MEDICAL ISOTOPES COMMITTEE

Place: Administrative Conference Room

Time: 1300 Hours

Chairman: Col Robert P. Turk, Chairman, Dept. of Surgery

Members Present: Col E. Pantoja, Chairman, Dept. of Radiology
Major S.V. Rao, Alternate, Dept. of Pediatrics
Major F.J. Connolly, Committee Secy, Radiation Physicist

Members Absent: Lt Col G.W. Hinzman, Chairman, Dept. of Nuclear Medicine (Leave)
Major S.D. McDonald, Staff Endocrinologist (Duty)

Guests: Lt Col William K. Rundell, Chief, Vascular Service, Dept. of Surge
Lt Col Mary L. McLaughlin, Chief, Operating Room Service
Major Richard W. Houston, Gastroenterologist, Dept. of Medicine

Members of the Institutional Review Committee
Members of the Human Experimentation Subcommittee

Copper-64 Cupric Acetate for Liver Function Study for Wilson's Disease.

a. The Medical Isotopes Committee met in conjoint session with the Institutional Review Committee and the Human Experimentation Subcommittee to review and approve the use of radioactive Copper-64 Cupric Acetate to be administered to a patient on a one-tim basis.

b. Lt Col Rundell, the surgeon who is scheduled to operate on the patient on Thursday 12 April 1979, presented the clinical history of this patient with Wilson's Disease. The clinical history follows:

(1) This 21 year old woman first noticed in the spring of 1977, the onset of difficulty with speech, a marked difficulty of coordination of the right upper extremity and some difficulty with gait. She was first seen at Wright-Patterson in September 1977 and a suggestion of a demyelinating disease was made at that time. She was followed and ultimately returned in January 1978, where a diagnosis of Wilson's Disease was made. Th was based upon the finding of Kaiser-Fleischer rings in the cornea, decreased serum ceruloplasmin, increased copper stores in the liver on liver biopsy, and the general neurologic picture. She was begun on penicillamine at that time and has shown a progressive improvement in her neurologic picture.

(2) The patient had her first episode of upper GI hemorrhage in August 1978, which was a minor upper GI bleed and required no blood transfusion. She had a recurrent bleed in October 1978, and at that time was found to have upper GI hemorrhage from bleeding esophageal varices. She did have an episode of hepatic coma at that time and required 9 units of whole blood transfusion. She had a recurrent upper GI hemorrhage from her varices in February 1978, which required 6 units of whole blood transfusion, and because of the recurrent variceal hemorrhage, was ultimately referred back to this medical facility for consideration for a porto-systemic shunt procedure.

(3) In August 1978, the patient was seen by Dr. I. Herbert Scheinberg at the Albert Einstein College of Medicine, New York City, who evaluated her. In addition to penicillamine, he started her on BAL and has maintained an interest in this patient.

(4) At the time of the present hospitalization, rather massive esophageal varices were again noted. She has had two episodes of minor upper GI hemorrhage while under observation at this hospital. Each has required approximately 3 units of blood transfusion.

(5) Lt Col Rundell first saw this young woman approximately 3 weeks ago and because of the recurrent episodes of upper GI hemorrhage, has recommended that she undergo a porto-systemic shunt, specifically a spleno-renal shunt. In addition to the esophageal varices, the patient has a rather massive enlargement of the spleen, which is on the basis of congestive splenomegaly and has a picture of hypersplenism. At the time of the spleno-renal shunt, Lt Col Rundell has also recommended that the patient undergo splenectomy.

(6) Lt Col Rundell and Major Houston have contacted Dr. Scheinberg, who feels that there is a basic underlying enzyme defect in the liver, which accounts for the problem with Wilson's Disease. For that reason, his recommendation has been that approximately two hours prior to the proposed operation, the patient be given radioactive Copper-64 in an amount of approximately 1-2 mg copper and 1 millicurie of Copper-64. At the time of the operation, approximately 2 hours after receiving the radioisotope, a biopsy of the liver in an amount of approximately 5 gm will be taken and will be given to Dr. Scheinberg for use as a laboratory evaluation of the enzymatic defect of Wilson's Disease.

(7) Lt Col Rundell is of the opinion that administration of this radioisotope will in no way interfere with or hinder the surgical care of this patient. It will be of value to the patient only in the sense of better understanding the basic pathology of Wilson's Disease, and possibly the identification of the specific enzyme deficiency which may be corrected. It is understood that the total amount of radiation delivered to the patient has not been shown to produce any harmful effects.

(8) Lt Col Rundell has conselled the patient on this proposal. She understands the proposal, the lack of provable benefit to her, and the lack of any known harmful effects occurring as a result of the administration of the radioactive copper.

(9) The diagnosis is:

(a) Wilson's Disease.

(b) Esophageal varices secondary to Wilson's Disease.

(c) Recurrent hemorrhage secondary to esophageal varices.

c. Major Connolly presented the details of the licensing problems associated with the use of this radiopharmaceutical and some of the attendant radiation safety problems.

(1) Lt Col Rundell approached Major Connolly on 5 April 1979 regarding the use of this radiopharmaceutical. Since this radiopharmaceutical is principally used for clinical research and diagnosis, most predominately by Dr. I. Herbert Scheinberg, it has not been approved for general use by the Food and Drug Administration and the U.S. Nuclear Regulatory Commission.

(2) Major Connolly contacted Dr. Scheinberg on 5 April 1979 to obtain some details regarding the use of this radioisotope. Dr. Scheinberg is authorized to use the Copper-64 Cupric Acetate at Albert Einstein College of Medicine, Yeshiva University, under the provisions of their New York City Broad License No. 188-7. This N.Y.C.

license does not, however, permit Dr. Scheinberg to use the radioisotope at other facilities. As a consequence, Major Connolly determined that the following approvals had to be obtained prior to its use at this medical facility:

(a) Approval of the Food and Drug Administration.

(b) Approval of the U.S. Nuclear Regulatory Commission.

(c) Approval of the USAF Radioisotope Committee at Brooks AFB, Tx.

(d) Approval of the Medical Isotopes Committee at this medical center.

(e) Approval of the Institutional Review Committee at this medical center.

(f) Approval of the Human Experimentation Subcommittee at this facility.

(3) On 6 April 1979, Major Connolly discussed this matter with Dr. Martin Nissel at the Food and Drug Administration, Washington, D.C. (Tel: 301-443-4260). Later that morning, Dr. Nissel returned the phone call to Major Connolly and stated that an Emergency IND (Investigational New Drug) Permit No. 16300 was approved for this Medical Center to use Copper-64 Cupric Acetate on a one-time basis for the study of Wilson's Disease in the patient. The documents for the IND will be sent to Major Connolly.

(4) On 6 April 1979, Major Connolly also discussed this matter with the U.S. Nuclear Regulatory Commission, License Management Branch, Washington, D.C. (Tel: 301-427-4232). His discussions with Mrs. Patricia Vacca and Dr. William Walker, Jr., indicated that the U.S.N.R.C. would approve a license amendment for this radiopharmaceutical provided that the USAF Radioisotope Committee, Brooks AFB, Tx concurred.

(5) On 6 April 1979, Major Connolly discussed the subject with Captain Ricci, Acting Secretary, USAF Radioisotope Committee, Brooks AFB. Approval was granted by Captain Ricci for the use of this radiopharmaceutical and for direct communication with the U.S.N.R.C. Copies of documents for licensing with the U.S.N.R.C. were to be sent to Captain Ricci.

(6) On 9 April 1979, a telegraphic message was sent to the U.S.N.R.C. requesting a one-time use amendment to our Byproduct Material License No. 34-04682-01 for the use of the Copper-64 Cupric Acetate. On 10 April 1979, Mrs. Patricia Vacca of the U.S.N.R.C. telephoned Major Connolly to state that Amendment No. 32 to the license had been issued on 10 April, and the documents would be sent to Major Connolly through the USAF Radioisotope Committee.

(7) On 6 April 1979, arrangements were made by telephone between Major Connolly and Dr. I. Herbert Scheinberg, Albert Einstein College of Medicine, for Dr. Scheinberg to send a copy of his curriculum vitae, bibliography and sample informed consent for consideration and approval by our Medical Isotopes Committee, Institutional Review Committee and Human Experimentation Subcommittee. These documents arrived on 10 April.

(8) Major Connolly also discussed the physical parameters of Copper-64. Copper-64 is a radioisotope with a physical half-life (decay time) of 12.8 hours and an estimated biological half-life (biological elimination time) of about 80 days. The net effective half-life (combination of physical and biological decay times) is approximately 12.7 hours. Copper-64 has a complex radioactive decay scheme, decaying to stable Nickel-64 by electron capture and positron emission 62% of the time and decaying to stable Zinc-64 by beta particle emission 38% of the time. The principal energies are: 0.656 MeV positron (19%), 0.573 MeV beta particle (38%), 1.34 MeV gamma photon (0.5%), 0.511 MeV positron annihi-

lation photons (2 photons 19%), and low-energy photons of 8.3 KeV (43%) due to electron capture. If the patient is given 1 millicurie of Copper-64, the expected whole body dose to the patient is estimated to be 260 millirads (approximately equivalent to the skin dose from 5 PA and lateral chest films), and the expected dose to the patient's liver based on a 45% uptake by the liver is estimated to be 4 to 7.5 rads (approximately equivalent to the dose from 1-2 upper GI series). The hazards to medical personnel will be from the gamma radiation and possible contamination of surgical equipment and gloves (gamma + beta radiation).

(9) Major Connolly stated that he would be present during the entire surgical procedure to monitor personnel and equipment for radiation hazards, and to advise on necessary precautions. Arrangements are to be made with Lt Col McLaughlin for the use of the operating room and equipment needed to minimize any possible radiation hazards and to contain the spread of radioactive contamination. Major Connolly stated that the surgical procedure involving the use of a recently administered radioisotope is new to this medical facility, and neither he nor any other members of the staff have had prior experience in this type of situation. Nevertheless, exposures to medical personnel during the procedure are expected to be within the limits of occupational exposure.

d. Major Connolly presented the credentials of Dr. I. Herbert Scheinberg for approval by the Medical Isotopes Committee for the use of Copper-64 Cupric Acetate for the study of this patient's disease. Dr. Scheinberg is Professor of Medicine and Head of the Division of Genetic Medicine at Albert Einstein College of Medicine, Yeshiva University, Bronx, New York. Dr. Scheinberg has been studying Wilson's Disease for more than 25 years and is considered to be an expert in this area. Dr. Scheinberg will administer the 1 millicurie Copper-64 dose to the patient at about 0600 hours on 12 April 1979, and will take a 5 gram liver biopsy specimen to New York for analysis. Lt Col Rundell and Major Connolly will be present when the radioisotope is administered to the patient.

e. The Medical Isotopes Committee granted approval for the use of this radiopharmaceutical on a one-time basis, under the conditions specified above.

f. The proposed patient "informed consent" was also presented for consideration by the Institutional Review Committee and the Human Experimentation Subcommittee. Both of these committees granted approval for the procedure.

6. The next meeting of the Committee will be at the call of the Chairman or the Secretary.

ROBERT P. TURK, Colonel, USAF, MC
Chairman, Medical Isotopes Committee
Chairman, Department of Surgery

FRANCIS J. CONNOLLY, Major, USAF, BSC
Secretary, Medical Isotopes Committee
Radiation Physicist

APPROVED/DISAPPROVED:

BEALER T. ROGERS, JR.
Colonel, USAF, MC
Commander

GUNTER R. MENG
Colonel, USAF, MC
Director, Hospital Services