benefit you directly.

FLUORODEOXYGLUCOSE PET SCANNING (FDG)

After injection of radioactive fluorodeoxyglucose, the tumor cells become radioactive, allowing us to see the tumors on the PET scan. These FDG scans will be performed as clinically indicated procedures.

You will not be permitted to eat anything for 6 hours before the test is started, but will be allowed to drink as much water as you wish. If possible, you should drink 2 to 3 glasses of water before the test. The entire study will take about 2 hours. FDG PET scanning is done in the Nuclear Medicine Department of the NIH Clinical Center. You will receive an injection of FDG and after 1 h of resting quietly; standard scans will be obtained over portions of your body. Scanning takes approximately 1 h. During this time you will need to lie very still. If for any reason you feel that you cannot continue the scan once it has begun, the scanning can be stopped and you can be removed from the camera immediately. However, the information from the scan may be lost.

After the scan is finished, you will be asked to empty your bladder at every 90 minutes for the next 6 hours to remove the radioactivity in the urine.

Urine Testing Urine for biochemical diagnosis of pheochromocytoma will be collected for 24 hours and sent to the Department of the Laboratory Medicine at the NIH Clinical Center. Any of several medications can interfere with the test results, and so all medications you are taking must be reviewed.

Genetic Testing Pheochromocytoma can be associated with a genetic change called a mutation. If all your genetic information (DNA) were a book, the genes would be words, and a mutation would be a typographical error in one of the words. To detect such a genetic typo, we will collect 3-7 ml of your blood and extract the DNA. We may compare the DNA in your blood cells with that from people who do not have a pheochromocytoma or with the DNA in tumor cells.

Biopsy The biopsy will determine if you have pheochromocytoma. This is especially important in a situation such as when your fluorodopamine PET scan is positive but your plasma catecholamine and metanephrine levels are normal or if you have metastatic pheochromocytoma. The biopsy will be performed after you will be given appropriate medicine to prevent the action of catecholamines released from a possible pheochromocytoma during the biopsy. The medicine includes alpha and beta blockers given for at least 3-5 days prior to the biopsy. The biopsy will be done either by a surgeon or by an interventional radiologist under local anesthesia. There will be an anesthesiologist and endocrinologist at the bedside during the biopsy.

Cell Culture If you have a pheochromocytoma removed surgically, we may also try to grow the cells in a cell culture. This is because we believe that the area of pheochromocytoma research in general would benefit from establishment of a human pheochromocytoma cell line. Having available a human pheochromocytoma cell line should help us study the potential for malignancy or recurrence, develop and test new imaging techniques, and evaluate potential new treatments.

HAZARDS, RISKS, INCONVENIENCES, AND DISCOMFORTS

Pain Inserting an i.v. catheter can cause local discomfort, clotting, bleeding, or infection. There is a slight, but definite risk of entering an artery, rather than a vein, and this could result in bleeding, bruising, or communication between the artery and vein. We have available a sound wave detector that enables us to "see" the vein even in difficult cases. We estimate less than a 1% risk of local complications other than bruising. Bruising or mild discomfort can last for several days following the procedure. These complications are generally transient, and permanent damage is extremely rare.

Biopsy Although our surgeons and interventional radiologists have vast experience with biopsies of various organs or bones, inserting a needle in the area of interest can cause local discomfort, bleeding, or infection. Discomfort will be treated with standard pain medication, usually tylenol or tylenol with codeine. A few stitches might be placed to close the skin wound**.**

Allergy Some people are allergic to iodinated radiographic contrast agents. If you have any allergy to those agents, you must let us know, to ensure that alternative imaging studies are used, appropriate pre-treatments are given, and appropriate anti-allergic medications are immediately available.

Pregnancy If you are a woman of child-bearing age, we will perform a urine or blood test for pregnancy within 24 hours before any test involving radioactivity. If you are pregnant, no imaging studies such as flurodopamine and fluorodopa PET, MIBG, octreotide, and bone scans and contrast CT will be performed. If you are more than 26 weeks pregnant, you cannot be studied in the NIH Clinical Center.

Blood sampling No more than 310 ml (about 11 ounces) of blood will be taken for this study. You will not be accepted into the study if the total amount of blood required for all testing, is more than the recommended NIH guideline amount for research subjects (450 ml, or about one pint over any six-week period).

Unexpected findings Because of the investigational nature of this study, we may not understand the significance of all the findings from the various tests. For instance, PET or MIBG scanning may identify abnormalities that are not tumors. Such results are called false positive results. If unexplained or unusual findings occur, we may recommend other tests to help explain these findings and determine their significance.

We will not recommend surgery if only the fluorodopamine PET or MIBG scans are positive. Instead, we will require that at least one of the conventional imaging tests (CT or MRI) also be positive. Thus, some patients with positive imaging will have surgical confirmation of pheochromocytoma and others not.

Follow-Up You may return for follow-up conventional imaging or PET scanning such as after surgery. The completeness of tumor resection will be evaluated by biochemical testing 1-2 months after the operation. You will be followed on a yearly basis thereafter. If pheochromocytoma recurs, or if you are not cured by initial surgery, you will be offered re-evaluation to localize residual tumor or recurrence. In such cases, the clinical, biochemical, and imaging tests may be repeated. This would take place only with your additional, separate consent**.** If no pheochromocytoma is found, the patients will be referred back to their primary physician.

Bladder catheter For your comfort and convenience, and at your request, you may have a bladder catheter inserted during the research testing. The use of a bladder catheter may be associated with local discomfort and an increased risk of urinary tract infection.

RADIATION

This study involves the use of radiation from PET scanning with fluorodopamine, fluorodopa and the associated transmission scan. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. Other radiographic and nuclear medicine studies are performed as part of standard clinical care. You may not participate in this study if you are pregnant or nursing. Unborn or nursing children are more sensitive to radiation than adults or children.

FLUORODOPAMINE AND FLUORODOPA

The total amount of radiation you will receive as a result of this research testing includes radiation from the administration of 1 mCi of fluorodopamine for each PET scan. You may undergo up to 3 fluorodopamine PET scans per year. You may have also up to 2 fluorodopa scans (12 mCi per scan) in 1 year. In addition you will have transmissions scans to account for body thickness using either a low dose CT scan (up to 7 per year) or radioactive pin sources. Radiation dose is commonly expressed in units called rem.

You may be repositioned in the PET scanner to visualize fluorodopamine or fluorodopa - derived radioactivity in a different field of view. Each time you are repositioned in the PET scanner, you undergo a brief transmission scan, which is required to check on the appropriateness of the positioning and also to correct the results for the different densities of body organs. Using the standard way of describing radiation dose, if you undergo 3 fluorodopamine PET scans, and 2 fluorodopa scans with their associated transmission scans you will receive up to 17.7 rem to your bladder wall, 6.6 rem to your kidneys, and 3.9 rem to your bone surfaces, with lower doses to all other organs.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of up to 4.2 rem if all studies are performed. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is below the dose guideline established by the NIH Radiation Safety Committee for adult research subjects (5 rems effective dose). The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving acceptable risk and necessary to obtain the research information desired.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in about 14 years from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, *An Introduction to Radiation for NIH Research Subjects*.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The absolute increase in your chance of getting a fatal cancer, as a result of the radiation exposure received from this research study, is 0.17 percent. Therefore, your total risk of fatal cancer may increase from 25 percent to 25.17 percent. This change in risk is very small and cannot be measured directly. Compared with other everyday risks, such as flying in an airplane or driving a car, this increase is considered slight.

One concern some people may have about radiation exposure is the effect on fertility or on the possibility of causing harm to future children (i.e., genetic risk). The doses received in the research study are well below the levels needed to affect fertility.

The fluorodopamine and fluorodopa that you receive are administered under an Investigational New Drug approval from the US Food and Drug Administration (FDA), with Peter Herscovitch, M.D. as the Sponsor. Both Sponsor and the FDA have access to the medical records of research subjects.

Please let us know if you have participated in research studies at the NIH or other institutions that have involved the use of radiation, to ensure that the total radiation dose from all studies is not excessive. Examples of such studies include X-ray studies, cardiac catheterization, fluoroscopy, or nuclear medicine studies.

DRUG AND CONTRAST DYE EFFECTS

Fluorodopamine and fluorodopa administered at the approved doses should not exert detectable pharmacological effects.

Glucagon testing can provoke attacks due to catecholamine release by a pheochromocytoma. These attacks are generally milder and of much shorter duration than spontaneous attacks and usually require no treatment. In the rare instance of an extremely large or sustained release of catecholamines, the blood pressure can be controlled readily by means of i.v. drugs (phentolamine and metoprolol). Both drugs are always immediately available for emergency use. Glucagon administration can also cause transient nausea, vomiting, or allergic reactions.

Clonidine often causes sedation and a decrease in blood pressure. Sometimes it produces a headache, dizziness, or generalized weakness. In such a situation, the patient is positioned in bed with the head down or legs up, and normal saline can be given i.v.

Standard imaging procedures. Standard imaging procedures require you to lie still, either in an enclosed tube (the MRI scanner) or in a more open "doughnut" (CT scanner). Some patients feel closed in or anxious in the MRI scanner. If this is a problem for you, we may give you a sedative, or use an alternative test. The approximate times for the studies are as follows: CT of neck, chest, abdomen, and pelvis 2 minutes; MRI of neck, chest, abdomen, and pelvis 1-2 hours. If CT is done using intravenous dye, you will be asked not to take any food 4 hours before the test. Occasionally, CT dye can cause hypertensive crisis. You may also have blood sampling done shortly before and immediately after CT scan is completed. A physician from our research team will be drawing blood samples and supervise you during CT scan. FDG scans take up to 2 h total, MIBG scans up to 3-4 hrs over 2 days, octreotide up to 1.5- 3h over 1 or 2 days.

MIBG scintigraphy. To block thyroid hormone accumulation of radioiodine generated from deiodination of [^{131}I]-MIBG or [^{123}I]-MIBG, you will be required to take medication called SSKI or potassium perchlorate (if you are allergic to iodides), 1 day before and up to 7 or 3 days after [^{131}I]-MIBG or [^{123}I]-MIBG administration, respectively.

OTHER GENERAL ISSUES RELATED TO THIS PROTOCOL

RESEARCH USE OF STORED HUMAN SPECIMENS AND DATA

During your participation in this protocol, samples of your body fluids (e.g., blood, urine) and tissues (e.g., tumor tissue taken at surgery) may be collected and stored for ongoing and future research purposes. Data about your condition will also be collected. The research carried out on these samples and the data collected will help in understanding how pheochromocytomas develop and how different forms of these tumors, including those that have become malignant, might be better diagnosed and treated. Much of this research using stored human specimens and data will be carried out by NIH investigators, under the direction of the Principal Investigator of the protocol. However, some research involving your samples and data collected under the protocol may also be carried out as part of collaborations with investigators at centers outside of the NIH. In the latter situation, your samples will be coded so that your identity as the source of those samples will be protected and remain confidential to the non NIH investigators directly involved in the research. Any data that is shared will also have identifying information removed before it can be used for collaborative research with investigators at centers outside the NIH.

GENETIC TESTING

Samples of your blood cells or genetic material (DNA) will be used either for the diagnosis or for research about your medical condition. The research will be done at the NIH. No other testing or research will be done using your DNA unless you give specific permission, as indicated below. There are certain risks from tests run on genetic samples. Instances are known in which a patient has been required to furnish genetic information as a precondition for application for health insurance and/or a job.

There are ways your life could be affected by learning information that may be discovered by genetic testing. One factor to consider in thinking about whether or not to participate in this study includes the potential effects on your psychological well-being. In other words, how might you feel about yourself if information is provided to you about risks that could affect your own future health or that of your children? Some individuals may feel anxious or depressed or

suffer additional stress as a result of learning genetic information about themselves or their children. You may experience similar feelings. We will try to help you or refer you to someone if you experience these feelings.

1. Unanticipated medical information. During the course of this or future investigations, it is possible (although not likely) that we may obtain unanticipated information about your health or genetic background. If this information is considered to be relevant to your health care, we will provide it either to you or to your referring physician.

2. Release of medical records. In the course of applying for certain types of insurance (e.g., medical insurance, life insurance, or disability insurance), people are often asked to sign forms that authorize insurance companies to obtain their medical records. If you sign such a release form at some point in the future, it is possible the insurance company would present this signed release form to the Clinical Center of the (NIH). In that event the NIH would comply with your request to provide the insurance company with your medical record. It is possible that the information contained in your medical record might affect the willingness of the insurance company to sell you insurance.

3. Family relationships. During this study or in future studies, we may learn information about relationships within the family that are medically relevant. We will not ordinarily provide this type of information to any family member or the referring physician. However, we may make exceptions under an extraordinary circumstance if this information were required for the medical care of the individuals involved. If we are convinced that this is necessary, we will provide the information to the physician providing medical care to the patient.

4. Participation in other research studies. This consent form specifically refers to your participation in the research protocol described above. In the future, we may invite you to participate in other studies. Even if you sign this consent form, you are not obligated to participate in these other research protocols. If you are asked to participate in these other studies, you will be provided with additional consent forms. As stated in the Introduction to this protocol, you are free to withdraw from any or all research studies at any time without penalty or loss of any benefits to which you are otherwise entitled.

5. Collection, research and storage of biologic material.

It should be clear samples we collect from you will be used only for research to search for an underlying genetic association with your medical condition. No other testing or research will be conducted on your body and blood samples unless you specifically give permission (as stated above).

The DNA and plasma collected from your blood will be stored in freezers contained in a secured building on the NIH campus. The samples will be inventoried and stored by codes defined by us.

Researchers within NIH, as well as from outside NIH, may be involved or interested in using the samples of your DNA to help us pursue our objectives or their own individual research projects. The use of any DNA samples can be controlled by those who provide them, namely you. Therefore, we ask your guidance and concurrence concerning future use of your DNA samples.

Deleted: **1. Future research involving genetic material.** Our research plans have been summarized in the first two sections detailing the purpose and background of this investigation. In the course of the research, we will obtain samples of your blood. In addition, it is possible that some information obtained from these studies will be published in the medical literature. However, your identity will not be included in these publications. ¶

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I give permission to use my blood cells or DNA sample(s) in future research studies, under the following conditions:

_____ I give my permission to use my blood cells or DNA sample(s) in future research studies about known or suspected pheochromocytoma or neurocardiologic disorders as judged important by the investigators.

_____I wish to be re-contacted if future research studies are considering using my blood cells or DNA sample(s). After the study has been explained, I will then decide if I want my samples to be included in the study.

_____Under no circumstances shall my blood cells or DNA sample(s) be used in future research studies.

The Principal Investigator will not share any genetic test results unless you give us permission to do so by signing a separate permission form.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY AND RIGHTS UPON REFUSAL OR WITHDRAWAL FROM THIS STUDY

The choice to enter or not enter this study is entirely voluntary. Before you decide to enter or not, you should understand, what the doctor has explained and what you have read about the research study. If you decide not to participate, your enrollment in any other NIH protocol will not be affected. If you begin this study, you have the right to withdraw at any time.

As noted above, many other physicians and centers are experienced in the evaluation and treatment of patients with pheochromocytoma. These centers will commonly rely on many of the same tests that we use to determine the cause of your symptoms. While some tests that we perform are not widely available (such as fluorodopamine PET scanning) they may not be critical to your specific case.

We cannot predict which patients will benefit from the additional tests offered in this study. If you are not sure that you wish to participate in this study, let us know at any time, and we will refer you to other physicians and medical centers experienced in the evaluation and treatment of patients with pheochromocytoma.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Karel Pacak, M.D., Ph.D., D.Sc.; Building 10, CRC, Room 1E-3140, Telephone: 301-496-1211 or Karen T. Adams, CRNP; Building 10, CRC, Room 1E-3140, Telephone: 301 402-7785.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM NOVEMBER15, 2006 THROUGH NOVEMBER 14, 2007.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____