DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 24, 2000

George R. Newkome, Ph.D.
Vice President for Research
University of South Florida
4202 East Fowler Avenue, ADM 200
Tampa, Florida 33620-5950

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1284

Research Project: Water Handling and ADH Regulation in Moderately-High Altitude Natives
Principal Investigator: Dr. German Ramirez
IRB Protocol Number: 3465

Dear Dr. Newkome:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your September 20, 1999 report regarding the above referenced research project. OHRP apologizes for the delay in responding to your report.

OHRP Findings

Based upon its review of your September 20, 1999 report, as well as copies of the relevant Institutional Review Board records provided with your prior report of February 19, 1999, OHRP makes the following determinations regarding the above referenced research project:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111 stipulate specific criteria that must be satisfied in order for the IRB to approve research involving human subjects. OHRP finds that the IRB failed to ensure that the investigators submitted sufficient information in the protocol application, continuing review reports, and protocol amendments for the IRB to make the determinations required under 45 CFR 46.111. For example, OHRP notes the following:

(a) The IRB-approved protocol involved a series of procedures that would have posed greater risk for individuals with a variety of medical disorder including hyponatremia, hypernatremia, renal failure, heart failure, peptic ulcer disease, and

gastritis. While the protocol did list "any major organ disease process (cardiac, kidney, lungs, thyroid, etc.)" as an exclusion criterion, the protocol failed to stipulate a specific plan for ruling out such disorders in prospective subjects. For example, obtaining the results of a baseline serum chemistry profile to measure serum electrolytes and creatinine would have been appropriate before proceeding with the research procedures. Having failed to solicit such information, the IRB was unable to ensure that risks to subjects were minimized, as required by HHS regulations at 45 CFR 46.111(a)(1).

(b) The IRB-approved protocol provided no information on the source of prospective subjects or the procedures for recruiting subjects. Such information is relevant to IRB determination about whether informed consent will be sought from each prospective subject in accordance with the requirements of HHS regulations at 45 CFR 46.116. In particular, information about the relationships between the investigators and the potential subjects is relevant to the IRB determination regarding whether informed consent will be sought under circumstances that minimize the possibility of coercion or undue influence.

OHRP is concerned that some nephrology fellows and residents were recruited by Dr. Ramirez, the Director of the Division of Nephrology at the University of South Florida (USF), without the IRB having been informed of this in the protocol application.

(2) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds no evidence that the IRB reviewed and approved the following protocol modifications:

(a) Enrollment of 10 subjects living at sea-level during the one-year period following initial IRB approval in June 1994. In particular, OHRP notes the following:

(i) The IRB-approved protocol title references only "moderately-high altitude natives."

(ii) The initial IRB-approved protocol application proposed to enroll a total of 10 subjects.

(iii) The initial IRB-approved protocol application stated that measurement of total body water and ability to handle a free water load were to be measured in "HA" (i.e., "high altitude") natives and "each volunteer was to serve as their own control."

(iv) The initial IRB-approved informed consent document stated: "This research is designed to study the functioning of a hormone called antidiuretic hormone or ADH in persons living in moderately high altitude conditions. . . . Ten persons will participate."

(v) The first continuing review Research Progress Report dated April 30, 1995, indicated that 10 native subjects living at high altitude in South America and 10 subjects adapted to sea level in Tampa, Florida were enrolled during the first year of this research.

(vi) There is no written documentation that the investigator submitted, or the IRB approved, a protocol amendment proposing the enrollment of 10 subjects living at sea level during the first year of this project.

(b) The procedure under which the same 5 subjects were subjected twice to the hypertonic saline infusion test, once with indomethacin and once without indomethacin, in a randomly determined order. In particular, OHRP notes the following:

(i) In the May 12, 1997 Application for Change in Procedures, the principal investigator described the protocol modification as follows:

> "In order to more specifically investigate the role of prostaglandins (PGE2) in the secretion of AVP. . . . Oral indomethacin (25mg) will be administered to 5 moderately high altitude volunteers and 5 sea level control volunteers three times a day before the test day, then one dose the morning of the test (at 6 am). At 0800 the morning of the test day, a urine sample will be collected (baseline) (10ml aliquot). An IV will be inserted in a large vein and a calculated amount of hypertonic saline will be administered over the next 30 minutes. The calculation is obtained by using the formula: 100ml per m^2BSA as we previously reported (1). Blood will be drawn every 60min for the measurement of sodium, potassium, osmolality, arginine vasopressin (AVP), creatinine and the urine volume will be measured every 30min and an aliquot saved for the measurement of sodium, potassium, osmolality, creatinine, prostaglandin (PGE2), aquaporin-2 (AQP-2). The total estimated blood loss for this test is approximately 90mls."

(ii) The copy of the May 12, 1997 Application for Change in Procedures provided to OHRP by USF included a single data collection sheet entitled "INDOMETHACIN & HYPERTONIC SALINE TEST."

(iii) The IRB-approved informed consent document submitted with the May 12, 1997 Application for Change in Procedures described the indomethacin/hypertonic saline infusion test as follows:

> "[The test] involves receiving a medication called indomethacin the day before and the hypertonic saline infusion test day. You will be asked to take 25 mg of indomethacin by mouth three times the day before the infusion test, and one more dose of indomethacin at 6 am the morning of the test. During the test, you will have a temporary IV (indwelling catheter) placed in a vein in your arm for which blood samples will be drawn. This IV will remain in place for the duration of this test. You will be asked to empty your bladder before beginning the test. A salt solution will be given to you through the needle in your arm over 30 minutes. During the next three hours, at intervals of 30 minutes, urine samples will be collected and measured. Over the same three hours, at hourly intervals, blood samples will be collected to measure the levels of various hormones. The total blood to be withdrawn will be approximately 13 tablespoons. A physician and a nurse will be with you at all times during the study.

(iv) In a June 10, 1998 continuing review Research Progress Report, the principal investigator reported the following:

> "Five normal men living at SL in Tampa, Florida have recently been enrolled to receive a hypertonic saline infusion test, with and without indomethacin, 7 days apart. All subjects were randomly given an intravenous infusion test, with and without indomethacin ingestion, 7 days apart."

(v) There is no written documentation that the investigator submitted, or the IRB approved, a protocol amendment proposing the procedure under which the same 5 subjects were subjected twice to the hypertonic saline infusion test, once with indomethacin and once without indomethacin, in a randomly determined order.

(3) OHRP finds that the informed consent documents reviewed and approved by the IRB for this research failed to include an adequate description of the following elements of informed consent required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): the expected duration of the subject's participation and a complete description of the procedures to be followed. For example, with respect to the indomethacin/hypertonic saline infusion test, the IRB-approved

informed consent document failed to describe (i) the procedure under which the subjects were to undergo the hypertonic saline infusion test twice, once with indomethacin and once without indomethacin, in a randomly determined order; and (ii) the expected 7-day interval between the two infusion tests.

(b) Section 46.116(a)(2): An adequate description of the reasonably foreseeable risks and discomforts. For example, OHRP notes the following:

(i) The POTENTIAL RISKS section in the informed consent document approved by the IRB in 1996 states that "there are no known side effects from the administration of . . . indomethacin, or vasopressin in the amounts described earlier." Such a statement inappropriately minimized the potential risk of harms or discomforts associated with administration of indomethacin.

(ii) The POTENTIAL RISKS section of the informed consent documents approved by the IRB in 1997 and 1998 lacked an appropriate description of the potentially serious complication that can result from a rapid induction of hypernatremia from hypertonic saline administration.

(c) Section 46.116(a)(3): An adequate description of any benefits to the subject or others that may *reasonably* be expected from the research. In particular, the POSSIBLE BENEFITS TO THE RESEARCH section for all informed consent documents approved between 1994 and 1998 stated that "no guarantees can be made to the participant that his treatment will be beneficial." Such a statement was inappropriate since this research in healthy volunteers was not investigating any therapeutic intervention for the subjects.

(4) In view of the above findings, OHRP finds that the IRB's continuing review of this research protocol was not substantive or meaningful.

(5) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP finds that the following protocol changes approved by the IRB Chairperson under expedited review procedures significantly exceed the limitation of a minor change:

(a) The February 29, 1996 Application for Change in Procedure. This protocol change involved the following new experiments: (i) administration of four doses of indomethacin over a 24-hour period, followed by an oral water challenge test, in 5 subjects living at high altitude; and (ii) subcutaneous injection of vasopressin, followed by serial urine collections, in 5 subjects living at high altitude and 5 subjects living at sea level.

(b) The May 12, 1997 Application for Change in Procedures. This protocol change involved the following new procedures:

(i) Administration of four doses of indomethacin over a 24-hour period.

(ii) An intravenous infusion of hypertonic 5% saline at a dose of 100 mg/mm^2 BSA.

(iii) Serial blood and urine collections in 5 subjects living at high altitude and 5 subjects living at sea level following hypertonic saline infusion.

OHRP notes that the above modifications introduced new experiments that involved greater than minimal risk to the subjects.

OHRP acknowledges that Dr. Ramirez has left USF. Furthermore, OHRP notes that the above findings are indicative of the serious deficiencies in USF's system for protecting human subjects previously identified in the June 12, 1998 Food and Drug Administration Warning Letter that are the focus of another on-going OHRP compliance oversight investigation at USF. Therefore, OHRP is closing its compliance oversight investigation of this matter.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Barry B. Bercu, Chairperson, IRB-01/02, USF
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