NRC FORM 374
(7-94)

U.S. NUCLEAR REGULATORY COMMISSION

MATERIALS LICENSE

Amendment No. 38

Pursuant to the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974 (Public Law 93-438), and Title 10, Code of Federal Regulations, Chapter I, Parts 30, 31, 32, 33, 34, 35, 36, 39, 40, and 70, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, possess, and transfer byproduct, source, and special nuclear material designated below; to use such material for the purpose(s) and at the place(s) designated below; to deliver or transfer such material to persons authorized to receive it in accordance with the regulations of the applicable Part(s). This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954, as amended, and is subject to all applicable rules, regulations, and orders of the Nuclear Regulatory Commission now or hereafter in effect and to any conditions specified below.

399558

Licensee	
1. Hutzel Hospital	In accordance with letter received June 27, 1996 3. License Number 21-03001-01 is amended in its entirety to read as follows:
2. 4707 St. Antoine Detroit, MI 48201	4. Expiration Date February 28, 2001
	5. Docket or Reference No. 030-02024

6. Byproduct, Source, and/or Special Nuclear Material	7. Chemical and/or Physical Form	8. Maximum Amount that Licensee May Possess at Any One Time Under This License
A. Any byproduct material identified in 10 CFR 35.100	A. Any radiopharmaceutical identified in 10 CFR 35.100	A. As needed
B. Any byproduct material identified in 10 CFR 35.200	B. Any radiopharmaceutical identified in 10 CFR 35.200	B. As needed
C. Any byproduct material identified in 10 CFR 35.300	C. Any radiopharmaceutical identified in 10 CFR 35.300	C. As needed
D. Any byproduct material identified in 10 CFR 35.400	D. Any brachytherapy sources identified in 10 CFR 35.400	D. As needed
E. Any byproduct material identified in 10 CFR 35.500	E. Sealed sources identified in 10 CFR 35.500	E. As needed
F. Any byproduct material identified in 10 CFR 31.11	F. Prepackaged Kits	F. As needed
G. Hydrogen-3	G. Any	G. 500 millicuries
H. Carbon-14	H. Any	H. 99 millicuries
I. Iodine-131	I. Any	I. 1 curie

270095

o/c 2 ML 30 SD

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number 21-03001-01

Docket or Reference Number 030-02024

Amendment No. 38

6. Byproduct, source, and/or special nuclear material	7. Chemical and/or physical form	8. Maximum amount that licensee may possess at any one time under this license
J. Iodine-125	J. Any	J. 1 curie
K. Phosphorus-32	K. Any	K. 500 millicuries
L. Sulfur-35	L. Any	L. 100 millicuries

9. Authorized Use:

A. Medical use described in 10 CFR 35.100.

B. Medical use described in 10 CFR 35.200.

C. Medical use described in 10 CFR 35.300.

D. Medical use described in 10 CFR 35.400.

E. Medical use described in 10 CFR 35.500 in devices which have been evaluated and approved for licensing purposes by the U.S. Nuclear Regulatory Commission or an Agreement State.

F. through H. In-vitro studies.

I. through L. To be used for in-vitro studies and animal studies.

CONDITIONS

10. Licensed material shall be used only at the licensee's facilities located at 4707 St. Antoine, Detroit, Michigan 48201.

11. A. Radiation Safety Officer: Ray A. Carlson, M.S.

B. Alternate Radiation Safety Officer: Nandalal Bagchi, M.D.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number
21-03001-01

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030-02024

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12. Authorized Users:

A. Kenneth M. Nowicki, M.D., for material in 10 CFR 35.100, 35.200, 35.300 and 35.500.

B. William E. Powers, M.D., for material in 10 CFR 35.400 and 35.500.

C. Nandalal Bagchi, M.D., for technetium-99m for thyroid imaging iodine-131 for diagnosis and therapy.

D. Thomas R. Brown, Ph.D., for hydrogen-3 and iodine-125 for in-vitro studies and iodine-131 for in-vitro and animal studies.

E. Jerry C. Rosenberg, M.D., for hydrogen-3 and carbon-14 for in-vitro studies.

F. Arnold M. Herskovic, M.D., for material in 10 CFR 35.400 and 35.500.

G. Navinchandra J. Parekh, M.D., for material in 10 CFR 35.100, 35.200, 35.300 (excluding iodine-131 for thyroid carcinoma) and 35.500.

H. Joseph Wiener, M.D., for in-vitro studies.

I. G. C. Critchfield, M.D., for in-vitro studies.

J. Paul Lattin, D.O., for material in 10 CFR 35.400 and 35.500.

K. Vaneerat Ratanatharathorn, M.D., for material in 10 CFR 35.400 and 35.500.

L. Ihn Hwan Kim Han, M.D., for material in 10 CFR 35.400 and 35.500.

M. Khusid Ahmad, M.D., for material in 10 CFR 35.400 and 35.500.

N. Young H. Kim, M.D., for material in 10 CFR 35.400 and 35.500.

O. Jack D. Sobel, M.D., for hydrogen-3 and carbon-14 for in-vitro studies.

P. Joan C. Stryker, M.D., for material in 10 CFR 35.500.

Q. Arthur Porter, M.D., for material in 10 CFR 35.400 and 35.500.

R. Jeffrey Forman, M.D., for material in 10 CFR 35.400 and 35.500.

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S. Laurie Gaspear, M.D., for material in 10 CFR 35.400 and 35.500.

T. Amr Aref, M.D., for material in 10 CFR 35.400 and 35.500.

U. David Donath, M.D., for material in 10 CFR 35.400 and 35.500.

V. Lawrence P. Davis, M.D., for material in 10 CFR 35.100, 35.200, 35.300 and 35.500.

W. James Fontanesi, M.D., for material in 10 CFR 35.400 and 35.500.

X. Michael P. Diamond, M.D., for material in 10 CFR 10 CFR 35.100.

Y. Winston W.K. Koo,, M.B.B.S., for hydrogen-3, iodine-125 and iodine-131 for in-vitro studies.

13. Pursuant to Title 10, Chapter 1, Code of Federal Regulations, Part 40, "Domestic Licensing of Source Material," the licensee is authorized to possess, use, transfer, and import up to 999 kilograms of depleted uranium contained as shielding material in the molybdenum-99/technetium-99m generators authorized by this license.

14. The licensee shall maintain records of information important to safe and effective decommissioning at 4707 St. Antoine, Detroit, Michigan per the provisions of 10 CFR 30.35(g) until this license is terminated by the Commission.

15. The licensee shall follow procedures contained in Appendix C, "Model Procedure For Calibrating Dose Calibration," Regulatory Guide 10.8, Revision 2, August 1987.

16. The licensee shall follow procedures contained in Appendix K, "Model Guidance For Ordering and Receiving Radioactive Materials," Regulatory Guide 10.8, Revision 2, August 1987.

17. The licensee shall maintain records of the individuals who have received training as described in application dated June 29, 1990, Item 8.1, "Personnel Training Program."

18. The licensee shall maintain the imaging room where xenon-133 is used at negative pressure.

19. As an exemption from Section 34.40(a), 10 CFR Part 35, the licensee may release patients from the medical institution while undergoing therapy with the Collaborative Ocular Melanoma Study Brachytherapy Plaques as describe in letter dated May 18, 1992.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number
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030-02024

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20. Except as specifically provided otherwise in this license, the licensee shall conduct its program in accordance with the statements, representations, and procedures contained in the documents, including any enclosures, listed below, except for minor changes in the medical use radiation safety procedures as provided in 10 CFR 35.31. The Nuclear Regulatory Commission's regulations shall govern unless the statements, representations, and procedures in the licensee's application and correspondence are more restrictive than the regulations.

A. Application dated June 29, 1990 (excluding Items 9.1.A, 10.17, and 10.18); and

B. Letters dated July 5, 1989, January 29, 1991 (with attachments), February 18, 1992 (Model Procedure for Calibrating Dose Calibrator only), July 20, 1992 (except Items 4 and 5), and October 21, 1996.

FOR THE U.S. NUCLEAR REGULATORY COMMISSION

Date 11/1/96

By James Mullauer
Nuclear Materials Licensing Branch, Region III

COPY

BETWEEN:

LICENSE FEE MANAGEMENT BRANCH, ARM
AND
REGIONAL LICENSING SECTIONS

(FOR LFMS USE)
INFORMATION FROM LTS

PROGRAM CODE: 02120
STATUS CODE: 0
FEE CATEGORY: 7C 2B
EXP. DATE: 19960228
FEE COMMENTS:
DECOM FIN ASSUR REQD: N

RECEIVED
REGION 1

LICENSE FEE TRANSMITTAL

A. REGION

1. APPLICATION ATTACHED
   APPLICANT/LICENSEE: HUTZEL HOSPITAL
   RECEIVED DATE: 951129
   DOCKET NO: 3002024
   CONTROL NO.: 399558
   LICENSE NO.: 21-03001-01
   ACTION TYPE: AMENDMENT

2. FEE ATTACHED
   AMOUNT:
   CHECK NO.: X

3. COMMENTS
   X addl docs
   39811-R4

SIGNED D. Hersey
DATE 11-30-95

B. LICENSE FEE MANAGEMENT BRANCH (CHECK WHEN MILESTONE [illegible] ERED /__/)

1. FEE CATEGORY AND AMOUNT: 7C 2B FEE NOT REQUIRED

2. CORRECT FEE PAID. APPLICATION MAY BE PROCESSED FOR:
   AMENDMENT ✓
   RENEWAL
   LICENSE

3. OTHER

SIGNED AC
DATE 12/5/95

RECEIVED BY LFDCB
Date Dec. 4 1995
Log Dec 4 III
By AC
Date Completed 12/5/95

PLEASE TYPE

398111
HIC PROTOCOL NUMBER

REQUEST FOR REVIEW OF HUMAN SUBJECTS
PROTOCOL REVIEW FORM

TITLE OF PROJECT: Testosterone Induced Insulin Insensitivity
(Subsection II: Testosterone Administration)

IS THIS A RESEARCH PROPOSAL? X DISSERTATION/THESIS? _____

NAME OF PRINCIPAL INVESTIGATOR: Michael P. Diamond, M.D.

DEPARTMENT: Obstetrics and Gynecology

OFFICE ADDRESS Hutzel Hospital PHONE #: 993-8331

NAME(s) OF ANY CO-PI(s): Charla M. Blacker, M.D., Kenneth A. Ginsburg, M.D., Richard E. Leach, M.D. and Kamran S. Moghissi, M.D.

WSU FACULTY/STUDENT STATUS (if applicable): Professor

INCLUSIVE DATES OF PROJECT: Present - April 1988

SOURCE OF FUNDING (if any): NIH RO1 HD28984

WILL FUNDS FOR PROJECT BE PROCESSED THROUGH WSU? YES X NO
IF NOT WSU, WHERE?

ARE THERE ANY COSTS TO THE SUBJECTS AS A RESULT OF THEIR PARTICIPATION IN THIS RESEARCH STUDY? YES NO X . IF YES, A STATEMENT TO THAT EFFECT MUST BE INCLUDED IN THE CONSENT FORM. **(SEE REVISED ENCLOSURE #3)**

DOES THIS PROJECT REQUIRE EITHER AN INVESTIGATIONAL NEW DRUG (IND) NUMBER OR AN INVESTIGATIONAL DEVICE EXEMPTION (IDE) FROM THE FOOD AND DRUG ADMINISTRATION? YES NO X . IF YES, PLEASE PROVIDE THE NUMBER ASSIGNED _____.

COMMITTEE APPROVAL WILL NOT BE GIVEN UNTIL ALL NECESSARY IND OR IDE NUMBERS HAVE BEEN OBTAINED AND SUBMITTED TO THE IRB OFFICE.

ADD'L info - 398111
FEE NOT REQUIRED

I. EXPERIMENTS IN WHICH HUMAN SUBJECTS ARE TO BE USED:

A. How and from what sources will human subjects be obtained? If any type of advertisement is to be used to recruit subjects, a copy must be submitted to the HIC for approval.

Subjects will be recruited from the clinics of the Department of Obstetrics and Gynecology, as well as from written advertisement (see attached).

B. How many subjects will be used in this study?

One group of 12 normal females will be studied.

C. What is the age range of the subjects?

Ages 18-40

D. NIH policy states that "NIH staff and peer advisory groups are to ensure that applications/proposal & awards for extramural support for clinical research studies involving human subjects include <u>appropriate representation of women and minorities, unless a compelling justification is made for their exclusion or inadequate representation</u>." Explain how you intend to comply with this policy or give justification for the exclusion or inadequate representation of women and/or minorities.

Only female subjects will be included since we are evaluating the effect of increased testosterone levels on insulin action in women.

Subjects inclusion will be independent of race and ethnicity.

E. Since only two reviewers will have COMPLETE copies of your research protocol, give a concise, but complete, summary of the experimental procedures in which human subjects will be used so that all committee members can evaluate the project. (PLEASE DO NOT REFER TO PAGE NUMBERS IN THE PROTOCOL)

Subjects: Studies will be performed in regularly menstruating women (18-40) without any major organ system disease. Subjects will have normal basal levels of testosterone, free testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS). Pregnant or lactating women will be excluded. Confirmation of absence of pregnancy will be by serum pregnancy tests, and instructions will be given to use barrier contraception if sexually active. All subjects will be within 20% of ideal body weight (based on 1983 Metropolitan life Insurance Tables), and have a waist/hip ratio of <0.75.[18] Subjects taking oral contraceptives or other medications will be excluded.

Experimental Protocol: In this study, we will give subjects micronized testosterone to increase their serum testosterone level. Three pairs of study types will be performed in 12 subjects for each study type. Prior to starting testosterone therapy, all subjects will have a pregnancy test to exclude pregnancy, and will be instructed to use a barrier means of contraception throughout the duration of the study. For 3 days prior to each study, subjects will be placed on a diet containing 200-250 grams of carbohydrate. For all studies, subjects will be placed NPO at 10 PM the evening prior to the study day. Subjects will have body fat distribution determined by magnetic resonance imaging (MRI), by caliper measurement of skinfold thickness at six locations, and by measuring the waist/hip ratio. Elevation of the serum testosterone level will be accomplished by oral administration of micronized natural testosterone at a dose shown during our preliminary studies sufficient to reach a mildly elevated mean level of 1.0-1.4 ng/ml. Subjects will therefore receive 2.5 mg of micronized testosterone qid for two weeks.

Study #1: This study is a two hour oral glucose tolerance test. This test takes approximately three hours for completion.

Prior to initiation of the study, blood will be drawn to check each subject's hematocrit. Anemic individuals will not be studied. Female subjects will also have a pregnancy test to exclude pregnancy.

The morning of the study, subjects will have two intravenous catheters placed, the first in an antecubital vein, which will be used for infusion of the test substances described below. The second catheter will be placed in the wrist vein, which will be used for blood sampling, and will be placed in the hot hand box (70°C).

Study #2. Each subject will have a hyperglycemic clamp study performed. For the female subjects this will be done initially during the midfollicular (days 3-10) phase of the menstrual cycle. The precise time during the menstrual period will be documented by menstrual history as is customarily done in the clinical practice of reproductive endocrinology, and will be confirmed by the actual hormonal determination of estradiol, estrone, progesterone, and 17-hydroxyprogesterone on the day of study.

This study will consist of a two hour hyperglycemic clamp which will be performed to quantitate the early, late, and total insulin responses and to provide a measure of overall glucose tolerance under hyperglycemic conditions. Briefly, the plasma glucose concentration will be acutely raised and maintained 125 mg/dl above the fasting value by a primed-variable glucose infusion for 2 hours. All blood samples will be obtained from arterialized venous blood using the hot hand technique. The urine glucose concentration and volume will be determined at the end of the study. Additionally, resting metabolic rates will be measured intermittently over the entire course of the sampling period. This hyperglycemic clamp study will take approximately 4 h to complete. Subjects will be fed a meal at the completion of this study and then discharged.

Study #3. A two step euglycemic hyperinsulinemic clamp study will be performed to quantitate insulin-mediated glucose and amino acid metabolism and to determine the mean clearance rate (MCR) of insulin. This study will be completed during the follicular phase of the menstrual cycle.

At the initiation of the study, subjects will] receive a bolus injection of labelled sodium b .carbonate ($NaH^{13}CO_3$), labelled leucine (-[1-^{3}C]leucine) and labelled glucose ([3-^{3}H]glucose or [6,6-$^{2}H_2$]glucose) to prime the CO_2, leucine and glucose pools, respectively. A continuous infusion of the leucine and glucose isotopes will then be started and continued throughout the remainder of the study. Following a two hour equilibration of the isotopes and a 30 min basal sampling period, a continuous infusion of insulin (graded doses at 0.15, 0.6, 1.2, 2.5, 5.0 or 10 mU/kg.min) will be administered over a 5 hr period. The 5 hr experimental period will be divided into two 2.5 hr periods with different doses of insulin randomly offered each period. Plasma glucose will be monitored every 5 min and exogenous glucose (D-20) will be given to keep the subjects blood glucose levels constant.

Blood samples will be obtained from the superficial hand vein every 10 min during the basal period and the final 30 min of each experimental period. Simultaneous with the blood samples, breath samples will be taken from the subject via a Douglas bag. Additionally, resting metabolic rates will be measured intermittently over the entire course of the sampling periods.

At the conclusion of the study, the glucose infusion will be continued for up to 30 min following the discontinuation of the isotope tracers and insulin infusion. Catheters will be removed, subjects fed a meal and discharged. The time for completion of this study is approximately 8 hrs.

Subjects will undergo each set of the three study types twice, once prior to treatment with micronized testosterone and once again during micronized testosterone treament.

F. Please explain the rationale for and the significance of the experimental procedures described above.

Evidence from a variety of sources, including animal [1,2] and epidemiologic[3-8] studies suggest that hyperinsulinism is associated with an increased risk of coronary vascular complications. Hyperinsulinemia is characteristically seen in both obesity and Type II (adult onset) diabetes, conditions that predispose individuals to atherosclerotic disorders.[5,9] Epidemiologic data has also linked hyperandrogenism, hyperinsulinemia, and coronary vascular disease in women with polycystic ovarian syndrome.[10-12]

The association of hyperandrogenism and hyperinsulinism may result from either insulin stimulation of androgen production, androgen induction of hyperinsulinemia. If both relationships exist, a vicious cycle would be established. Insulin stimulation of androgen accumulation has been identified in several reports.[13-16] Androgen induction of hyperinsulinemia, may result either directly by stimulating pancreatic insulin secretion, or indirectly by inducing tissue insensitivity to insulin with subsequent compensatory hyperinsulinism. Unfortunately, many of the reports evaluating the association between hyperandrogenism and hyperinsulinism have included subjects with acanthosis nigricans (AN) (in whom insulin receptor defects have been characterized) or women with anti-insulin antibodies. While serving to focus attention on the issue of hyperandrogenism and insulin sensitivity, the tendency to focus on subjects with AN has to some extent drawn attention away from physiological questions. The key issue that needs to be clarified is the relationship of testosterone to insulin insensitivity in the much larger and more important group of hyperandrogenic women without AN.

Recently, we have unequivocally demonstrated that exogenous administration of synthetic androgen causes insulin insensitivity! After only short term (10-12 days) administration of 17-alpha-methyltestosterone to regularly cycling women, we found glucose uptake to be dramatically reduced in both euglycemic, hyperinsulinemic clamp studies and hyperglycemic clamp studies. Additionally, in female dogs in which we also used the euglycemic, hyperinsulinemic clamp technique, the natural androgen testosterone caused a pronounced fall in glucose utilization. Thus, these three separate studies consistently show that androgens directly modulate the action of insulin, and reduce total body insulin sensitivity. These findings are also consistent with the recent report of Hulmang et al[17] who also used the euglycemic clamp technique and showed that treatment of oophorectomized female rats with testosterone enanthate decreased whole body glucose uptake.

In this proposal, we seek to assess the effect of natural testosterone per se on carbohydrate, protein, and lipid metabolism. To assess this issue, studies will be conducted before and after administration of micronized testosterone in safflower oil at doses which we have previously been demonstrated to read peak testosterone concentrations of approximately 1.3 ng/ml (normal 0.2-0.6 ng/ml), and to remain elevated for six hours.

II. WHERE WILL THE RESEARCH PROJECT BE CONDUCTED?

Hutzel Hospital

III. DESCRIBE THE NATURE AND DEGREE OF POTENTIAL RISKS TO THE HUMAN SUBJECTS PARTICIPATING IN THE PROJECT:

A. A total of approximately 500 cc of blood will be drawn during the euglycemic and hyperglycemic clamp studies. The total blood loss for all studies combined is within the guidelines established by the American Red Cross. Subjects will be questioned about previous blood loss within the two months prior to their participation in the present study. If the cumulative blood loss exceeds that established by the American Red Cross they will be excluded from the study. All subjects will be warned that they should not participate in any other studies that require blood donation for at least two months after completion of the present study protocol.

B. A small polyethylene catheter will be placed into an antecubital vein for the infusion of test substances. Withdrawal of blood samples will be from an "arterialized" hand vein (Use of the "arterialized" hand vein allows attainment of venous samples which are equivalent to arterial samples with regard to levels of glucose, metabolites, hormones, and 3-^{3}H-glucose. This allows avoidance of the discomfort and morbidity associated with arterial catheterization. It should be noted that the PI helped validate the use of this technique [22]). Local hematomas have been observed in about 0.1% and local mild pain occurs in less than 0.5%.

C. The total dose of 3-^{3}H-glucose to be administered to a subject will be less than 900 uCi/year. Even though the dose of radioisotope is well within acceptable limits for radiation exposure, we will suggest that subjects discuss their participation in this study before participating in future studies requiring radioisotopes.

D. Drug Administration

Glucose. Glucose infusion in the hyperglycemic clamp studies is designed to cause hyperglycemia and to counterbalance the metabolic effects of insulin. No side effects of glucose are known.

Insulin. There is a potential for subjects to develop signs of hypoglycemia during the insulin infusion. This would include shakiness, diaphoresis, tachycardia, and drowsiness. This risk is minimized by measuring plasma glucose levels every 5-10 min during insulin infusion, and infusing glucose to prevent hypoglycemia.

Testosterone. In our experience, women receiving methyltestosterone for up to two weeks (the duration to be given in this study) have had no adverse effects. In the literature, patients receiving androgen administration have occasionally been reported to experience nausea, weight gain, increase in acne, menstrual irregularity; if these side effects are excessive, the drug will be discontinued and the study dropped. With more prolonged administration than will be utilized in this study (e.g. one year), androgen side effects may develop (e.g. increased hair growth and voice changes).

E. In this proposal, magnetic resonance imaging of body fat distribution will be performed with 1.5 T magnet. Use of these magnets in individuals without metallic implants is not know to present a health hazard.

IV. WHAT PRECAUTIONS WILL BE TAKEN TO MINIMIZE THE RISKS DESCRIBED ABOVE?

A. Any subject with a history of heart disease, peripheral vascular disease, chest pain, pulmonary disease, asthma, or hepatic disease will not be studied. No pregnant patients will be studied. Patients with a hematocrit less than 35% will not be studied.

B. There are no risks associated with indirect calorimetry.

C. Pregnant women will not be allowed to participate in the present study protocol. Therefore, if any women of child bearing potential wishes to participate in the study, they will have to have a negative pregnancy test as measured by radioimmunoassay of the β-subunit of hCG.

D. Glucose will be monitored frequently to avoid hypoglycemia both during and after the study.

E. The total radiation dose of tritiated glucose is very low. The label is lost irreversibly to body water. Previous evaluation has demonstrated loss of plasma radioactivity within 24 h.

F. Magnetic resonance imaging is not known to cause health hazards except in individuals with pacemakers or metallic implants. Individuals with metallic implants will be excluded from the study.

V. DESCRIBE THE PROVISIONS TO BE TAKEN TO MAINTAIN THE CONFIDENTIALITY OF RECORDS AND THE ANONYMITY OF HUMAN SUBJECTS:

All documents and data collected as a result of this study will be retained by the investigator. Access to this material will be available only to the research investigator and his staff; except in those instances when the data collected will become part of the subject's medical/clinical record. If results of this study are to be published, only code numbers will be used for identification purposes. Participants will not be identified by name.

VI. ARE THERE ANY BENEFITS TO THE HUMAN SUBJECTS AS A RESULT OF THEIR PARTICIPATION IN THIS RESEARCH STUDY?

There are no personal benefits to be gained by participating in this study.

VII. LIST THE QUALIFICATIONS OF THE PRINCIPAL INVESTIGATOR AND THOSE OF ANY CO-PI WHO WILL BE INVOLVED IN CARRYING OUT THIS STUDY:

The PI is specialty certified in Obstetrics and Gynecology and subspecialty certified in Reproductive Endocrinology and Infertility. He has been involved in the conduct of metabolic clamp studies since the early 1980's, has performed over 200 clamp studies, and has published multiple papers on their methodology and applications.

WHEN AN APPROVAL STATEMENT IS ISSUED BY THE IRB, SUCH APPROVAL IS BASED ON THE PROTOCOL AND CONSENT FORM SUBMITTED WITH THIS APPLICATION FORM. IN SIGNING THIS APPLICATION FORM, THE PRINCIPAL INVESTIGATOR AGREES THAT HE/SHE WILL BE RESPONSIBLE FOR THE CONDUCT OF THE INVESTIGATION AS APPROVED AND THAT INFORMED CONSENT WILL BE OBTAINED FROM EACH HUMAN SUBJECT INVOLVED AND SUCH SIGNED INFORMED CONSENT WILL BE KEPT ON FILE UNDER THE JURISDICTION OF THE PI. IF THERE ARE CHANGES IN THE PROTOCOL AND/OR CONSENT FORM, SUCH CHANGES MUST BE SUBMITTED TO THE IRB FOR REVIEW AND APPROVAL PRIOR TO THEIR IMPLEMENTATION. IT SHOULD BE UNDERSTOOD THAT APPROVAL BY THE HIC DOES NOT CONSTITUTE ANY ACCEPTANCE OF RESPONSIBILITY FOR THE CONDUCT OF THE INVESTIGATION BY WAYNE STATE UNIVERSITY OR ANY OTHER INSTITUTION FOR WHICH THE HIC SERVES BY AGREEMENT AS AN INTERNAL REVIEW BOARD. MEDICOLEGAL RESPONSIBILITY MUST REMAIN WITH THE INVESTIGATOR(S).

Michael P. Diamond, M.D. — Name of PI (Type)

Professor — Title

Signature — Date

ALTHOUGH THE HIC HAS THE RESPONSIBILITY TO REVIEW THE SCIENTIFIC OR EDUCATIONAL MERIT OF A RESEARCH PROPOSAL IN EVALUATING THE RISKS TO HUMAN SUBJECTS, IT DEPENDS ON REVIEW AT THE SCHOOL/DEPARTMENTAL LEVEL FOR CERTIFICATION OF SUCH MERIT. THE SIGNATURE OF THE APPROPRIATE DEAN/CHAIRPERSON OR THAT OF AN AUTHORIZED INDIVIDUAL DESIGNATED TO SIGN IN HIS/HER ABSENCE INDICATES THAT THE PROPOSAL HAS BEEN REVIEWED AND FOUND TO BE SCIENTIFICALLY/EDUCATIONALLY SOUND.

David B. Cotton, M.D., Professor, Chairman and Chief, Dept. Ob/Gyn

Name of Dean/Chairperson (please type) or Authorized Designee — Title

Signature — Date

REFERENCES

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17. Hulmang A, Svedberg J, Jennische E, Bjorntorp P: Effects of testosterone on muscle insulin sensitivity and morphology in female rats. Am J Physiol 259:E555, 1990.
18. Peiris AN, Mueller RA, Smith GA, Struve MF, Kissebah AH: Splanchnic insulin metabolism in obesity. J Clin Invest 78:1648, 1986.
19. DeFronzo RA: Glucose intolerance and aging: evidence for tissue insensitivity to insulin. Diabetes 28:1095, 1979.
20. Abrumrad NN, Rabin D, Diamond MP, Lacy WW: Use of a heated superficial hand vein as an alternative site for the measurement of amino acid concentrations and for the study of glucose and alanine kinetics in man. Metabolism 30:936-940, 1981.
21. Diamond MP, Hallarman L, Starick-Zych K, Jones TW, Connolly-Howard M, Tamborlane WV, Sherwin RS: Suppression of counterregulatory hormone response to hypoglycemia by insulin per se. J Clin Endocrinol Metab 72:11391, 1991.
22. Thieband D, Jacot E, DeFronzo RA, Mueder E, Jeqnier E, Felber JP: The effect of graded doses of insulin on total glucose uptake, glucose exudation, and glucose storage in man. Diabetes 31:957, 1982.

23. DeFronzo RA, Tobin JD, Andres R: The glucose clamp technique: a method for quantifying insulin secretion and resistance. Am j Physiol 6:214, 1979.
24. DeFronzo RA, Ferrannini E, Hendler R, Felig P, Wahren J: Regulation of splanchnic and peripheral glucose uptake by insulin and hyperglycemia. Diabetes 32:35, 1983.
25. Elahi D, Meneilly GS, Minaker KL, Andersen DK, Rowe JW: Escape of hepatic glucose production during hyperglycemic clamp. Am J Physiol 257:E704-E711, 1989.
26. Flakoll PJ, Kulaglat M, Frexes-Steed M, Hourani H, Brown LL, Hill JO, Abumrad NN: Animo acids augment insulin's suppression of whole body proteolysis. Am J Physiol E839-E874, 1989.
27. Allsop JR, Wolfe RR, Burke JF: Tracer priming the bicarbonate pool. Am J Physiol 45:137-138, 1978.

NOV 0 5 1996

Ray A. Carlson, M.S.
Radiation Safety Officer
Hutzel Hospital
4707 St. Antoine
Detroit, MI 48201

Dear Mr. Carlson:

Enclosed is Amendment No. 38 to your NRC Material License No. 21-03001-01 in accordance with your request.

Please review the enclosed document carefully and be sure that you understand all conditions. If there are any errors or questions, please notify the U.S. Nuclear Regulatory Commission, Region III office at (630) 829-9887 so that we can provide appropriate corrections and answers.

Please also note that the expiration date on your NRC license was extended five years in accordance with 10 CFR 30.36(2).

Please be advised that your license expires at the end of the day, in the month, and year stated in the license. Unless your license has been terminated, you must conduct your program involving byproduct materials in accordance with the conditions of your NRC license, representations made in your license application, and NRC regulations. In particular, note that you must:

1. Operate in accordance with NRC regulations 10 CFR Part 19, "Notices, Instructions and Reports to Workers; Inspections," 10 CFR Part 20, "Standards for Protection Against Radiation," and other applicable regulations.

2. Notify NRC, in writing, within 30 days:

   a. When an authorized user or Radiation Safety Officer permanently discontinues performance of duties under the license or has a name change; or

   b. When the licensee's mailing address changes (no fee is required if the location of byproduct material remains the same).

3. In accordance with 10 CFR 30.36(b) and/or license condition, notify NRC, promptly, in writing, and request termination of the license when you decide to terminate all activities involving materials authorized under the license.

399558

4. Request and obtain a license amendment before you:

   a. Receive or use byproduct material for a clinical procedure permitted under Part 35 but not permitted by your license issued pursuant to this Part;

   b. Permit anyone, except individuals described in 10 CFR 35.13(b), to work as an authorized user under the license;

   c. Change Radiation Safety Officers;

   d. Order byproduct material in excess of the amount, or radionuclide, or form different than authorized on the license;

   e. Add or change the areas of use or address or addresses of use identified in the license application or on the license; or

   f. Change ownership of your organization.

5. Submit a complete renewal application with proper fee or termination request at least 30 days before the expiration date of your license. You will receive a reminder notice approximately 90 days before the expiration date. Possession of byproduct material after your license expires is a violation of NRC regulations. A license will not normally be renewed, except on a case-by-case basis, in instances where licensed material has never been possessed or used.

In addition, please note that NRC Form 313 requires the applicant, by his/her signature, to verify that the applicant understands that all statements contained in the application are true and correct to the best of the applicant's knowledge. The signatory for the application should be the licensee or certifying official rather than a consultant.

You will be periodically inspected by NRC. Failure to conduct your program in accordance with NRC regulations, license conditions, and representations made in your license application and supplemental correspondence with NRC will result in enforcement action against you. This could include issuance of a notice of violation, or imposition of a civil penalty, or an order suspending, modifying or revoking your license as specified in the General Policy and Procedures for NRC Enforcement Actions. Since serious consequences to employees and the public can result from failure to comply with NRC requirements,

prompt and vigorous enforcement action will be taken when dealing with licensees who do not achieve the necessary meticulous attention to detail and the high standard of compliance which NRC expects of its licensees.

Sincerely,

Original Signed By
James R. Mullauer, M.H.S.
Health Physicist
Nuclear Materials Licensing Branch

License No.: 21-03001-01
Docket No.: 030-02024

Enclosure: Amendment No. 38

DOCUMENT NAME: M:\03002024.CL6

To receive a copy of this document, indicate in the box: "C" = Copy without attachment/enclosure "E" = Copy with attachment/enclosure "N" = No copy

OFFICE	DNMS/RIII							
NAME	JMULLAUER:jaw							
DATE	11/ /96							

OFFICIAL RECORD COPY

Wayne State University
DMC Hutzel Hospital

October 21, 1996

James Mullauer
Nuclear Regulatory Commission
Region III
801 Warrenville Road
Lisle, IL 60532-4351

Dear Mr. Mullauer.

This is additional information and changes in our amendment request:

1. Change the request for Dr. Winston Koo from "in vivo use" to "in vitro use". Attached are copies of Dr. Koo's training and experience.

2. Delete the Institute for Women's Medicine location (Livonia, Southfield & Warren). No materials were ever used or received at any of these locations. This was verified for the Warren location during the recent NRC inspection.

3. Delete Gerald L. Buchel, M.S. as an alternate radiation safety officer.

4. Delete Dr. John W. Wolfe, M.D. and Jaroslow Muz, M.D. as authorized users.

5. Delete the request for Dr. Michael Diamond since the requested use of H-3 and C-14 are authorized under 10CFR35 for research. (Please make note of this approval under 10CFR35 since I needed some paperwork on this for the hospital administration).

6. Add the use of our storage shed. This has been an existing building on hospital grounds and has been inspected many times. However, its description in the license is unclear. Attached is a drawing of the building. The construction is concrete block with two steel garage type doors. The floor is raised wood and the ceiling is shingled. The building is closed to the elements. The materials stored are I-131 waste from therapy patients for decay; H-3, C-14, S-35 waste in barrels awaiting shipment for disposal.

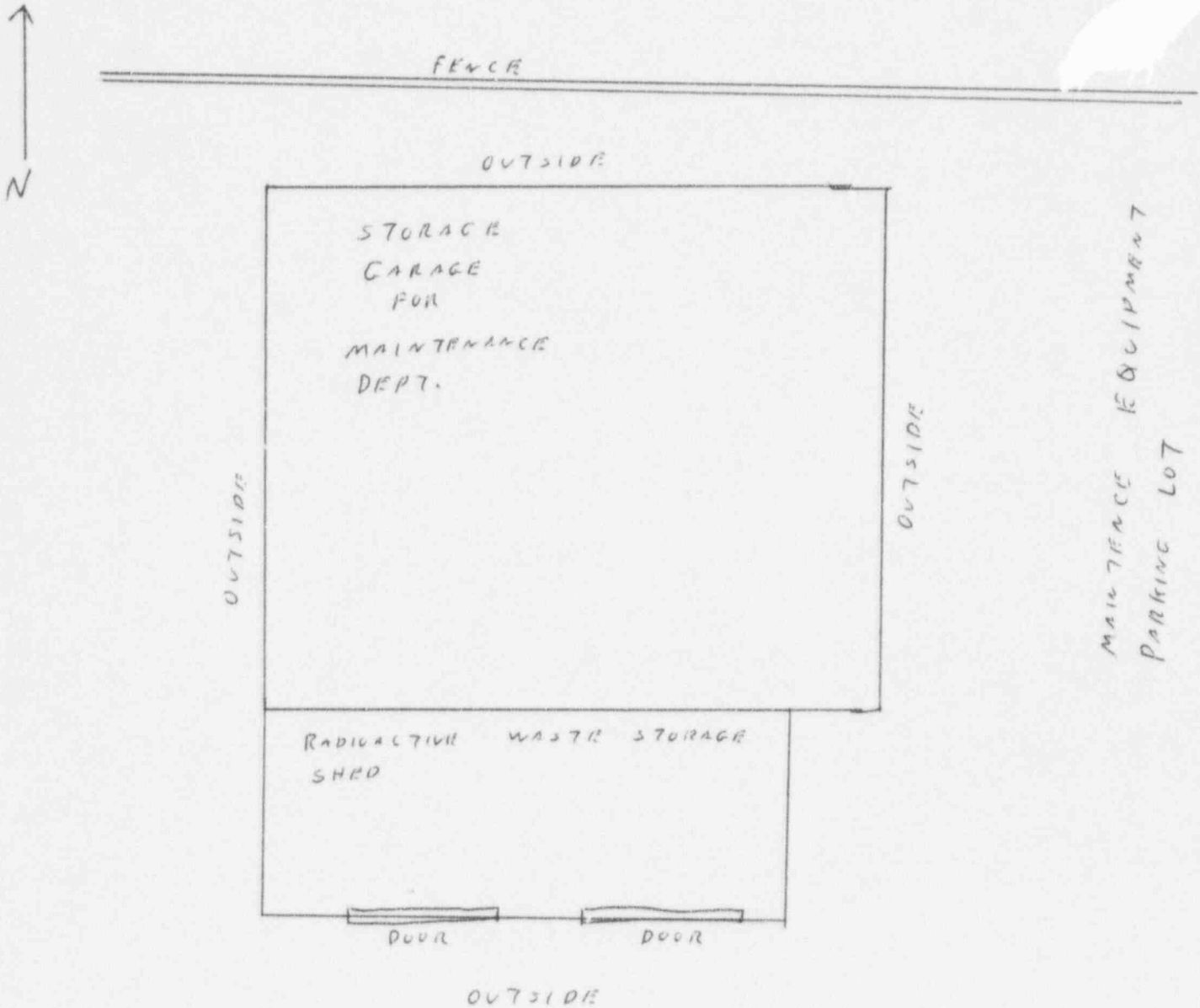
7. Please add Dr. James Fontanesi as previously requested for brachytherapy. Dr. Fontanesi is a board certified radiation therapist.

If there are any questions, please contact me at (313) 455-4730.

Sincerely,

Ray A. Carlson, M.S.
Radiation Safety Officer

pm; 10-22-96



1. THE DOORS ARE ROLL UP TYPE GARAGE DOORS WITH LOCKS.
2. WOOD FLOOR
3. THE ENTIRE AREA IS SURROUNDED BY A 10 FOOT FENCE WHICH IS KEPT LOCKED EXCEPT WHEN BEING THE MAINTENANCE DEPT. IS MOVING EQUIPMENT IN OR OUT OF THE LOT.

STATEMENT OF TRAINING AND EXPERIENCE

NAME: Dr. Winston Koo, Professor of Pediatrics, Obstetrics and Gynecology
Wayne State University/Children's Hospital of Michigan/Hutzel Hospital
SOCIAL SECURITY NO.: 288-78-0681
DATE: 8/6/96

TYPE OF TRAINING	ON THE JOB (circle)	FORMAL COURSE (circle)	WHERE TRAINED	DURATION OF TRAINING
Principles & practices of radiation protection	(Yes) No		Univ. of Cincinnati, OH, and Univ. of TN, Memphis, Div. of Neonatology (studies associated with clinical protocols) Univ. of Cincinnati, Div. of Immunobiology (Lab training)	6 yr 1 mo
		(Yes) No	Univ. of Cincinnati, OH: a) Div. of Immunobiology b) Radiation Safety Course Hutzel Hospital, Detroit, MI: Radiation Safety Course	1 mo 1 mo 4 h
Radioactivity measurement standardization & monitoring techniques & instruments	(Yes) No		Univ. of Cincinnati, OH and Univ. TN, Memphis Div. of Neonatology Univ. of Cincinnati, OH Div. of Immunobiology	6 yr 1 mo
		(Yes) No	Univ. of Cincinnati, OH: a) Div. of Immunobiology b) Radiation Safety Course Hutzel Hospital, Detroit, MI: Radiation Safety Course	1 mo 1 mo 4 h
Mathematics & calculations basic to the use & measurement of radioactivity	(Yes) No		Univ. of Cincinnati, OH and Univ. TN, Memphis Div. of Neonatology Univ. of Cincinnati, OH Div. of Immunobiology	6 yr 1 mo
		(Yes) No	Univ. of Cincinnati, OH: a) Div. of Immunobiology b) Radiation Safety Course	1 mo 1 mo
Biological effects of radiation	(Yes) No		Univ. of Cincinnati, OH and Univ. TN, Memphis Div. of Neonatology Univ. of Cincinnati, OH Div. of Immunobiology	6 yr 1 mo
		(Yes) No	Univ. of Cincinnati, OH: a) Div. of Immunobiology b) Radiation Safety Course	1 mo 1 mo

EXPERIENCE WITH RADIATION (Actual use of Radioisotopes or equivalent)

ISOTOPE	MAXIMUM AMOUNT	WHERE EXPERIENCE WAS GAINED	DURATION OF EXPERIENCE	TYPE OF USE
^{125}I (liquid and solid), ^{3}H	Hundreds of millicuries	Univ. of Cincinnati and Univ. Tennessee, Memphis: in vitro radioreceptor assay and radioimmunoassay. Use of single photon absorptiometry with ^{125}I source UT Memphis: use of dual energy x-ray absorptiometry in the measurement of body composition, including bone mineralization	6 yr 1 yr	Biological and Clinical Research

CERTIFICATION FOR USE OF RADIATION

Original must be filed with the Radiation Safety Committee. A copy will be returned to the individual completing this form. This form must be completed before beginning work with radiation.

NAME Winston Koo DATE OF BIRTH 4/22/49 SEX M

HOME ADDRESS 4223 Cherry St., Cincinnati

HOME PHONE

UNIVERSITY TITLE Research Scholar DEPT. NAME Pediatrics MAIL LOC.

LOCATION OF LABORATORY Neonatology Division, 6th Fl, MSB PHONE

LOCATION OF OFFICE Neonatology Division, 6th Fl, MSB PHONE

FACULTY SUPERVISOR (for graduate students, technicians, University employees).

(a) I WISH TO ENROLL IN THE NEXT RADIATION SAFETY CLASS ____

(b) I CERTIFY THAT I HAVE RECEIVED INSTRUCTION IN THE SAFE USE OF RADIATION, THAT I HAVE READ AND UNDERSTAND THE UNIVERSITY OF CINCINNATI RADIATION SAFETY MANUAL AND THE REGULATIONS OF THE U. S. NUCLEAR REGULATORY COMMISSION.

DATE 12/5/84

Signed by:

APPLICANT CERTIFIED BY: 1. Completing University of Cincinnati Course on 4/5-6/1-84
Date

2. Previous Training ____

Kenneth M Fritz
(Radiation Safety Officer)

12/11/84
Date

FOR INDIVIDUALS HAVING PREVIOUS RADIATION EXPERIENCE:

APPLICANT HAS HAD ADEQUATE TRAINING AND EXPERIENCE AT
(Institution)

from ____ Mo. ____ Yr. to ____ Mo. ____ Yr. under the supervision of

(Name and Title)

NOTE: YOU ARE REQUIRED TO READ AND UNDERSTAND THE UNIVERSITY OF CINCINNATI RADIATION SAFETY MANUAL AND REGULATIONS OF THE NRC.

The original of this form is to be sent to the Radiation Safety Office, University Hospital, Mail Location 569, before beginning work with radiation.

THE UNIVERSITY OF TENNESSEE
MEMPHIS
The Health Science Center

Lois VAN VLEET College of
Radiation Safety O
800 Madison Avenue, Memphis, TN
(901) 528

17 November 1993

MEMORANDUM

TO: Dr. Winston Koo

FROM: David Edwards
Radiation Safety Officer

RE; Application for Use of Radioactive Material
RSC# R93-328-50

You have been approved by the Radiation Safety Ad Hoc Committee for Non-Human Use for the use of H-3 1,25 Dihydroxyvitamin D; I-125 Antigen, 25 Hydroxyvitamin D, Calcitonin, Osteocalcin or Antibody, 0.2 mCi total.
The approval is granted under the following conditions:

1. This approval must be renewed annually. Each year you will be contacted by the Radiation Safety Office to address renewal of the approval for an additional year.

2. The radioactive material will be possessed and used in accordance with the appropriate procedures in the University of Tennessee, Memphis Radiation Safety Manual and in such manner as to insure compliance with the Tennessee Radioactive Material Broad License held by the University of Tennessee, Memphis.

3. All radioactive waste will be handled and processed in accordance with the Radiation Safety Office's policies and procedures.

4. The radioactive material will be possessed and used in accordance with the statements and procedures contained in the enclosed application. Please note any modifications and/or conditions to the original application.

If this protocol is used as part of a grant application, please insert the RSC# in item 12 of the "Document Review/Approval Sheet".

If you need clarification and/or assistance with the above, please call this office.

hdm
Enclosure

THE UNIVERSITY OF TENNESSEE
MEMPHIS
The Health Science Center

College of Medicine
Department of Pediatrics
853 Jefferson Avenue, 2nd Floor, Memphis, TN 38163

MEMORANDUM

TO: David Edwards, Radiation Safety Officer, Radiation Safety Office, S110 Van Vleet

FROM: Winston Koo, MBBS, FRACP, Associate Professor of Pediatrics and Obstetrics and Gynecology, Newborn Center

DATE: May 19, 1994

RE: Use of Additional Radioactive Compound

Pursuant to our conversation this morning, I am requesting the extension of our previously approved application for the use of radioactive material labeled with ^{3}H and ^{125}I isotopes (RSC #R93-328-50) to include the use of another chemical form. It consists of mouse monoclonal IgC labeled with ^{125}I in a bovine/mouse/horse protein matrix for the measurement of bone alkaline phosphatase. The above material is available in the form of a commercial kit with radioactivity less than 10 µCi/kit. The personnel and location of our laboratory remain the same.

WK/rg:K-497

Approved
6/3/94
150

6/2/94

THE UNIVERSITY OF TENNESSEE
MEMPHIS
The Health Science Center

Radiation Safety C
800 Madison Avenue, Memphis, TN 3
(901) 528

3 November 1994

MEMORANDUM

TO: Dr. Winston Koo

FROM: David Edwards
Radiation Safety Officer

RE: Extension of Approval for Radioactive Material Application(s)

The approval for your radioactive material application(s) as listed on the attached "Radiation Source Approval" sheet will be extended until November, 1995.

If we can be of any assistance, please contact this office.

hdm

Enclosure

CONVERSATION RECORD

TIME: 2 p.m. DATE: 7/8/96

○ VISIT ○ CONFERENCE × TELEPHONE

○ INCOMING
× OUTGOING

NAME OF PERSON(S) CONTACTED OR IN CONTACT | ORGANIZATION (OFFICE, DEPT.ETC.) | TELEPHONE NO.

Ray Carlson, RSO
Hutzel Hospital
313-455-4730

SUBJECT

Amendment for human research

SUMMARY

I spoke to Ray to inform him that I talk with Kevin Null and both Kevin and I agree that in order for Dr. Diamond to perform his research project, he needs to be listed as an authorized user of 35.100. Ray will send all training info as required by 35.910, training for 35.100.

Also, provide Koo's training and experience with RAM. His vitae shows no ram experience.

This action is certified by _____

ACTION REQUIRED

NAME OF PERSON DOCUMENTING CONVERSATION | SIGNATURE | DATE

James R. Mullauer James Mullauer 7/9/96

ACTION TAKEN

SIGNATURE | TITLE | DATE

Wayne State University
DMC Hutzel Hospital

Peter R. Miller, M.D.
Chief, Department of Radiology

James Mullauer
Nuclear Regulatory Commission
Region III
Materials Licensing Section
801 Warrenville Road
Lisle, IL 60532-4351

Dear Mr. Mullauer:

As per our telephone conversation concerning control number 98111 for Hutzel Hospital, it is acknowledged that the request to add the use of H-3 and C-14 for in-vivo studied as outlined in the amendment request is authorized under 10 CFR 35.

In addition, we wish to have the following persons added as authorized users:

Michael P. Diamond, M.D. for in-vitro and in-vivo research studies using H-3, C-14 and I-125.

Winston W.K. Koo, M.B.B.S. (CV attached) for in-vivo studies using H-3, I-125 and I-131.

James Fontanesi, M.D. for 35.400 and 35.500 (board certificate attached).

If there are any questions, please call me at (313) 455-4730.

Sincerely,

Ray A. Carlson, M.S.
Medical Physicist
ABR & ABMP Certified

300 Bank
Birmingham, MI 48009

29185 IR 67 310
JAMES FONTANESI MD
3259 E BRECKENRIDGE
BIRMINGHAM, MI 48010

6/08/88

DEAR DOCTOR FONTANESI:

I am pleased to inform you that you passed the oral examination. The American Board of Radiology voted on May 26, 1988 to grant you its certificate in RADIATION ONCOLOGY.

With personal congratulations, I am

Sincerely yours,

Kenneth L. Krabbenhoft

Kenneth L. Krabbenhoft, M.D.
Secretary

IMPORTANT INFORMATION

1. Please return the ENCLOSED "Request for Certificate Card" to the Board Office immediately. Delivery of certificates will take approximately 3-4 months.

2. Now that you have been certified by The American Board of Radiology, your name will be included in a Directory published by the American Board of Medical Specialties unless you specify otherwise in writing.

   It is your responsibility to notify your local and state medical organizations of your certification.

DATE OF PREPARATION: 2-8-96

CURRICULUM VITAE

WINSTON W. K. KOO

Office Address: Department of Pediatrics
Hutzel Hospital
4707 St. Antoine Blvd
Detroit, MI 48201

Telephone: (313) 745-7231
Fax: (313) 993-0198

EDUCATION AND TRAINING:

1972	M.B.B.S. (Honors) University of New South Wales, Sydney, Australia
1/73-8/74	Intern in Internal Medicine and Surgery, St. Vincent's Hospital, Sydney, New South Wales, Australia
8/74-12/80	Resident in Pediatrics/Neonatology, Prince of Wales Children's Hospital and Royal Hospital for Women, Sydney, New South Wales, Australia
4/82-4/85	Fellowship in Neonatology, Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio, USA
4/85-7/86	Research Scholar/Clinical Associate Physician (NIH Award): University of Cincinnati, Cincinnati, Ohio USA

UNIVERSITY APPOINTMENTS:

1986-90	Assistant Professor, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada
1990-95	Associate Professor, Departments of Pediatrics and Obstetrics and Gynecology, The University of Tennessee, Memphis, Memphis, Tennessee, USA
1992-95	Clinical Faculty, Department of Consumer Science and Education, Dietetic Internship and Residency Program, University of Memphis, Memphis, Tennessee, USA
1995-Present	Professor, Departments of Pediatrics and Obstetrics and Gynecology; Adjunct Graduate Faculty, Department of Nutrition and Food Sciences, Wayne State University, Detroit, Michigan, USA

HOSPITAL OR OTHER PROFESSIONAL APPOINTMENTS:

1980-82	Staff Specialist, Paediatric Intensive Care Unit, Westmead Centre, Sydney, Australia
1981-82	Visiting Specialist in Pediatrics, Prince Henry and Prince of Wales Hospitals, Sydney, Australia
1986-90	Staff Neonatologist, University of Alberta Hospitals, Edmonton, Alberta, Canada
1990-95	Active Member, Medical Staff, The Regional Medical Center, Memphis, Tennessee, USA
1992-95	Consulting Medical Staff, Le Bonheur Children's Medical Center, Memphis, Tennessee, USA

1995-Present Active Staff, The Detroit Medical Center (Children's Hospital of Michigan, Hutzel Hospital), Detroit, Michigan, USA

SOCIETY MEMBERSHIPS:

1980 Fellow, Royal Australasian College of Physicians
1985 Member, American Society for Bone and Mineral Research
1986 Member, American Society for Parenteral and Enteral Nutrition
1986 Fellow, American College of Nutrition
1989 Member, American Society for Clinical Nutrition
1989 Member, American Institute of Nutrition
1989 Member, Society for Pediatric Research
1990 Member, American Association for Clinical Chemistry
1991 Member, Southern Society for Pediatric Research
1994 Specialty Fellow, American Academy of Pediatrics
1995 Member, American Federation for Clinical Research

MEDICAL LICENSURE:

1972 New South Wales Medical Board, Australia, No. MPO 41056
1988 The State Medical Board, Ohio, No. 35-05-6369
1990 Tennessee Board of Medical Examiners, No. 20562
1995 Michigan Board of Medicine, No. 4301066856

CERTIFICATION:

1972 ECFMG - Educational Council for Foreign Medical Graduates Certification, No. 1816982
1979 VQE - Visa Qualifying Examination
1980 FRACP - Fellow, The Royal Australasian College of Physicians, No. 3476
1987 LMCC Examination of the Medical Council of Canada
1987 TOEFL - Test of English as a Foreign Language, Princeton, NJ
1987 FLEX - Federation Licensing Examinations, Federation of State Medical Boards of the United States, Inc., FIN 490422901
1988 The Medical Council of Canada, Certificate of Registration, No. 65330
1990 Basic Life Support CPR Certification, American Heart Association
1990 Regional Trainer #1298390, Neonatal Advanced Life Support; Instructor #2785884, Pediatric Advanced Life Support, American Heart Association/American Academy of Pediatrics
1991 Advanced Cardiac Life Support, American Heart Association
1991 Diplomate, American Board of Pediatrics, No. 47027 General Pediatrics Certifying Examination ID 219111
1993 Diplomate, American Board of Pediatrics, Sub-board of Neonatal-Perinatal Medicine No. 2632 Examination ID 219111

HONORS/AWARDS:

1. One of twenty top passes by an overseas student in the Leaving Certificate Examination, State of New South Wales, Australia
2. Undergraduate Scholarship, School of Medicine, University of New South Wales, Sydney, Australia
3. Life Member, University of New South Wales Union #5482, Sports Association #550, and Alumni Association #6839584
4. Young Investigator Award, American College of Nutrition: "Aluminum in Parenteral Nutrition: A Preventable Problem?"
5. Biography listed in:

American Board of Medical Specialists Directory of Board Certified Medical Specialists, 26th ed., 1994
Who's Who in the South and Southwest, 24th ed., 1995-1996
International Who's Who in Medicine, 2nd ed., 1995
Dictionary of International Biography, 23rd ed., 1995

SERVICES:

1. **Patient Care**

Attending in NICU and Progressive Care Nursery

2. **Professional**

Reviewer, "Newborns Who Need Special Nutritional Care," National Services in Perinatal Care, Second Edition, 1992, Food and Nutrition Board, Institute of Medicine and National Academy of Sciences, Washington, DC, 1991

Expert Contributor, International Programme on Chemical Safety (ICPS): Non-occupational Exposure to Lead, World Health Organization (WHO)/International Labor Organization (ILO)/Organization for Economic Cooperation and Development(OECD)/Commonwealth of Australia, October 1992

Participant, Lead-Bone Metabolism Workshop, National Institute of Environmental Health Services, Department of Health and Human Services, Research Triangle Park, NC, September 1993

Ad Hoc Consultant/Reviewer: Canadian Foundation for Ileitis and Colitis; Thrasher Research Fund; American Institute of Biological Sciences NIH/ADAMHA Alcohol, Drug Abuse, and Mental Health Administration; Public Health Service; National Academy of Sciences/American Institute of Biological Sciences; Drug Evaluations, American Medical Association; Ad Hoc working group on pediatric parenteral multivitamin product shortage, American Society for Parentinal and Enteral Society, May 1995

3. **Journal/Editorial Activity**

Ad Hoc Reviewer
Archives of Pediatrics and Adolescent Medicine
American Journal of Clinical Nutrition
Australian and New Zealand Journal of Medicine
European Journal of Clinical Nutrition
Journal of the American College of Nutrition
Journal of Pediatric Gastroenterology and Nutrition
Journal of Parenteral and Enteral Nutrition
Pediatric Research
The Journal of Pediatrics

Contributing Editor
Journal of the American College of Nutrition, 1994 -

4. **Boards and Committees**:

1978-80 Member, Committee for Control of Cross Infection and Committee of Perinatal Statistics, Royal Hospital for Women, Paddington, Sydney, Australia
1981-82 Member, Sydney Metropolitan Disaster Medical Plan Working Party, Australia

1984-86 Member, Nutrition Support Committee, University of Cincinnati Medical Center and Children's Hospital Medical Center, Cincinnati, Ohio

1984-86 Associate Coordinator, Neonatal Research Protocols, University of Cincinnati Medical Center and Children's Hospital Medical Center, Cincinnati, Ohio

1986-88 Member (1986-1988), Chairman (1987-1988), TPN Advisory Committee, University of Alberta Hospitals, Edmonton, Alberta, Canada

1986-90 Contributor and Examiner, Development of Objective Structured Clinical Examination (OSCE) for Medical Students and Fellows in Neonatal-Perinatal Medicine, University of Alberta, Edmonton, Alberta, Canada

1988-90 Chairman, Nutrition Support Service Committee, University of Alberta Hospitals and Northern Alberta, Edmonton, Alberta, Canada

1988-90 Member, Ph.D. Candidate Examination Committee, Faculty of Pharmacy and Pharmaceutical Services, University of Alberta, Edmonton, Alberta, Canada

1991-95 Chairman (1991-1992), Member (1991-), Nutrition Support Service, Newborn Center, The University of Tennessee, Memphis, Memphis, Tennessee

1988- Member (1988-) and Chairman (1991-1993), Pediatrics Council; Member: Board of Directors (1993-), American College of Nutrition

1995- Member: Sections on Critical Care, Gastroenterology and Nutrition, Perinatal Pediatrics, and Transport Medicine, American Academy of Pediatrics

1995- Member: Research Committee, Nutrition support team steering committee; Children's Hospital of Michigan, Detroit, Michigan

1995- Member: Perinatal HIV Task Force, Quality assurance committee, Department of Pediatrics; Hutzel Hospital, Detroit, Michigan

1995- Member: Pediatric Investigation Committee, Children's Hospital of Michigan and Wayne State University, Detroit, Michigan

TEACHING EXPERIENCE:

Medical - Associated Teaching Hospitals:

1979-80 University of New South Wales
1981-82 Sydney University
1984-86 University of Cincinnati
1986-90 University of Alberta
1991-95 The University of Tennessee, Memphis
1995- Wayne State University

Nursing - Associated Teaching Hospitals:

1976-80 University of New South Wales
1981-82 Sydney University
1983-86 University of Cincinnati
1986-90 University of Alberta
1996- Wayne State University

Trescillian Nurses:

1980-81 Trescillian, Petersham, Sydney, Australia

Food and Nutrition Sciences:

1989-90 University of Alberta
1992-95 Memphis State University

Outreach Perinatal Training Program:

1987-89 The Northern and Central Alberta Perinatal Program Community Teaching, Fort McMurray, Smoky Lake, Alberta
1991-95 Neonatal Resuscitation Program, Regional Medical Center, Memphis, Tennessee

Neonatal Resuscitation Program:

1993-95 Regional Medical Center, Memphis, Tennessee
1995- Children's Hospital of Michigan, Detroit, Michigan

Pediatric Advanced Life Support Course:

1991-95 Le Bonheur Children's Hospital, Memphis, Tennessee

Students and Research Trainees:

1987 Barbara Yip, Summer Studentship; Alberta Heritage Foundation for Medical Research, Edmonton, Alberta

1988-90 Clinical Supervisor for June Ke, Ph.D. Candidate, Faculty of Pharmacy, University of Alberta

1992-95 Jocelyn Walters, M.Sc., Department of Pediatrics, The University of Tennessee, Memphis

1993 Quynh Vu, NICU Elective Rotation, Year 6 Medical Student, University of Missouri, Kansas City, Missouri

1995 Mouhanad Hammami, M.D., Department of Pediatrics, The University of Tennessee, Memphis

RESEARCH SUPPORT:

1. Title: Bone Mineralization in High Risk Infants
   Source: National Institutes of Health, Division of Research Resources, Clinical Associate Physician Award, 3 MO1 RR00123-21S1
   Dates: April 1, 1984 - March 31, 1986
2. Title: Infant Nutrition: Mineral/Trace Metal Metabolism
   Source: National Institutes of Health, CRC Grant RR 00123, RR68
   Dates: December 1, 1982 - July 1, 1986
3. Title: Rickets in Infants
   Source: Mead Johnson and Company
   Dates: January 1, 1984 - December 31, 1986
4. Title: Calcium and Phosphorus Nutrition in High Risk Infants
   Source: National Institutes of Health (NICHD), Grant RO1HD 18505
   Dates: January 1, 1985 - December 31, 1987
5. Title: Calcium, Phosphorus, Vitamin D Metabolism, and Bone Mineralization in Children With Chronic Lead Exposure
   Source: International Lead Zinc Research Organization, LH342B
   Dates: October 1, 1985 - October 1, 1987
6. Title: Aluminum and Bone Disease in Infants of Very Low Birth Weight
   Source: Mead Johnson and Company
   Dates: December 1, 1986 - December 1, 1987
7. Title: Aluminum Contamination in Nutrient Products
   Source: LyphoMed Inc.
   Dates: March 1, 1987 - March 1, 1988
8. Title: Parenteral Nutrient and Drug Interaction
   Source: Special Services and Research Committee, University of Alberta Hospitals
   Dates: February 15, 1988 - August 15, 1988
9. Title: Vitamin Requirements of Formula-fed Preterm Infants
   Source: Ross Laboratories
   Dates: September 1, 1988 - August 31, 1992
10. Title: Parenteral Nutrient and Drug Interaction
    Source: Medical Research Council (MRC) Canada, MA-10685
    Dates: July 1, 1989 - June 30, 1991
11. Title: Enteral Nutrient and Drug Interaction
    Source: Special Services and Research Committee, University of Alberta Hospitals
    Dates: July 11, 1989 - July 10, 1990
12. Title: Body Composition of Infants
    Source: UT Medical Group
    Dates: October 1, 1991 - September 30, 1992
13. Title: Role of Dietary N-3 Fatty Acids in Premature Infants
    (Co-Investigator; PI - Susan E. Carlson, PhD)
    Source: National Institutes of Health, National Eye Institute, R01 EY08770

Dates: January 1, 1990 - December 31, 1992

14. Title: Bone Mineralization in Infants
    Source: Hologic Company
    Dates: April 1, 1992 - June 30, 1994
15. Title: Growth and Biochemical Profile of Infants Fed Different Infant Formulas
    Source: Ross Laboratories
    Dates: September 10, 1992 - September 9, 1994
16. Title: Effects of Maternal Calcium Supplementation on the Newborn Infants of Patients Enrolled in the Trial of Calcium for Preeclampsia Prevention
    Source: National Institutes of Health, National Institute of Child Health and Human Development, N01-HD-1-3126
    Dates: September 30, 1993 - March 31, 1995
17. Title: Effects of Calcium Supplementation During Pregnancy on Maternal Bone Mineralization
    Source: Smith Kline and Beecham
    Dates: March 1, 1994 - June 30, 1995
18. Title:
    a. Body Composition of Infants and Children
    b. Effect of Recombinant Human Macrophage Colony Stimulating Factor (M-CSF) on Bone Mineralization in Patients With Congenital Osteopetrosis
    c. Effect of Chronic Maternal Calcium Supplementation on
       (i) Changes in Body Composition of the Mother and Fetus
       (ii) Calcium Homeostasis in the Newborn

    Source: National Institutes of Health, CRC Grant USPHS RR00211-29
    Dates:
    a. February 27, 1992 - June 30, 1995
    b. November 17, 1992 - June 30, 1995
    c. March 19, 1993 - June 30, 1995
19. Title: Role of Dietary N-3 Fatty Acids in Premature Infants
    (Co-Investigator; PI - Susan E. Carlson, PhD)
    Source: National Institutes of Health, National Institute of Child Health and Human Development, 9 RO1 HD31329-04
    Dates: September 1, 1993 - August 31, 1997
20. Title: Growth and Bone Mineralization in Preterm Infants
    Source: Ross Laboratories
    Dates: December 1, 1994 - December 1, 1997

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8. Koo WWK, Guan ZP, Tsang RC, Laskarzewski P, Neumann V: Growth failure and decreased bone mineral of newborn rats with chronic furosemide therapy. Pediatric Research 20:74-78, 1986.

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13. Koo WWK, Kaplan LA, Horn J, Tsang RC, Steichen JJ: Aluminum in parenteral nutrition solution - sources and possible alternatives. Journal of Parenteral and Enteral Nutrition 10:591-595, 1986.
14. Koo WWK, Tsang RC, Steichen JJ, Succop P, Babcock D, Oestreich AE, Noseworthy J, Horn J, Farrell MK: Parenteral nutrition for infants: Effect of high versus low calcium and phosphorus content. Journal of Pediatric Gastroenterology and Nutrition 6:96-104, 1987.
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18. Koo WWK, Kaplan LA, Krug-Wispe SK: Aluminum contamination of infant formulas. Journal of Parenteral and Enteral Nutrition 12:170-173, 1988.
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39. Steichen JJ, Koo WWK: Mineral nutrition and bone mineralization in full-term infants. Monatsschrift Fur Kinderheilkunde 140(9 Suppl 1):S21-S27, 1992.
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48. Koo WWK, Krug-Wispe S, Succop P, Tsang RC, Neylan M: Effect of different vitamin A intakes in very low birth weight infants. American Journal of Clinical Nutrition 62:1216-1220, 1995
49. Carlson SE, Ford AJ, Werkman SH, Peeples JM, Koo WWK: Visual acuity and fatty acid status of term infants fed human milk and formulas with and without docosahexaenoate and arachidonate from egg yolk lecithin. American Journal of Clinical Nutrition (Accepted)

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51. Koo WWK: Laboratory assessment of nutritional metabolic bone disease in infants. Clinical Biochemistry (Accepted)
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53. Koo WWK, Krug-Wispe S, Tsang RC, Succop P: Changes in plasma vitamin E and lipids associated with different levels of vitamin A and D intake from preterm infant formula. (In preparation)
54. Koo WWK, Wang W, Palmieri GMA, Walters J, Arheart KL: Effect of recombinant macrophage colony-stimulating factor on growth and bone mineralization in children with osteopetrosis. (In preparation)

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5. Koo WWK, Tsang RC: Calcium, phosphorus and vitamin D needs of the high risk newborn. In Nowak AJ and Erenberg A (eds), Factors Influencing Orofacial Development in the Ill, Preterm Low Birth Weight, and Term Neonate. Publication Office of Maternal and Child Health, Bureau of Health Care Delivery, U.S. Department of Health and Human Services, 1985, pp 30-41.
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17. Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Koo WWK, Tolley EA: The effect of marine oil-supplemented formulas with and without eicosapentaenoic acid on the n-3 and n-6 fatty acid status and growth of premature infants, presented (S. Carlson) before the Fifth Scientific Meeting of the Society for Research on Polyunsaturated Fatty Acids (PUFA), Tokyo, Japan, November 1992. In Yasugi T, Nakamura H, Soma M (eds). Advances in Polyunsaturated Fatty Acid Research, New York, Excerpta Medica, 1993, pp 261-264.
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26. KooWWK, Tsang RC: Building Better Bones: Calcium, Magnesium, Phosphorus, and Vitamin D. In Tsang RC, Nichols B, Zlotkin S (eds), Nutrition During Infancy: Principles and Practice. Philadelphia, Hanley and Belfus Inc., (in press)

SPEAKER AND SCIENTIFIC SESSIONS ORGANIZER/MODERATOR:

1. "Bone Mineralization in Infants." Ohio Dietetic Association 64th Annual Meeting, Columbus, Ohio, April 1985
2. "Parenteral Nutrition for Infants." Good Samaritan Hospital, Cincinnati, Ohio, August 1985
3. "Complications of Parenteral Nutrition for Infants." Prince of Wales Children's Hospital, Sydney, Australia, August 1986
4. "Potential Effects of Lead Exposure on Bone Mineralization." Lead and Zinc Technical Committees Meeting, International Lead Zinc Research Organization, Inc., Amelia Island, Florida, September 1986
5. "Calcium Metabolism in the Neonate." Postgraduate Course on Nutritional Care of the Premature Infant, American Society for Parenteral and Enteral Nutrition 12th Clinical Congress, Las Vegas, Nevada, January 1988
6. "Intravenous Vitamin D and Calcium and Phosphorus Needs in Preterm Infants"; "Aluminum Toxicity and Bone Mineralization in Preterm Infants." Postgraduate Symposium on New Perspectives and Update in Neonatal-Perinatal Medicine, University of Southern California (LAC-USC Medical Center) Los Angeles, California, June 1988
7. "Trace Metal Toxicity." Postgraduate Course on Micronutrient Requirement for Low Birth Weight Infants (Course Director), American Society for Parenteral and Enteral Nutrition 13th Clinical Congress, Miami Beach, Florida, February 1989

8. "Minerals and Vitamins in Pediatrics." Poster Session Moderator, American College of Nutrition 30th Annual Meeting, Norfolk, Virginia, September 1989
9. "Nutritional Bone Disease in Infancy," Speaker; "Case Study in Neonatal Bone Disease," Clinical Workshop Moderator; Fall Postgraduate Course on The Technology of Nutrition. Support: From Bench to Bedside American Society for Parenteral and Enteral Nutrition, Cleveland, Ohio, September 17, 1990
10. "Metabolic Bone Disease of Infancy." Twenty-second Memphis Conference on the Mother, Fetus, and Newborn, The University of Tennessee, Memphis, Memphis, Tennessee, September 28, 1990
11. "Mineral Requirements in the Neonate Receiving TPN." Pediatric Surgery Lecture Series LeBonheur Children's Medical Center, Memphis, Tennessee, October 3, 1990
12. "Pediatrics/Obstetrics Oral Session," Co-Chairperson; "Mineral Requirements of Low Birth Weight Infants," Plenary Session Speaker, American College of Nutrition 31st Annual Meeting, Albuquerque, New Mexico, October 14, 1990
13. "Meeting Calcium Needs With Parenteral and Enteral Nutrition in the Preterm Infant," Speaker and Workshop Co-Chairman, Third Annual Carnation Symposium on Bare Bones Nutrition: Current Clinical Perspectives on Calcium Nutriture in Pregnancy and Infancy, sponsored by the Perinatal Research Institute, Departments of Pediatrics and Obstetrics and Gynecology, University of Cincinnati Medical Center, Cincinnati, Ohio, November 16, 1990
14. "Vitamin D Requirement in Preterm Infants." Grand Rounds, Department of Pediatrics, The University of Tennessee, Memphis/LeBonheur Children's Medical Center, Memphis, Tennessee, December 5, 1990
15. "Parenteral Nutrition-Related Bone Disease." Pharmacists' Specialty Session, American Society for Parenteral and Enteral Nutrition 15th Clinical Congress, San Francisco, California, January 30, 1991
16. "Feeding a Baby That Cannot Tolerate Feeds." Ninth Annual Tennessee Conference on Perinatal and Neonatal Care, The Tennessee Perinatal Care System, Department of Health and Environment, Johnson City, Tennessee, May 23, 1991
17. "Methodology in Nutritional and Metabolic Research: Calcium." European Society for Pediatric Gastroenterology and Nutrition Summer School, La Tour de Peilz, Switzerland, July 14, 1991
18. "Dieting in Children." Pediatrics Symposium, Program Planner and Co-Chairperson, American College of Nutrition 33rd Annual Meeting, San Diego, California, October 12, 1992
19. "Nutritional Management of the Low Birth Weight Infant." Eleventh Annual Tennessee Conference on Perinatal and Neonatal Care, The Tennessee Perinatal Care System, Department of Health, Nashville, Tennessee, March 2, 1993
20. "Parenteral Nutrition Related Bone Disease in Pediatrics." Seventh Annual Meeting of the Indiana Society for Parenteral and Enteral Nutrition, Indianapolis, Indiana, April 30, 1993
21. "Parenteral Nutrition-Related Bone Disease." Maryland Society for Parenteral and Enteral Nutrition, Baltimore, Maryland, September 21, 1993
22. "Endocrine Regulation of Bone and Bone Mineral Metabolism." NIEHS Lead-Bone Metabolism Workshop, Research Triangle Park, North Carolina, September 27-28, 1993
23. "Body Composition and Metabolism in Pediatrics." Pediatrics Symposium, Program Planner and Co-Chairperson, American College of Nutrition 34th Annual Meeting, Chicago, Illinois, October 11, 1993
24. "Parenteral Nutrition in Infants." Memphis Area Association of Neonatal Nurses, Memphis, Tennessee, October 21, 1993
25. "Progress in Vitamin D and Calcium Nutrition in Infants." Pharmacists' Specialty Session, American Society for Parenteral and Enteral Nutrition, 18th Clinical Congress, San Antonio, Texas, January 31, 1994
26. "Parenteral Nutrition-related Bone Disease." Long Island Society for Parenteral and Enteral Nutrition, Long Island, New York, April 27, 1994
27. "Parenteral Nutrition in Infants." Grand Rounds, Department of Pediatrics, Tod Children's Hospital, Northeastern Ohio Universities College of Medicine, Youngstown, Ohio, May 13, 1994

28. "Neonatal Resuscitation." Residents' Conference, Department of Obstetrics and Gynecology, The University of Tennessee, Memphis, Memphis, Tennessee, July 20, 1994
29. "Feeding Strategies." Pediatric Surgery Grand Rounds, Department of Pediatrics, The University of Tennessee, Memphis/Le Bonheur Children's Medical Center, Memphis, Tennessee, July 27, 1994
30. "Obstetrics and Pediatrics Oral Session," Chairperson, American College of Nutrition 35th Annual Meeting, Atlanta, Georgia, October 7-9, 1994
31. "Use of Dual Energy X-ray Absorptiometry for Preterm Infants." Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, October 18, 1994
32. "Assessment of Metabolic Bone Disease in Infants." Sixth International Congress on Pediatric Laboratory Medicine, Vancouver, BC, Canada, July 22, 1995
33. "Post-Hospital Nutrition in the Preterm Infant." 106th Ross Conference on Pediatric Research, Colorado Springs, Colorado, August 18-20, 1995
34. "Vitamin D requirements in infants." Pediatric Professional Staff Meeting, Hutzel Hospital, Detroit, Michigan, September 25, 1995.
35. "Assessment of nutritional bone disease in infants." Seminar, Department of Nutrition and Food Science, Wayne State University, Detroit, Michigan, October 3, 1995.

CONVERSATION RECORD

TIME: 11 a.m.

DATE: 12/5/95

○ VISIT ○ CONFERENCE × TELEPHONE

○ INCOMING
× OUTGOING

NAME OF PERSON(S) CONTACTED OR IN CONTACT | ORGANIZATION (OFFICE, DEPT.ETC.) | TELEPHONE NO.

Ray Carlson, RSO
Hutzel Hospital
313-455-4730

SUBJECT

Amendment Request received 11/29/95

SUMMARY

I spoke to Ray concerning the following information.

1. We need the PI to address whether his sponsor, NIH, meets the criteria of 35.6. If so, an amendment is not necessary.

2. Need a signed original of the amendment request.

This action is certified by James Mullauer 11/4/96

ACTION REQUIRED

Ray will advise on his findings within 20 days

NAME OF PERSON DOCUMENTING CONVERSATION | SIGNATURE | DATE

James R. Mullauer
12/5/95

ACTION TAKEN

Jim Mullauer 12/5/95

SIGNATURE | TITLE | DATE

I spoke with Ray on 5/31/96 to inform that an amendment was not required for the research. The research is funded by NIH. In 15 days, Ray will request that he void the request for research and will add some M-S's to the license.