



Department of Energy

Oak Ridge Operations  
P. O. Box E  
Oak Ridge, Tennessee 37831

707091

October 11, 1985

*UNNUMBered Agr.  
ORAU & ORN  
(Research in brains  
Scanning in Patients  
w/Small vessel  
Atherosclerosis)*

Dr. William E. Felling  
Executive Director  
Oak Ridge Associated Universities  
Post Office Box 117  
Oak Ridge, Tennessee 37831

Dear Dr. Felling:

AGREEMENT BETWEEN ORAU AND THE UNIVERSITY OF TENNESSEE

This letter is in response to your August 9, 1985, letter to me, subject as above. ORAU is authorized to proceed with the work described in the agreement. Two signed copies of the agreement are enclosed.

Sincerely,

*W. R. Bibb*  
for William R. Bibb, Director  
Research and Waste Management Division

ER-122:Dunaway

Enclosure:  
Agreement

cc w/encl:  
J. J. Fowler, CC-10, ORO  
R. M. Poteat, CC-120, ORO

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AGREEMENT BETWEEN  
OAK RIDGE ASSOCIATED UNIVERSITIES  
AND  
THE UNIVERSITY OF TENNESSEE AT KNOXVILLE

This agreement entered into this 1st day of February, 1985 by and between Oak Ridge Associated Universities, Inc. (ORAU), P.O. Box 117, Oak Ridge, Tennessee 37831-0117, acting under agreement No. DE-AC05-76OR00033 with the United States Department of Energy, (DOE) and The University of Tennessee at Knoxville, (UT), Knoxville, Tennessee 37916.

WITNESSETH THAT:

WHEREAS, UT has patients on whom it wishes to have brain scans performed;  
and

WHEREAS, ORAU operates for DOE a facility which has government-owned equipment for performing brain scans; and

WHEREAS, ORAU is engaged in research in radiopharmaceuticals and recognizes this collaborative work with UT as beneficial to that research; and

WHEREAS, DOE has determined that it has a programmatic interest in this collaborative work and is therefore willing to have it performed in its facility using its equipment by ORAU under Contract No. DE-AC05-76OR00033 and have the cost of ORAU's participation be allowable under that contract;

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NOW THEREFORE, the parties agree as follows:

1. The research to be conducted is described in a protocol titled "<sup>68</sup>Ga-EDTA Pet Brain Scanning in Patients with Small Vessel Atherosclerosis" (dated December 1984) which is attached to and incorporated into this Agreement.

The specific participation by ORAU staff will be as follows:

- a. UT will refer the patients to ORAU/MHSD (Oak Ridge Associated Universities/Medical and Health Sciences Division) where they will receive an IV injection of <sup>68</sup>Ga-EDTA (furnished by ORAU) and subjected to brain scans using the ECAT-II scanner.
- b. During the scan, two ml samples of arteriolized venous blood will be drawn (a total of 12 samples) for assay of blood activity level needed for PET data correction. ORAU staff will draw the samples and assay them.
- c. ORAU will provide UT with the results of the scans.
- d. UT will assume responsibility for the patients at the conclusion of the scans.

It is understood and agreed that these same patients will be subjected to repeat scans at six to ten month intervals.

It is further understood that Dr. Karl Hubner will be the UT physician responsible for the study. Dr. James E. Crook will be the ORAU physician responsible for ORAU's participation. UT will be responsible for securing patients' consent forms as prescribed by ORAU before the patients are accepted into ORAU's facilities.

2. Each party agrees to bear the costs, including salaries and the cost of all equipment and supplies, of its participation.

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3. The parties agree that each retains all liability for the acts or omissions of its employees, agents and officers.

4. UT hereby grants ORAU the right to publish reports, technical or scientific papers or other publications arising from or related to this work or its results provided that such publication does not identify individual patients. UT will be furnished a copy of any manuscript to be submitted for publication and have thirty (30) days in which to provide any comments or suggestions on the manuscript. It is expected that most publications will be joint publications since the project being addressed in this agreement is a collaborative one.

5. This agreement may be terminated by either party thirty (30) days after receipt of a notice to terminate. There will be no cost associated with such termination.

6. It is understood and agreed that this agreement is entered into by ORAU for and on behalf of the Government; that title to all supplies furnished hereunder shall pass directly to the Government, as purchaser, at the point of delivery; that ORAU is authorized to, and will make payment hereunder from Government funds advanced and agreed to be advanced to it by the DOE, and not from its own assets, and administer this Agreement in other respects for the DOE, unless otherwise specifically provided for herein; that administration of this Agreement may be transferred from ORAU to the DOE or its designee, and in case of such transfer and notice thereof to UT ORAU shall have no further responsibilities hereunder and that nothing herein shall preclude liability of the Government for any payment properly due hereunder, if for any reason such payment is not made by ORAU from such Government funds.

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7. No member of, or delegate to, Congress or resident Commissioner shall be admitted to any share or part of this Agreement or any benefit that may arise therefrom; but this provision shall not be construed to extend to this Agreement if made with a corporation for its general benefit.

8. UT warrants that no person or selling agency has been employed or retained to solicit or secure this agreement upon an agreement or understanding for a commission, percentage, brokerage, or contingent fee, excepting bona fide employees or bona fide established commercial or selling agencies maintained by UT for securing business. For breach or violation of this warranty, ORAU or DOE shall have the right to annul this Agreement without liability.

9. It is expressly agreed by the parties hereto that this Agreement supersedes any and all previous agreement or agreements and constitutes the entire and only agreement between the parties relative to this work; that there are no other agreements, understandings, or covenants between the parties hereto of any kind, nature, or description, expressed or implied, which have not been set forth herein.

10. UT agrees that in any publication that results from this work, it will acknowledge the work of ORAU, and that it will submit a copy of any manuscript to ORAU thirty (30) days before submission for publication for ORAU's comments or suggestions.

11. Any invention first conceived or reduced to practice, and all technical data produced, under this Agreement will be subject to the patent provisions of the DOE-ORAU Contract No. DE-AC05-76OR00033 and The University of Tennessee.

12. Neither the Government, the DOE, ORAU, nor persons acting on their behalf makes any warranty express or implied (1) with respect to the

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accuracy, completeness or usefulness of any information furnished hereunder, (2) that the use of any such information may not infringe privately owned rights, (3) that the services, materials, or information furnished hereunder will not result in injury or damage when used for any purpose, (4) that the services, materials, or information furnished hereunder will accomplish the intended results or are safe for any purpose including the intended purpose, (5) that materials accepted for analysis or other service will not be destroyed, lost or otherwise altered in physical or chemical properties, (6) nor shall any implied warranty of merchantability or fitness for a particular purpose apply. Neither the Government, the DOE, ORAU, nor persons acting on their behalf will be responsible, irrespective of causes, for failure to perform the services or furnish the materials or information hereunder at any particular time or in any specific manner.

13. ORAU will have the right to make and keep patient records pertinent to the study assuring confidentiality of the information.

14. No patient will be accepted by ORAU unless he or she signs ORAU's form in which the patient consents to the treatment.

15. This agreement is of no force or effect until approved by the Department of Energy.

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IN WITNESS WHEREOF, the parties have executed this agreement as of the day and year first above written.

OAK RIDGE ASSOCIATED UNIVERSITIES, INC.

THE UNIVERSITY OF TENNESSEE

KNOXVILLE

BY <u><i>William C. Telling</i></u>	BY <u><i>[Signature]</i></u>
TITLE <u>EXECUTIVE DIRECTOR</u>	TITLE <u>VICE PRESIDENT</u>
DATE <u>AUG 9 1985</u>	DATE <u>AUG 7 - '85</u>

APPROVED BY U.S. DEPARTMENT OF ENERGY

BY *W. R. Bibb*  
TITLE WILLIAM R. BIBB, DIRECTOR  
RESEARCH AND WASTE MANAGEMENT DIVISION  
DATE 10/10/85

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PROTOCOL FOR: <sup>68</sup>Ga-EDTA PET BRAIN SCANNING IN PATIENTS WITH  
SMALL VESSEL ATHEROSCLEROSIS.

The purpose of this study is to determine whether areas of low density on CT scans of patients with focal or diffuse ischemic disease represent areas of changed blood brain barrier (BBB), permeability. CT attenuation in areas of interest at the level of the basal ganglia and the centrum semi-ovale will be compared to the regional concentrations of <sup>68</sup>Ga-EDTA using quantitative PET analysis. It is felt that PET imaging giving quantitative information in tomographic display is more suitable for this study than conventional <sup>99m</sup>Tc-pertechnetate brain scintigraphy.

Specific Aims:

Major objectives are (1) to explore the anatomical relationship between low density CT lesions and areas of increased BBB permeability, (2) to determine whether disruption of the BBB is not only present in low density areas but also in areas remote but functionally related to the ischemic area, and (3) to determine whether progression of the disease is associated with increasing permeability of the BBB or the development of new BBB defects.

Patient Selection Criteria:

10 patients (5 males, 5 females) with dementia of Alzheimer's type (DAT) and 10 patients (5 males, 5 females) with multi-infarct dementia (MID) will be included in this study.

All patients will be over 60 years of age and have undergone medical neurologic examination, psychometric testing (global deterioration scale and mental status questionnaire), CT scanning and will be classified accordingly to their Hachinski Ischemic Scale score. (See Ischemic Scores on next page)

**Lachensie Score**

Feature	Score
1. Abrupt onset	2
2. Stepwise deterioration	1
3. Fluctuating course	2
4. Nocturnal confusion	1
5. Relative preservation of personality	1
6. Depression	1
7. Somatic complaints	1
8. Emotional incontinence	1
9. History of hypertension	1
10. History of strokes	2
11. Evidence of associated atherosclerosis	1
12. Focal neurological symptoms	2
13. Focal neurological signs	2

**Neuropsychological Test Battery for Dementia Evaluation**

<i>Visual acuity (reading distance) with glasses</i>	<i>Language screening</i>
<i>Wide Range Achievement Test</i>	Naming
Reading (words)	10 easy objects
Arithmetic (level 1)	9 colors
<i>Mental status: Dementia rating</i>	12 body parts
Blissed et al. (3)	Sentence Repetition: Spreen and Benton
Kahn et al. MSQ (52)	Token Test (comprehension): Spreen and Benton
Mattis Dementia Scale (50)	Word fluency: Drachman and Leavitt categories (19)
<i>Wechsler Adult Intelligence Scale (WAIS)</i>	Auditory discrimination and phoneme articulation
Information	<i>Visual fields</i>
Digit Symbol	Single
Vocabulary	Double simultaneous stimuli
Similarities	<i>Auditory</i>
Digit Span	Single (acuity)
Verbal IQ*	Double simultaneous stimuli
<i>Raven's Matrices (colored or standard)</i>	<i>Fine motor coordination</i>
<i>Telling time (Fuld clocks without numbers)</i>	Purdue pegboard
<i>Gates-MacGinitie reading: Speed and accuracy test</i>	<i>Sensoricortical</i>
Level D	Stereognosis
	Face-hand (eyes open and eyes closed)
	Two-point discrimination
	<i>Learning and Memory</i>
<i>Fuld Object-Memory Evaluation (38)</i>	<i>Buschke-Fuld verbal list (53)</i>
Storage	Storage
Recalls	Recalls
Consistency	Consistency
Response to reminders	Recognition
Delayed recall	
Recognition	

\* IQ's estimated from tests listed.

## The minimum diagnostic requirements for DAT are:

### Criteria for clinical diagnosis of Alzheimer's disease

#### I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test, 'Blessed Dementia Scale,' or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

#### II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques;

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity; and

evidence of cerebral atrophy on CT with progression documented by serial observation.

#### III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

#### IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

#### V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

#### VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and  
histopathologic evidence obtained from a biopsy or autopsy.

#### VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

(Neurology, 34 July 1984).

For MID, the minimum diagnostic requirements are based on recommendations given in Multifactorial Dementia, Journal Neurol. Sci. 1979, 40, pages 97-103.

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**CONTROLS:**

10 age-matched ambulatory patients (5 males, 5 females) with unilateral strokes (at least 5 weeks into their recovery) will be asked to participate in the study with their informed consent. These control patients will have the same medical examination, psychometric testing, etc. as the DAT and MID patients. The reason for choosing stroke patients for controls is that IND-FDA approval to study stroke patients using <sup>68</sup>Ga-EDTA has been obtained already. <sup>68</sup>Ga-EDTA concentrations in the non-affected hemisphere of stroke patient will be considered as standard for an intact BBB.

**PROCEDURE:**

PET scans will be obtained by using the ORAU M&HSD's ECAT-II scanner. Transmission scans will be done for attenuation correction purposes prior to the injection of <sup>68</sup>Ga-EDTA. <sup>68</sup>Ga-EDTA will be administered by I.V.-injection of 0.23 mCi/kg (not to exceed a total of 5 mCi). Imaging of the brain will be started 2 minutes post-injection and will be continued for a maximum of one hour. Samples of 2 ml arterialized venous blood will be taken frequently (total of 12 samples) during the first 30 minutes after injection for assay of blood activity level needed for PET data correction.

**ANATOMICAL REGIONS OF INTEREST:**

- Cortical Regions:
  - frontal pole
  - frontal midline
  - frontal
  - central midline (sensory - motor)
  - central (sensory - motor)
  - temporal posterior
  - parietal
  - occipital

- Deep Structures:
  - Caudate
  - Putamen
  - Thalamus
  - Insula
  - Temporal lobe white
  - Occipital lobe white

Results of ROI analysis will be expressed in uCi/gm at time post injection rather than as a rate.

In order to address subjective (3), CT and <sup>68</sup>Ga-EDTA studies will be repeated at 6 to 10 months intervals.

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