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File Code No. 13-11-21
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715128

March 11, 1971

Campus Research Office

Re: Protocol Regarding USPH
Clinical Research Policy
USPH CA 08370, Lawrence
and Van Dyke

Gentlemen:

USPHS Grant CA 08370, "The Importance of Bone in Hematopoietic Marrow Function", involves two procedures done to, or requiring cooperation of the subject: 1) Intravenous injection of Fe-52 followed the next day by a two-hour period of scanning (lying on a bed); 2) Placement of an indwelling (plastic) needle in one peripheral antecubital vein and injection of F-18 in the opposite antecubital vein. Withdrawal of 1 ml blood samples at frequent intervals for a period of three hours. A whole body scan done 15 minutes and 3 hours after injection of the isotope.

Subjects will be patients undergoing study for diagnosis and treatment of diseases affecting the skeleton and blood. No normal volunteers will participate.

Procedure 1: Fe^{52} marrow distribution studies provide information about the marrow organ unobtainable by other means and has become a standard laboratory diagnostic procedure in the Donner Laboratory Clinic. This part of the study is undertaken for the patient's benefit.

Procedure 2: Determination of relative blood flow to the skeleton using F^{18} is a diagnostic procedure in bone disease but represents the primary research procedure in these studies as the information gained is of no direct benefit to the patient.

There should be no emotional or social deleterious effects upon the subject. Physical deleterious effects from the administration of radioactivity in the form of Fe-52 and F-18 represent the only possible hazard. This hazard is minimized by the highly sensitive positron scintillation camera and the short physical half-life of both isotopes. The upper limit of radiation dose to the bone marrow of a normal adult has been calculated to be 2.5 roentgens for a 100 μCi dose ("Human Bone Marrow Distribution Shown in vivo by Iron-52 and the Positron Scintillation Camera", Anger, H. O. and Van Dyke, D. C. Science, v.144, 1587-89, 1964). Because of its short half-life, F-18 delivers a relatively small radiation dose to the patient. Twenty-five percent of the administered dose is excreted via the urine. Assuming an intravenously administered dose of 200 μCi, and urine output at the normal rate of 1,500 ml/day, and that the bladder is empty at the time of administration (the condition that results in the highest radiation dose), the integral radiation dose to the bladder is about 0.5-1 rad. The average dose received by the rest of the body, excluding bone, is less than 20 millirads. Areas of bone that concentrate F-18 receive a higher dose that is difficult to estimate. However, assuming an extreme case where 1/10 of the administered dose is taken up by 10 gm of bone, the radiation dose is still below 1 rad. ("Bone Blood Flow Shown with F-18 and the Positron Camera." Van Dyke, D. C., Anger, H. O., Yano, Y., and Bozzini, C. Am. J. Physiol. 209:65-70, 1965.)

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The study involves human beings because no counterpart to most of the diseases being studied is known in animals.

Why the blood-forming marrow grows only in the most vascular parts of the skeleton is the subject of this research and it is believed that from these studies a better understanding of diseases involving the marrow will result.

Patients are informed as to the nature, potential risks and benefits of the procedures, and written consent is obtained prior to performance of the procedure. All information obtained during the course of the study is considered privileged communication.

This application for grant (or award) includes research procedures upon human subjects which conform to the policies of the Public Health Service and the University of California, Berkeley:

James R. Parr M.D.
Responsible Administrator

Principal Investigator

3005229

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Human Subject Protocol

The use of human subjects in the coming year will be confined to a study of erythropoietic marrow distribution, comparing radioactive iron (^{52}Fe) with Indium-chloride (^{111}In). It is important in diagnosis to have an accurate assessment of total erythropoietic marrow and its distribution. Our research requires that we make this determination using two different tracers. Iron is a physiological tracer but is not readily available and is less easily imaged than indium-chloride. It has already been established that in most instances the distribution of indium-chloride and radioactive iron are similar. However, there appear to be a limited number of patients in whom there is a discrepancy. By studying patients with different hematological disorders, both with iron and indium-chloride it is hoped to determine in which disease states indium-chloride does not give a true picture of erythropoietic marrow. All subjects will have the benefit of an accurate portrayal of their erythropoietic marrow with radioactive iron which will be valuable in their immediate management and prognosis. The additional indium-chloride scan will not help in their diagnosis.

The radioactive iron marrow distribution study provides information about marrow function and has become a standard laboratory diagnostic procedure in the Donner Laboratory Clinic. The upper limit of radiation dose to the bone marrow of a normal adult has been calculated to be 2.5 rads for a 100 μCi dose (Human Bone Marrow Distribution Shown *in vivo* of ^{52}Fe and the Positron Scintillation Camera. Anger, H.O. and Van Dyke, D.C., Science 144:1587-1589, 1964).

Indium-chloride has been approved by the FDA for advanced clinical trials in patients for the purpose of determining the sites

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and extent of marrow function. Indium-chloride is being used according to the protocol of Medi-Physics, Inc. The patients will receive no more than 2 mCi for adults weighing 70 kg or more and proportionately less for lighter people. Subjects under 18 years of age will not be studied unless there are exceptional indications. The radiation dose has been calculated to be 2.4 rads to the bone marrow, 4.5 rads to the liver, 0.5 rads to the total body, including the gonads, and 0.3 rads to the uterus, for each mCi of tracer administered.

Both isotope imaging techniques involve intravenous injection of a radioactive tracer and imaging 24 to 48 hours later. Imaging takes about 2 hours.

Subjects will be patients referred to the Donner Clinic and all age groups will be included. A complete hematological work-up including bone marrow cytology and ^{59}Fe tracer kinetics will be performed as part of the normal medical management of the patients. Both bone marrow imaging techniques involve similar risks to the patient as other nuclear medicine procedures and radiological tests.

The records and information obtained will be transmitted to the referring physician for use in the patient's immediate management. Medical privacy will be maintained. A copy of the consent form is attached.

John H Lawrence
Principal Investigator

James L. Bo[illegible]
Responsible Administrator

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for provision of required progress reports if a grant is awarded as the result of this application.

Date

Principal Investigator

3005231

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CONSENT TO ACT AS SUBJECT FOR
RESEARCH AND INVESTIGATIONS UNDER
USPH GRANT CA 08370

Your physician suspects that you have a problem involving your bones and bone marrow.

Patient's Name_____Date_____

1. I hereby authorize_____
   Name of person(s) who will perform procedures and investigations,
   and/or such assistants as may be selected by him to perform the following procedures and investigations:

   a. Inject radioactive iron today and take whole body scans the following day. The radioactive iron shows the places in the body where blood is manufactured.

   b. Inject radioactive indium, which is being investigated as a tracer (i.e., material that gives off a signal) to show the sites of blood formation. Take whole body scans, or pictures of the signals given off by the indium, 2 days later to compare with the scans taken with the radioactive iron. The indium scan is not essential for your diagnosis. Indium is cheaper and more readily available and is used in many centers in place of radioactive iron to look at the places in the body where blood is manufactured. In most patients iron and indium give the same answers. Our research has shown that in some blood disorders there are significant differences and that indium may not give an accurate picture. It is our aim to discover the types of blood disorders in which indium may be used.

2. The procedures and investigations listed above have been explained to me by _____.

3. I understand that the procedures and investigations described above involve the following possible risks and discomforts:

   a. The radioactive iron scan is necessary for the investigation of my suspected blood disease and involves some radiation to my bone marrow. The indium scan adds some further radiation dose, but the total radiation dose from both procedures is comparable to that received in special medical investigations using X-rays or radioisotopes.

   b. The radioactive tracers have been approved for experimental clinical trial by the Federal Drug Bureau.

   c. Discomforts: Both radioactive tracer tests involve the injection of a drug into a vein in the arm. Imaging procedures involve lying on a comfortable bed for extended periods (1-2 hours).

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d. Benefits: These studies will result in information leading to a better understanding of my disease. The two tests sometimes give different information and our research is aimed at determining the type of blood disorder in which this happens and what it means.

5. I understand that _____ will answer any inquiries I may have at any time concerning the procedures and investigations. I understand that I may terminate participation in the study at any time without prejudice to my medical care.

SUBJECT'S SIGNATURE: _____

WITNESS: _____

(If subject is a minor, or otherwise unable to sign, complete the following):

Subject is a minor (age: ____), or is unable to sign because

_____

_____

_____ _____

Father Guardian

_____

Mother