INSTITUTE: National Institute of Child Health and Human Development

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

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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 you may have pheochromocytoma, a tumor located either in or outside the adrenal gland, or may carry a genetic predisposition towards developing pheochromocytoma. Pheochromocytomas are a surgically correctable cause of chronic high blood pressure. The clinical features and consequences of pheochromocytoma result from release of substances 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.

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 locating the tumor 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), bone, octreotide, and fluorodeoxyglucose (FDG) positron emission tomography(PET) scans are types of nuclear medicine scans that are useful in identifying a pheochromocytoma but are not very sensitive and can miss a tumor. This protocol focuses on a new blood test and new imaging approaches, called fluorodopamine and fluorodopa positron emission tomographic (PET) scanning and MIBI scintigraphy.

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 and 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 any alcoholic beverages for 18 hours prior to blood testing and from taking Tylenol™ (generic name acetaminophen) in any form for 5 days prior blood testing. Water is the only permissible beverage.

If diagnostic tests indicate that you have a pheochromocytoma, you will be offered surgery at the NIH. You may benefit from the detection and removal of a 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 and number of tumors.

You may be offered genetic testing through the NIH to detect genetic mutations known to cause pheochromocytoma. If the results of the genetic testing indicate that you are positive for a mutation, we may extend the genetic testing opportunity to your first-degree relatives. Those that are positive for the mutation may be invited to the NIH for a history and physical examination, as well as relevant biochemical and imaging studies to detect pheochromocytoma. If pheochromocytoma is detected, the same management outlined above will be offered.

Pheochromocytoma can occur as part of diseases that run in families. At least four familial conditions are associated with pheochromocytoma: multiple endocrine neoplasia type 2 (MEN 2); von Hippel-Lindau (VHL) disease; neurofibromatosis type 1 (NF 1), and alteration of the gene for succinate dehydrogenase (SDHx). 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 with a genetic counselor.

As part of this protocol, we will be taking photographs of you at your first visit to facilitate facial recognition of patients by our medical team. Your photograph will be secured in a locked room and will only be used by members of our team for recognition purposes.

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.

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 will be made available to you and your physician.

BLOOD TESTS FOR PHEOCHROMOCYTOMA

We have found that the measurements of catecholamines and their breakdown products, 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 study considers this problem.

For blood tests you should remain in the lying position, resting, for at least 20 minutes before and during collection of the blood samples (10 cc, about 2 teaspoons). The samples are drawn without a tourniquet, through an indwelling i.v. catheter. No more than 10.5 mL/kg or 550 mL of blood will be drawn over an eight-week period.

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 and clonidine tests are usually done in the same testing session.

GLUCAGON STIMULATION TEST (FDA APPROVED)

This test is used to determine if a suspected pheochromocytoma can be stimulated to produce significant 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. catheter, 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 used to determine if you have high levels of plasma catecholamines being released 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. catheter for levels of catecholamines and metanephrines before and after clonidine is given. Clonidine often causes drowsiness and a fall in blood pressure, regardless of the presence of pheochromocytoma. These effects can last several hours 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.

BONE TURNOVER MARKERS

High levels of catecholamines may contribute to the development of osteoporosis. To screen for such a condition 2 ml of blood will be collected to measure 25(OH) vitamin D, parathormone, alkaline phosphatase, bone-specific alkaline phosphatase, and osteocalcin. Spots and twenty-four hour urine samples will be also collected to measure calcium, phosphorus, hydroxyproline, deoxypyridinoline, and pyridinoline.

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 (FDG) PET and DEXA scanning. You may undergo imaging studies before and after surgical treatment of pheochromocytoma. Fluorodopamine and fluorodopa PET scanning, and ^{99m}Tc-MIBI scintigraphy are considered research procedures.

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" shaped tube (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 [^{123}I]-MIBG or [^{131}I]-MIBG, you will be required to take medication called SSKI or potassium perchlorate (if you are allergic to iodides), 1 day before and 3-7 days after [^{123}I]-MIBG or [^{131}I]-MIBG administration, respectively.

DEXA SCANNING

Dual-energy x-ray absorptiometry (DXA) or bone densitometry (DEXA) is an X-ray often performed on the lower spine and hips. During DEXA examination, the patient lies on a padded table. An x-ray generator is located below the patient and an imaging device, or detector, is positioned above. DEXA is quick, lasting from 10-30 min and is painless. DEXA examination is equal to about 30 minutes of background radiation. This test is an excellent standard for measuring bone mineral density and diagnosis of osteoporosis.

FLUORODEOXYGLUCOSE (FDG) PET SCANNING

After injection of radioactive fluorodeoxyglucose (FDG), the tumor cells become radioactive, allowing the tumors to be seen on the PET scan. These FDG PET 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. 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 every 90 minutes for the next 6 hours to remove the radioactivie compound in the urine.

FLUORODOPAMINE AND FLUORODOPA PET SCANNING (RESEARCH SCAN)

The basis for visualization of pheochromocytoma in this study is PET scanning after injection of a synthetic, radioactive catecholamine called fluorodopamine or 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, it 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 to build proteins and transmit signals. Fluorodopa enters pheochromocytoma cells, they become radioactive and the PET scanner detects them. Also most cells in the body do not become radioactive after fluorodopa injection. You will receive a single oral administration of 200 mg of carbidopa 60 minutes prior to fluorodopa injection. This procedure increases the amount of fluorodopa in tumor. Carbidopa is a drug that is often used in the treatment of Parkinson disease.

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

^{99m}Tc-MIBI SCINTIGRAPHY (RESEARCH SCAN)

Pheochromocytomas consist of metabolically active cells that have high numbers of mitochondria, which are used to produce energy for the cell by using glucose as a fuel. In ^{99m}Tc-MIBI scanning we use a radioactive compound called ^{99m}Tc-MIBI that specifically visualizes mitochondria in cells with high metabolism. Tumor cells are expected to be more metabolically active than normal cells and to use more glucose as a consequence.

We hypothesize, that after injection of radioactive ^{99m}Tc-MIBI, this compound will be taken up more by pheochromocytoma cells than by surrounding tissues, allowing us to see the tumors.

You will not be permitted to eat anything for at least 3 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 scanning is done in the Nuclear Medicine Department. The scanner is shaped like a doughnut, and the part of your body being scanned is in the hole. A plastic catheter is inserted into an arm vein for injection of ^{99m}Tc-MIBI. During the injection you should feel nothing unusual. The first phase of the scanning takes 30 minutes and starts during the injection. Additional images will be taken for another 45 minutes (SPECT). You may be repositioned in the scanner in order to increase the field of view. In total, this test will take approximately 1.5 hours.

ADDITIONAL DIAGNOSTIC TESTING

URINE TESTING

Urine for biochemical diagnosis of pheochromocytoma will be collected 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, therefore, 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.

Samples of your blood cells or genetic material (DNA) will be used either for the diagnosis or for research about your medical condition. The genetic testing will be performed either by a CLIA certified laboratory or a non-certified laboratory (e.g. research laboratory). Even though the sensitivity and quality of the test parallel that of a certified laboratory, the

results from a non-certified laboratory will be classified as research and are not official. You may pursue genetic testing at a CLIA certified laboratory at your own cost. We may invite your family members to participate in the pheochromocytoma study based on the research test results or the CLIA certified results. The research may be done at the NIH. No other genetic testing will be done using your DNA unless you give specific permission, as indicated below. Genetic test results performed at a research laboratory can only be provided to you or those with whom you intend to share the results, under the Privacy Act of 1974, after you indicate your desire by signing a separate permission form.

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 information that may be discovered by genetic testing. Another 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.

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 are 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 try to grow the cells in a cell culture. We believe that pheochromocytoma research would benefit from the 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 a sound wave detector available 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 to ensure that appropriate allergy medications are made 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, imaging studies such as flurodopamine and fluorodopa PET, MIBG, octreotide, ^{99m}Tc-MIBI and bone scans and contrast CT will be not 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 (550 ml over any eight-week period).

Unexpected findings Because of the investigational nature of this study, we may not understand the significance of all findings. 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 to determine their significance.

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

Follow-Up You may return for follow-up conventional imaging or PET scanning at a later date, 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 the 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, you will be referred back to your 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, MIBI, the associated transmission scan and DEXA 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 and children.

FLUORODOPAMINE, FLUORODOPA, AND ^{99m}Tc-MIBI

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) and one ^{99m}Tc-MIBI scan (20 mCi per scan) per year. In addition

you will have transmissions scans to account for body thickness using either a low dose CT scan (up to 5 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, 2 fluorodopa scans, with their associated transmission scans, and one ^{99m}Tc-MIBI scan, you will receive up to 19.9 rem to your bladder wall, 7.4 rem to your kidneys, and 6.3 rem to your upper large intestine.
Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a maximum uniform whole-body exposure of up to 4.4 rem if all studies are performed. Usually, the amount of radiation exposure will not exceed 4.0 rem. These calculated values are known as the "effective dose" and are 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 15 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 0.18 percent. Therefore, your total risk of fatal cancer may increase from 25 percent to 25.18 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.

CONTRAST AND DRUG DYE EFFECTS

Fluorodopamine, fluorodopa and ^{99m}Tc-MIBI 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). These drugs are always immediately available for emergency use.
We, and many others, have used glucagon as a provocative test for pheochromocytoma for many years without significant adverse effects. 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.

OTHER GENERAL ISSUES RELATED TO THIS PROTOCOL

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.

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.

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, blood and urine samples unless you specifically give permission (as stated above).

The DNA and plasma collected from your blood and urine 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 the NIH, as well as from outside the 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.

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 choose to 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 authorized hospital accreditation organizations.

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. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

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: 301-402-4594 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 _____

Print Name _____

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 _____

Print Name _____

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 _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 22, 2009 THROUGH JULY 21, 2010.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____