CCI #: _____

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS

DRUG, DEVICE, AND GENE TRANSFER/GENE THERAPY
HUMAN SUBJECT RESEARCH PROTOCOL APPLICATION

I. ADMINISTRATIVE INFORMATION:

Check One:
☐ Expedited Review: Specify Expedited Category: _____ (Refer to the AECOM CCI list of **Expedited Categories.)**
☒ Full Review:

Principal Investigator Information
Last Name: Haddad First Name: Gabriel MI: G

Degree(s): M.D. Other:
NOTE: PI is required to have a faculty appointment at the level of Instructor or above. For exceptions, submit CV and protocol abstract to the CCI for approval by the Assoc. Dean for Academic Affairs before submitting Research Application.

Faculty Rank: Professor Payroll Source: Other Other:

Department/YU School: Pediatrics Division:

Office Address:

Office Phone: Fax #: E-Mail Address:

Administrative Contact Person (Student name, if applicable):

Last Name: Graham First Name: Roberta

Office Phone: Fax #: E-Mail Address:

II. PROTOCOL INFORMATION: Do Not Exceed Space Provided.

Protocol Title: Sleep mechanisms in children: role of metabolism

Brief Summary of Proposal: The purpose of this project is to measure glycogen, glutamate turnover rate and glutamate-glutamine cycling in wakefulness and sleep in adolescent children (13-17). We will also study a subset of children in the same way except after sleep deprivation. These measurements will be made using NMR spectroscopy. None of the studies proposed have been done in adults or children. Indeed, only a small part of what is proposed here has been done in animals with the use of invasive techniques. Our long-term goals include the study of children of various ages, from the very young infant to the adult. For simplicity and for practical and safety reasons, we are starting with this protocol which calls for the study of the older child or adolescent, ie, 13-17 years of age. Hence these studies have not been done in the adult or child and the metabolic processes that occur in sleep are very poorly defined. Furthermore, we and others have shown in the past that sleep processes are very different in the child when compared to the adult. Depending on the age, from infancy to adolescence and adulthood, sleep architecture and patterns are different, and the amount of sleep is different. It is also likely that brain processes are very different during sleep at various ages since sleep may have different roles and functions at various ages. In the future, we intend to study other age groups such as infants and adults.Our laboratory has had a long-standing interest in sleep in children, especially as it pertains to the control of respiration and obstructive sleep apnea. For the past 2 decades, we have engaged in clinical and basic research in the control of respiration, consequences of tissue hypoxia and the mechanisms that lead to cell adaptation or injury. The integration of our group with the group at the MR Center in this institution will allow us to address questions of importance in sleep research in children, an area of research that, at present, is very fertile. Our specific hypotheses are as follows: 1. Stage IV sleep, as compared to wakefulness, has a lower brain metabolic activity in children; this is reflected by a reduced glutamate turnover rate and this reduction is prevented by sleep deprivation. 2.Control mechanisms of glial glucose oxidation play an important role in glutamate/glutamine cycling and represent an important checkpoint in mechanisms of sleep deprivation. 3.Brain glycogen content increases during the course of sleep in children and sleep deprivation markedly lowers glycogen content. In this project, we will start with a few adults (n=5) to perform some studies and then focus on adolescents.

Risks: The risks of this study are minimal. Intravenous catheters used during the glucose or acetate infusion are associated with a mild pain upon insertion, and a small risk of localized bruise, hematoma and/or infection. Other than the needle stick for the local numbing (anesthesia) of the skin before the infusion is started, this is a painless procedure. Hence the risks in this whole study are minimal.

Benefits: The patients will not directly benefit from participation in this study. However, the benefits to society may be considerable. Better understanding of human brain mechanisms involved in sleep and wakefulness and the role of the glutamate/glutamine neurotransmitter cycle should further our efforts designed to develop treatments for several disorders involved in sleep.

III. FINANCIAL AND ORGANIZATIONAL INFORMATION:

A. FINANCIAL INFORMATION:

1. Will Funds, Supplies, Drugs/Devices, or Equipment be provided by **Any EXTERNAL** Source(s)? ☒ Yes[2] ☐ No[1]

[1]If no, go to section **IV (Key Personnel)**

[2]If yes, refer to the **"Sponsored Research"** Policy and complete the following:

2. Check *ALL* items being supplied: ☒ Funds ☒ Supplies ☒ Drugs/Devices ☒ Equipment

3. List All Items (Other than funding) to be supplied and the Source(s):

Item Supplied	**Source**

Note: Before funding from an external source can be accepted by the institution, a written agreement or documentation from the sponsor is required. (i.e. contract, letter, or grant award)

4. Support for this study will be received via:
☒ Grant ☐ Sub contract ☐ Contract ☐ Other, Specify: _____

5. Is funding from an external source PENDING? ☒ Yes[3] ☐ No

[3]If YES, complete the following:

Name of Agency/ Subcontractor/Company	**Total Project Period From**	**To**
National Institute of Health - NIH	9/23/2002	7/31/2006

6. Is an external source CURRENTLY providing funding? ☐ Yes[4] ☒ No

[4]If YES, complete the following:

Name of Agency/ Subcontractor/Company	**AECOM Grant #**	**Total Project Period From**	**To**

7. Is this a Multi Center Clinical Trial? ☐ Yes ☒ No

B. ORGANIZATIONAL INFORMATION:

For Program Projects, Center Grants, or Multiple Project Protocols, complete the following:

1. Is This A **Sub-Study** of an Umbrella (Overall Administrative File) Grant? ☐ Yes[5] ☐ No

[5]IF YES, indicate the CCI number of the approved Umbrella (Overall Administrative File) Grant: _____

ATTACH COPY OF GRANT AWARD LETTER OR BUDGET PROPOSAL FOR CURRENT GRANT PERIOD FOR EACH AGENCY.
FOR CONTRACTS, FORWARD ORIGINAL CONTRACT TO CCI FOR LEGAL COUNSEL REVIEW AND APPROVAL.

IV. KEY PERSONNEL:

List all individuals who contribute in a substantive way to the scientific development or execution of the project, whether or not they are grant funded.

	Name	Department	Institution	Role on Project
1.	Gabriel G Haddad	Pediatrics	AECOM	PI
2.	Jullie Pan	Neurology	AECOM	co-I
3.	Hoby Hetherington	Radiology	AECOM	co-I
4.	Lewis Kass	Pediatrics	Montefiore	co-I
5.				
6.				
7.				
8.				
9.				

Have **all** Key Personnel met the educational requirements concerning the Protection of Human Subjects? ☒ Yes ☐ No

V. RESEARCH SITES AND COLLABORATING INSTITUTIONS:

A. RESEARCH SITES: Indicate all sites where the informed consent process will take place *OR* where the research will be conducted: (For school research outside of Yeshiva University, specify specific schools and/or districts.)

☒ Moses
☐ Weiler
☐ MMC Off-Site Clinics
☐ JMC*
☐ NCB*

AECOM:
☐ Laboratory
☐ SVTN
☐ Kennedy Center
☐ DOSA
☐ CERC

☐ GCRC (Weiler) In-Patient
☐ GCRC (Forch.) Out-Patient
☒ MRRC
☐ Other (list below)
Site 1: _____
Site 2: _____
Site 3: _____

YU Schools:
☐ Yeshiva
☐ Stern
☐ Cardozo
☐ Ferkauf
☐ Wurzweiler
☐ AECOM

***NOTE:** Research involving JMC or NCB requires HHC approval. (Complete HHC-641 form)
Send completed HHC 641 to the CCI office with this completed application if the protocol is funded by an AECOM grant award, or any Key Personnel are AECOM employees.
Send completed HHC 641 to Howard Nadel, Director, Research Center, JMC, Building 5, Room 230 (918-7232) for all other research involving JMC or NCB.

B. COLLABORATING INSTITUTIONS:
Does this protocol involve a collaborating institution? ☐ Yes[1] ☐ No[2]

[1]If yes, list collaborating institution(s) and name of collaborating investigator/contact:

	Institution:	Investigator/Contact:	Phone:
1.	Yale	Edward Novotny	
2.	Yale	Doug Rothman	
3.			
4.			

Is AECOM the primary institution? ☒ Yes[3] ☐ No[4]

[3]If YES, research cannot be initiated at the collaborating institution(s) until IRB approval from the collaborating institution(s) is obtained and provided to the CCI Office.

[4]If NO, research cannot be initiated at AECOM until IRB approval from the primary collaborating institution is obtained and provided to the CCI office and CCI approval is obtained.

VI. RESEARCH PARTICIPANT INFORMATION:

A. ENROLLMENT NUMBERS:

Specify the anticipated ***total*** number of subjects to be enrolled at the research sites listed above. 48/grant

period

If this is a multi center study, specify the anticipated ***total*** number of subjects to be enrolled at ***all*** centers.

B. RECRUITMENT SOURCES: Check source(s) of subjects and controls:

☐ Hospital In-patients ☐ Hospital Out-patients ☐ Private Practice Patients
☐ AECOM/MMC/JMC/NCB Employees ☐ AECOM/YU Students ☒ General Public
☐ Other (Specify)

C. RECRUITMENT METHOD AND MECHANISM: Check method(s) of recruitment of subjects and controls (when applicable) and provide a brief description of how they will be recruited:
NOTE: There are two sections for recruitment, one for Subjects and one for Controls.

1. SUBJECTS:
a. Who will recruit subjects? Lewis kass

b. Source of subject recruitment: (Check all that apply):

☐ Physician Referral
☐ Hospital or Physician Records (Indicate all institutions and departments whose records will be accessed.):

☒ Radio/TV Announcement ☒ Newspaper Announcement ☒ Recruitment Letter
☒ Bulletin Board Posting ☐ Internet ☐ Random Telephone Contact

NOTE: All Public Announcements, Postings, Recruitment letters, and Telephone dialogs must be approved by the CCI prior to use. If possible, submit proposed recruitment text with the CCI application. Refer to the "**Advertisement Policy"**, and the "**Informed Consent Policy"**.

☐ Database (Indicate all institutions and departments whose database or records are to be accessed.)

Check the Origin of the database:
☐ Public Record, Specify:
☐ Medical Facility* (hospital, Private Practice, etc.), Specify**:**
☐ Commercial Sources, Specify:
(For commercial sources, provide brochure or other written information.)
☐ Other, Specify:

***NOTE:** Authorization from participating departments and institutions (including IRB approval) is generally required and should be provided to the CCI prior to use of databases.

If authorization is **NOT** required for access to the database explain below.

c. Provide a brief description of how subjects will be recruited.

2. CONTROLS: (If recruitment method and mechanism are the same as for subjects above or, no controls will be enrolled, indicate with a check) ☐ Not Applicable

a. Who will recruit controls? Lewis Kass

b. Source of controls recruitment: (Check all that apply):

☐ Physician Referral
☐ Hospital or Physician Records (Indicate all institutions and departments whose records will be accessed.):

☒ Radio/TV Announcement ☒ Newspaper Announcement ☒ Recruitment Letter
☒ Bulletin Board Posting ☐ Internet ☐ Random Telephone Contact

NOTE: All Public Announcements, Postings, Recruitment letters, and Telephone dialogs must be approved by the CCI prior to use. If possible, submit proposed recruitment text with the CCI application. Refer to the "**Advertisement Policy"**, and the "**Informed Consent Policy**."

☐ Database (Indicate all institutions and departments whose database or records are to be accessed.)

Check the Origin of the database:

☐ Public Record, Specify

☐ Medical Facility* (hospital, Private Practice, etc.), Specify

☐ Commercial Sources, Specify
(For commercial sources, provide brochure or other written information.)

☐ Other, Specify

***NOTE:** Authorization from participating departments and institutions (including IRB approval) is generally required and should be provided to the CCI prior to use of databases.

If authorization is **NOT** required for access to the database explain below.

c. Provide a brief description of how controls will be recruited.
These will be recruited through advertisements. Dr. Kass will be in charge of this recruitment.

D. POPULATION INCLUSION/EXCLUSION:
Research studies are required to include human subjects of all genders, races and ethnic groups, as well as minors (age 0-17).

Is any gender, race or ethnic group *excluded*?	☐ Yes[1]	☒ No	☐ N/A
Are pregnant women *excluded*?	☐ Yes[1]	☐ No	☒ N/A
Are non-pregnant women *excluded*?	☐ Yes[1]	☐ No	☒ N/A
Are minors *excluded*?	☐ Yes[1]	☒ No	☐ N/A
Are non-English speaking subjects *excluded*?	☐ Yes[1]	☒ No	☐ N/A

[1]If YES to any of the above questions, provide a clear **justification** for the **exclusion(s)** below:

E. SUBJECT POPULATION:
NOTE: Refer to the appropriate policy for the inclusion of the following subject populations.

Women In Labor	**HIV Human Subjects**	**Fetal Tissue**	**Minors**
AECOM/YU Students	**Patients in Significant Pain**	**Enrollment of Incapacitated Subjects**	

Check all classes of the population which may require special protections that may be enrolled in this study:

☐ Patients who may not be capable of giving informed consent[2] (e.g. mental retardation, dementia, acute psychiatric disorders)

☐ Patients who have an altered mental status[2] (e.g. patients who are under the influence of sedatives or narcotics, etc.)

☐ Women in Labor[2] ☐ Patients in Significant Pain[2] ☐ Fetal Tissue ☐ HIV ☒ Minors[3] (0-17)

[2]Research involving these categories requires **Full Committee** Review.

[3]If minors are to be enrolled, INDICATE AGES: 13-17 years

NOTE: *Some* research involving minors may receive **Expedited** Review. Refer to the "**Expedited Review Guidelines".**

Will minor's assent be obtained? ☒ Yes ☐ No ☐ Minors not included in study

For this study, are you requesting that minors' assent be waived? ☐ Yes[4] ☐ No

[4]If YES, specify the age group: 13-17 years **NOTE:** Detailed justification must be provided in the protocol.

VII. <u>INFORMED CONSENT:</u>

A. INFORMED CONSENT DOCUMENTATION, ALTERATION, OR WAIVER:
Under federal regulations and committee policy, subjects are required to sign the informed consent document at the conclusion of the consent process. Refer to the CCI '**Informed Consent Policy"**. Complete the questions below and provide a narrative in the protocol.

1. Will written informed consent be obtained from participants? ☒ Yes ☐ No[1]
[1]If No, explain below:

Consent form from parental permission/young adult and individual

2. Is consent being obtained at a time when the subject's decision making capacity might be impaired? ☐ Yes[2] ☒ No
[2]If YES, how and from whom will consent be obtained? Refer to the Policy **"Enrolling Incapacitated Subjects**" and explain in detail below:

3. Are you requesting a waiver of informed consent? ☐ Yes[3] ☒ No

[3]If YES, complete the "**Request for Waiver of Informed Consent**" form. Refer to the **"Informed Consent Policy".**

4. Are you requesting a waiver of the Documentation of informed consent? ☐ Yes[4] ☒ No

[4]If YES, complete the **"Request for Waiver of Documentation of Signed Consent"** form. Refer to the **"Informed Consent Policy"**.

NOTE: Provide a detailed narrative of the informed consent procedure in the protocol and, if applicable, include justification for any alteration and the altered consent mechanism.

B. INFORMED CONSENT PROCESS:

Informed consent is a process that takes place between the potential subject and the researcher/research team, before, during, and sometimes after the study. Subjects are required to receive a full explanation of the research protocol and all the required elements of informed consent. They are to be provided the opportunity to ask questions and have their questions answered by a knowledgeable member of the research team. Non English-speaking subjects are required to have a translator present during the consent process. **The consent process is subject to monitoring**.

When applicable, provide the following information:

1. When and where will the informed consent process take place? ☐ N/A

In CHAM outpatient clinic

2. Who will provide information to potential subjects and answer questions in the informed consent process? ☐ N/A

Dr. Lewis Kass/Dr. Gabriel G. Haddad

NOTE: The person conducting this discussion must sign the Informed Consent Document.

3. if non-English speaking subjects are to be enrolled, who will serve as the translator? Translator in the hospital

NOTE: A translator is required to be present for the entire consent process.

VIII. CONFIDENTIALITY:

A. RESEARCH RECORDS and/or MEDICAL RECORDS

Researchers must ensure the confidentiality of the information gathered in the study.

May the **research records** be reviewed by others beside the research team? (e.g., sponsors, collaborators, FDA etc.) ☒ Yes[1] ☐ No

[1]If YES, specify who may have access: NIH and collaborators

May subjects' **medical records** be reviewed by others beside the research team? ☐ Yes[2] ☒ No

[2]If YES, specify who may have access:

Specify below how confidentiality will be ensured (e.g., will the records be secured in a locked file cabinet; who will have access to the records; will the records be identifiable or coded; will computer records be encrypted, etc.):

All data will be acquired using computerized techniques and will be saved on disc files as coded data. Data will be stored in databases that are password-protected, only known to this group of investigators.

May the information be given to other researchers for subsequent research projects? ☒ Yes[3] ☐ No

[3]If YES, will the information be anonymous (un-coded and **NOT** linked to subjects)? ☒ Yes ☐ No[4]

[4]If NO, Subject's consent is required.

B. AUDIO/VIDEO TAPING:

Will subjects be audio or video taped during this study? ☐ Yes* ☒ No

*If YES, refer to the "**Audio/Video Taping**" Policy.

IX. DRUG/DEVICE STUDIES: NOTE: Refer to the "**Investigational Drug/Device**" Policy**.**

A. USE OF DRUG: Drug studies must be reviewed by the Pharmacy Department. Sign-off by the Pharmacy is required on the signature page.

Does the research protocol involve the use of a drug? ☒ Yes[1] ☐ No[2] [2]If no**,** Go to **B (Use of Device)**

[1]If YES, provide the drug names (generic and brand) and storage site.

	Brand Drug Name	Generic Drug Name	Storage Site[3]
1.	Glucose (13C)	Same	MR Center
2.	Acetate (13 C)	Same	MR Center
3.			

4. _____
5. _____

[3]Drugs not stored in the Pharmacy require a storage waiver. If Applicable, Complete the **"Drug Storage Waiver"** Form.

Does the research protocol involve the use of an FDA approved drug(s) according to the drug label, i.e. in an approved manner for an approved population? ☒ Yes ☐ No

INVESTIGATIONAL USE OF DRUGS:

Does the research protocol involve the use of an FDA approved drug in a manner that is different from the drug label? ☐ Yes[4] ☒ No

Does the research protocol involve the use of an FDA approved drug for a different population than approved? ☐ Yes[4] ☒ No

Does the research protocol involve the use of an *unapproved combination* of approved drugs? ☐ Yes[4] ☒ No

Does the research protocol involve the use of a non FDA approved drug? ☐ Yes[4] ☒ No

[4]If YES to any of the above questions, complete **"Use of Investigational Drug"** Form.

NOTE: If Multiple drugs or combinations will be used, a separate "**Use of Investigational Drug"** Form for each agent or combination is required.

NOTE: AECOM policy generally requires indemnification from the protocol sponsor for drug studies. The CCI Office will forward contracts/indemnification documents to legal counsel and institutional officials for review and approval.

B. USE OF A DEVICE

Does the research protocol involve the use of a device? ☒ Yes ☐ No[1]
[1]If no, go to section **X (Adverse Event Reporting)**

Does the research protocol involve the use of an FDA approved device in an approved manner for an approved population? ☒ Yes ☐ No

INVESTIGATIONAL USE OF DEVICE:

Does the research protocol involve the use of an FDA approved device in a manner that is different than originally labeled/approved or for a different population? ☐ Yes[2] ☒ No

Does the research protocol involve the use of an investigational device? ☐ Yes[2] ☒ No
[2]If YES, complete the **"Investigational Use of Medical Device"** form

Will this device be used physically on or in the human subject? ☒ Yes ☐ No

NOTE: AECOM policy generally requires indemnification from the protocol sponsor for device studies. The CCI Office will forward contracts/indemnification documents to legal counsel and institutional officials for review and approval.

X. <u>ADVERSE EVENT REPORTING:</u>

Will you be able to adhere to the Committee's policy regarding the reporting requirements for Deaths and Serious Events (within 48 hours of PI's knowledge) and Unanticipated Events (within 30 days of PI's knowledge)? ☒ Yes ☐ No*

Will you be able to adhere to the Committee's policy requiring the reporting of Deaths and Serious Adverse Events that occur within six months after the subject has received the final study intervention? ☒ Yes ☐ No*

***If NO, provide an explanation in the protocol.**

XI. <u>DATA SAFEY MONITORING BOARD:</u>

Has a DSMB been established for the oversight of this study? ☐ Yes[2] ☒ No[1]
[1]If NO, go to section **XII (Costs and Remuneration)**
[2]If Yes, answer the following:

1. Who has established the DSMB? _____
2. Attach documentation that identifies the composition and credentials of the DSMB members.
3. How frequently will the DSMB meet/report to the Principal Investigator?

XII. COSTS AND REMUNERATION:

A. SUBJECT REMUNERATION:

Will Subjects be reimbursed for travel expenses, child care costs, etc? ☒ Yes[1] ☐ No

Will Subjects be paid for their participation is the research? ☒ Yes[1] ☐ No

[1]If YES, refer to the "**Remuneration"** and "**Transportation"** Policies. Information regarding payment/remuneration must be clearly indicated in the "Procedures" section of the Informed Consent Document.

B. CHARGES FOR TESTS/PROCEDURES:

List all tests/procedures to be conducted under this study. For each indicate whether they are to be performed for standard clinical care and/or research purposes. Also indicate whether subjects (or their insurer) will be billed:

	Test/Procedure	Standard Clinical Care	Research	Billed to Subject/Insurer
1.	Sleep study in CHAM	☐	☒	☐
2.	Sleep/wakefulness study in the MR Center	☐	☒	☐
3.	IV infusion (13C glucose or acetate)	☐	☒	☐
4.	IV blood sampling	☐	☒	☐
5.	No experimental subjects-all healthy controls, 13-17 years of age and adults	☐	☒	☐
6.		☐	☐	☐
7.		☐	☐	☐
8.		☐	☐	☐
9.		☐	☐	☐

Drugs

Will subjects (or their insurers) be responsible for the cost of any **drugs** received in this study? ☐ Yes* ☒ No

*If YES, specify: _____

4.

XIII. HUMAN SPECIMENS:

Investigators are permitted to collect non-anonymous specimens (including those that are coded and can be linked back to the donor) for research only when the specimens are obtained with appropriate informed consent. Refer to the document entitled, "**Human Specimen Policy".**

NOTE: Left-over specimens from clinical care that are NOT linked to patients do not require consent and may be considered "exempt" research.

A. SPECIMEN COLLECTION:

1. Will human specimens be collected under this study? ☒ Yes[2] ☐ No[1]
   [1]If NO, go to section **XIV (MRI)**
   [2]If YES, answer all questions in this section.

2. Will specimens be collected under a *different* protocol approved by the AECOM CCI/MMC IRB? ☐ Yes[3] ☒ No
   [3]If YES, provide CCI or IRB # _____

3. Will specimens be left over from standard clinical care? ☐ Yes[4] ☒ No
   [4]If YES, specify:

   (a) Type of Specimen(s) _____

   (b) How and Where Obtained _____

4. Will specimens be collected from *outside* institutions, agencies, clinicians, private practice physicians, investigators, others? ☐ Yes[5] ☒ No
   [5]If YES, specify: _____

   If YES, copies of IRB approval from all outside institutions should be obtained and submitted to the CCI prior to initiation of the collaboration. Specimens generally cannot be received without appropriate approvals.

5. Will you destroy the specimens once this study is complete? ☒ Yes ☐ No[6]

[6]If NO, Future Specimen language is required in the consent document(s). See "**Human Specimen Policy"**.

6. Will the sponsoring company, agency, or collaborating scientists receive specimens from *this* study? ☐ Yes[7] ☒ No

[7]If YES, will the shared specimens be destroyed upon completion of this study? ☐ Yes[8] ☐ No[9]

[8]If YES, provide written verification from the sponsoring company, agency or collaborating scientists that the specimens will be destroyed at the conclusion of the study.

[9]If NO (shared specimens will *NOT* be destroyed upon completion of the study), Future Specimen language is required in the consent document(s). See "**Human Specimen Policy"**

Copies of IRB approval from all outside institutions should be obtained and submitted to the CCI prior to initiation of the collaboration. Specimens generally cannot be distributed without appropriate approvals.

7. Will tests be performed that will yield information that might affect the subject's insurability? ☐ Yes[10] ☒ No

[10]If YES, Insurability language is required in the "Risks" section of the Informed Consent Document.

B. GENETIC RESEARCH:

New York State Law Definition of Genetic Test:

"Genetic test shall mean any laboratory test of human DNA, chromosomes, genes, or gene products to diagnose the presence of a genetic variation linked to a predisposition to a genetic disease or disability in the individual or the individual's offspring; such term shall also include DNA profile analysis." The CCI/IRB also includes any genotyping or measurement of certain metabolites associated with heritable diseases.

1. Will tests be performed that will yield genetic information? ☐ Yes[1] ☒ No[2]

[1]If YES, specified consent language is required. Refer to the "**Human Specimen Policy"**

[2]If NO**,** go to section **XIV (MRI)**

2. Will the test results be disclosed to the participants? ☐ Yes ☐ No

3. Will formal genetic counseling be provided? ☐ Yes[3] ☐ No

[3]If YES, check below:

☐ By a Certified Genetic Counselor
☐ By a Physician
☐ Other, Specify _____

NOTE: If counseling of any type is provided, participants must be told who will provide the counseling.

XIV. MRI

Will the study involve MRI? ☒ Yes ☐ No[1]

[1]If NO, go to section **XV (RADIOISOTOPES/OTHER SOURCES OF IONIZING RADIATION)**

Will contrast and/or sedation be used? ☐ Yes[2] ☒ No

[2]If YES for the use of contrast and/or sedation**, Full Committee Review** is required**.**

XV. RADIOISOTOPES/OTHER SOURCES OF IONIZING RADIATION:

NOTE: Studies involving Radiation or Radioisotopes require approval by the Radiation Committee prior to CCI approval.

Will the study involve the use of radioisotopes or other sources of ionizing radiation (e.g. x-rays?) ☐ Yes[1] ☐ No[2]

[1]If YES, complete the '**Use Of Ionizing Radiation"** Form
[2]If NO, go to section **XVI (Conflict of Interest)**

Will contrast and/or sedation be used? ☐ Yes[3] ☐ No

[3]If YES for the use of contrast and/or sedation**, Full Committee Review** is required**.**

Will the resources of the Department of Radiology or Nuclear Medicine at AECOM/MMC and/or JMC/NCB be utilized? ☐ Yes ☐ No

Are the tests *above and beyond* what would ordinarily be required for standard clinical care? ☐ Yes ☐ No

NOTES: For Tests/Procedures that involve resources of the JMC/NCB Department of Radiology/Nuclear Medicine, the appropriate Chairman's signature(s) is required on the Signature Page.
For Tests/Procedures that are *beyond* standard clinical care and involve resources of the AECOM/MMC Department of Radiology/Nuclear Medicine, the appropriate Chairman's signature(s) is required on the Signature Page.

XVI. CONFLICT OF INTEREST:

NOTE: Refer to http://www.aecom.yu.edu/home/cci/financial_coi_policy.htm for a full description of this policy.

The PI and each of the Key Personnel (for the COI requirement, Key Personnel are those assigned to work on the protocol at either AECOM, MMC, JMC, or NCB) are required to fill out and sign a Conflict of Interest Disclosure Form, found on page 12 of this document.

XVII. CANCER RELATED STUDIES:

Is the study population for this protocol primarily cancer patients? ☐ Yes* ☒ No

*If YES, the AECOM Cancer Protocol Review Committee (CPRC) is required to review and approve this protocol prior to CCI approval.
NOTE: The PI is responsible for submitting the CCI Protocol directly to the CPRC. The CPRC will notify the CCI of CPRC Approval.

XVIII. RECOMBINANT DNA - GENE TRANSFER - GENE THERAPY:

The concept of gene transfer/gene therapy encompasses treatment of any pathophysiological state on the basis of the transfer of gene material, complementary DNA, full-length genes, RNA, or oligonucleotides.

Does this protocol involve any of these procedures in humans? ☐ Yes* ☒ No

*If YES, review and comment by the NIH Recombinant DNA Advisory Committee (RAC) is required prior to submission to the AECOM Institutional Biosafety Committee (IBC) and to the CCI. IBC approval is required prior to CCI review. The CCI will forward the protocol to the IBC for review. Refer to the NIH Recombinant DNA Guidelines and flow chart.

XIV ASSURANCES OF THE PRINCIPAL INVESTIGATOR

As Principal Investigator of a research project to be carried out under the auspices of Yeshiva University, I assume responsibility for the:

1. Conduct of this research protocol in accordance with applicable federal and state regulations, and all institutional policies and procedures:
   - As PI, I accept responsibility for the protection of the rights and welfare of human research participants and will conduct this study in accordance with federal regulations 45 CFR 46, the federally approved AECOM Multiple Project Assurance, and CCI policies and procedures. I also accept responsibility for compliance with the institutional "Conflict of Interest Policy" and "Patent Policy."

   NOTE: All the above named documents are available on the CCI Home Page or in the AECOM Faculty Handbook.

2. Protection and privacy of research subjects:
   - As PI, I will make every possible effort to prevent release of information leading to a breach of privacy. No published or unpublished report or oral or visual presentation of any aspect of this study will include any material that will permit identification of any individual subject to any person or agency other than to the named collaborators of this study, the sponsors of the protocol, the appropriate Federal agencies, the participating institutions, and the Committee on Clinical Investigations.
   - If the research involves HIV, or if during the course of the research HIV-related information becomes known, I will maintain confidentiality to the extent required by New York State law.

3. Conduct of the protocol as approved by the appropriate departmental authorities and institutional committees:
   - I will obtain all of the required approvals prior to review of the protocol by the CCI.
   - I will obtain the appropriate federal agency documents and institutional committee approvals in accordance with federal, committee, and institutional requirements. Such committees include the NIH Recombinant DNA Advisory Committee (RAC), Institutional Biosafety Committee (IBC), General Clinical Research Center Research Committee, the Cancer Center Protocol Committee (CCPC), and the Radiation Safety/Radioisotope Committee.

4. Submission of all protocols and grant applications for CCI Review:
   - I will submit all protocols and grant applications to the CCI, including those that may be exempt from CCI approval under federal regulations. Exempt research requires CCI verification of the exemption status.

5. Submission of Progress Reports to the CCI for Re-certification:
   - For continuing re-certification of the research project, I will submit the required Progress Report and applicable attachments to the CCI, at intervals as determined by the CCI (which may not exceed 365 days from the prior date of approval).

6. Reporting and Approval of Proposed Amendments for Ongoing Research Activity:
   - I will implement changes to the protocol or the informed consent only subsequent to CCI review and approval, except when necessary to avoid immediate potential harm to subjects.

7. Obtaining Informed Consent:
   - I will ensure that research subjects are properly informed about the details of the research study, are provided the opportunity to have all questions answered, and have had all the elements of the informed consent document explained to them. I will ensure that members of the research team designated to conduct the informed consent process are knowledgeable about the study. I will submit requests to the CCI to implement a waiver of informed consent, to alter the elements of informed consent, or to waive the requirement for an informed consent document.

8. Reporting all Adverse Events
   - I will be responsible for submitting all adverse event reports to the CCI, protocol sponsor, and federal agencies, as required by all parties.
   - I will be responsible for ensuring compliance with the CCI/IRB Adverse Event Policy, which requires reporting Internal Deaths and Serious Events within 48 hours of the PI's knowledge and Unanticipated Events within 30 days of the PI's knowledge. External Deaths, Serious Events, and Unanticipated Events must be reported within 30 days of the PI's knowledge.

I certify that I agree to abide by all the guidelines noted above:

_____ _____

Signature Date

CCI #_____

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS
CONFLICT OF INTEREST DISCLOSURE FORM

The PI and each of the Key Personnel (for the COI requirement, Key Personnel are those assigned to work on the protocol at either YU/AECOM, MMC, JMC, or NCB) are required to fill out and sign a Conflict of Interest Disclosure Form.

Principal Investigator Name: Gabriel G. Haddad

Protocol Title: Sleep mechanisms in children: role of metabolism

You are required to disclose any financial interest that you or your spouse or your dependent children have related to this research or its sponsor.

'Financial Interest' includes anything related to this research of monetary value, including cash, recruitment bonuses, consulting fees or honoraria, stocks or other ownership interests, and patents copyrights or other intellectual property rights, and royalties from intellectual property rights, if the total payment or ownership interest in one year to the Investigator (including payments to his or her spouse and dependent children) is expected to be more than $10,000 and/or constitutes more than five (5%) percent ownership interest in a single organization.

The term 'Financial Interest' does not include:

(a) Salary or other remuneration received from the University or Medical Center;
(b) Holdings in mutual funds;
(c) De minimis gifts whose aggregate value does not exceed $250 per annum; or reasonable business expenses, including travel and meals provided in the regular course of business.

Please answer all questions below:

1. With relationship to this research or its sponsor, do you or your spouse or dependent children have 'financial interest' that may yield income exceeding $10,000 over the prior twelve months or anticipated during the forthcoming twelve months? ☐ YES* ☒ NO

   *If YES, describe amount and identity of person with interest: _____

2. With relationship to this research or its sponsor, do you or your spouse or dependent children have an equity interest with a value greater than, or equal to, $10,000 (current market value) or 5% or greater ownership interest? ☐ YES* ☒ NO

   *If YES, describe amount and identity of person with interest: _____

3. Do you or your spouse or dependent children have an intellectual property interest on an actual or planned patent, patent application, or a copyright of software for the product under study that is assigned or will be assigned to a party other than the University or the Medical Center? ☐ YES* ☒ NO

   *If YES, describe amount and identity of person with interest: _____

4. Are you aware of any financial interests of either YU/AECOM, MMC, or the NYCHHC that exceed $10,000 (current market value) in income, $10,000 or 5% or greater equity interest, or intellectual property/patent income that exceeds these limits? ☐ YES* ☒ NO

   *If YES, describe amount and identity of institution with interest: _____

An answer of 'YES' to any of the above questions requires review of the potential conflict of interest by institutional procedures. You may be asked by either the MMC or the CCI Administrative Office to provide additional information to facilitate further review by the Committees.

Name: Gabriel G. Haddad

Signature: **Date:** 9/22/2002

Please return this form, completed and signed, to the AECOM CCI:
1300 Morris Park Avenue, Belfer 1002; Bronx, NY 10461; Fax: (718) 430-8817

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS

APPROVALS

Signature, Principal Investigator	Date
To be completed by the Chairman (or Designee), Primary Participating Dept. I approve of this protocol. ☒ Furthermore, to the best of my knowledge, there are no potential conflicts of interest that are reportable consistent with the CCI/IRB Financial Conflict of Interest Policy (http://www.aecom.yu.edu/home/cci/financial_coi_policy.htm). -or- ☐ I know of one or more conflicts and have notified the CCI (fax: 430-8817, E-mail: hopkins@aecom.yu.edu). **Signature, Chairman (or Designee), Primary Participating Dept.**	Date
SIGNATURES OF THE FOLLOWING ARE REQUIRED ONLY WHERE APPLICABLE Refer to Approval Guidelines for Required Signatures	
Signature, Division Chief, for Department of Medicine studies	Date
Signature, Chairman, Pathology	Date
Signature, Director, Laboratories	Date
Signature, Chairman, Radiology	Date
Signature, Chairman, Participating Department/Division	Date
Signature, Director of Weiler Hospital Pharmacy	Date
Signature, Director of JMC/NCB Hospital Pharmacy	Date
Signature, Person Authorizing Access to Database	Date
Signature	Date
Signature	Date
Signature, Dean of AECOM/YU School	Date

Signature, Chairman, Committee on Clinical Investigations	Date

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS

REQUEST FOR WAIVER OF INFORMED CONSENT

Per the Code of Federal Regulations Title 45, Part 46.116 (d) an IRB is **ONLY** permitted to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent (i.e. a waiver of informed consent) if four very specific criteria are met.

Principal Investigator Name: _____

Protocol Title:

1. Does the research present **more** than minimal risk of harm to the subject? (Minimal risk is defined as the probability and magnitude of harm or discomfort are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological tests).

Yes ☐ No ☐

2. Will the waiver adversely affect the rights and welfare of the subjects? Yes ☐ No ☐

3. Can the research be practicably carried out without the waiver? Yes ☐ No ☐

4. Will the subjects be provided with additional pertinent information after participation, whenever appropriate?

Yes ☐ No ☐

Indicate below why the research could not practicably be carried out without the waiver.

_____ _____

Principal Investigator's Signature Date

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS

REQUEST FOR WAIVER OF SIGNED DOCUMENTATION OF CONSENT

Per the Code of Federal Regulations Title 45, Part 46.117 (c) an IRB is **ONLY** permitted to approve a consent procedure which does not require a subject's signature when at least one of two specific criteria are met.

Principal Investigator Name: _____

Protocol Title:

1. Would the consent document be the **ONLY** identifiable link between the subject and the research, **AND** would there be potential harm to the subject if the confidentiality of the consent document were breached?

Yes ☐ No ☐

Indicate below how a breach of confidentiality would be harmful to the subject:

2. **(a)** Does the research present **more** than minimal risk? (Minimal risk is defined as the probability and magnitude of harm or discomfort are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological tests).

Yes ☐ No ☐

2. **(b)** Does the research involve any procedures for which written consent is normally required outside of the research context?

Yes ☐ No ☐

_____ _____

Principal Investigator's Signature Date

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS
USE OF INVESTIGATIONAL DRUG FORM

THIS FORM MUST BE COMPLETED FOR ALL INVESTIGATIONAL DRUG STUDIES

NOTE: An IND or exemption (waiver) is required for all investigational drug studies. To obtain an IND #, FDA form 1571/1572 must generally be filed with the FDA by the Sponsor/Investigator. Refer to the **"Investigational Drug/Device"** Policy for further information. For approved drugs used in an investigational manner, a waiver may be approved by the CCI in accordance with FDA regulations. For IND exemption, complete the "IND Exemption Request (Waiver) Form."

A copy of this form must be placed in the patient's medical chart.
Any drug administered under a research protocol for a non-FDA approved use, for use in a non-approved population, or in a non-approved form, is considered investigational.

If more than one investigational drug is being used in a protocol, a separate form must be completed for each drug used.

Generic Drug Name and Brand Name, if known: Glucose	IND #: _____ Request for Exemption: ☒	
Drug Manufacturer: Baxter		Phase
Dosage Form and Strength: 13C glucose, 20%		
Investigational Study Title:		
Principal Investigator: Gabriel G. Haddad	Telephone: 718-430-4127	Emergency Phone: 203-531-0633
Physicians Authorized to Prescribe: Haddad, Pan, Hetherington, Kass		
Pharmacologic Properties: raises bloog glucose level		
Side Effects and Toxicity: Hyperglycemia, hyperosmolality		
Antidote: stop infusion, give insulin + KCl		
Dosing Guidelines for this protocol (dose, route, frequency, duration of therapy, etc.) Used in glucose clamps		
Reconstitution and Stability Data: available as USP injection		
Essential Compatibility Data: NA		
IV Fluids: NA		
Other Drugs: No interactions		
Other Miscellaneous Information (i.e., storage, precautions, special instructions): NA		

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS
DRUG STORAGE WAIVER FORM

It is hospital policy that all investigational drugs be stored by the Department of Pharmacy. However, in instances where this is not practical, Principal Investigators may obtain approval from the Department of Pharmacy and CCI to store their own drug supplies. To obtain approval, complete and sign this waiver, obtain pharmacy approval, and return to the CCI prior to review of the protocol. If drugs are to be stored in the GCRC, approval from the GCRC director is also required.

Brand and Generic Name & Strength of Drug: Glucose, acetate

Location of Drug Storage: MRRC

To assist you in the proper storage of Investigational Drugs, it is essential that you adhere to the following guidelines:

1. Store your investigational drugs in a locked, secure area.
   (For information on storing Controlled Substances, refer to the guidelines listed in the Controlled Substances Handbook. This may be obtained from the Department of Pharmacy).

2. Store your investigational drugs appropriately. (i.e. room temp., refrigeration).
   check one: ☐ Room Temperature ☐ Refrigerated ☐ Frozen

3. Label all your investigational drugs appropriately prior to dispensing.

4. Maintain accurate inventory logs that reflect the receipt and dispensing of any investigational drugs.

5. Return any unused investigational drugs to the Pharmacy upon study completion.

By signing this form, Principal Investigators agree to follow the above guidelines. If you have any questions regarding this matter, contact the Department of Pharmacy (Weiler: 904-2825, Moses: 920-2940, JMC: 918-4556).

Gabriel G Haddad
Principal Investigator Name (print)

Principal Investigator Signature Date

Director of Pharmacy Signature Date

The following signature is required if drugs are to be stored in the GCRC:

GCRC Director Signature Date

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS

INVESTIGATIONAL USE OF MEDICAL DEVICE FORM

1. Name of Device: 4tesla MR device technically investigational but is within FDA category of safe magnetic fields and is used widely in research
2. Manufacturer of Device: Varian Inc, established at AECOM as part of the iamaging center

3. Will device be custom-built? Yes ☐ No ☒

4. Does the study involve a "**Significant Risk**" device ☐, or a "**Non-Significant Risk**" device ☐ .

5. **SIGNIFICANT RISK DEVICE:**
FDA defines a **significant risk** device as one that presents a potential for serious risk to the health, safety, or welfare of a subject; and is an implant, is used in supporting or sustaining human life, is of substantial importance in diagnosing curing, mitigating, or treating disease, otherwise prevents impairment of human health, or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject." An investigation involving a significant risk device **requires submission of an IDE application** to the FDA and FDA approval of the investigation. MMC/IRB/AECOM CCI approval is required prior to conducting clinical trials of the investigational device.

a. Has the sponsor (company or the investigator) applied to the FDA for an IDE? Yes ☐ No ☐
If **YES,** What is the IDE number? _____

b. Has the application been approved by the FDA? Yes ☐ No ☐ Pending ☐

6. **NON-SIGNIFICANT RISK DEVICE (NSRD): (Note:** NSRD studies do *NOT* require an IDE application to the FDA.)
If the study involves a "NSRD," explain the reasons(s) for that determination.

The FDA considers 4 Tesla magnets to be within the safe range for exposure to magnetic fields and do not have significantly more hazard than the standard 1.5 Tesla devices. This is true for all projects that will use 4Tesla magnets. It is also what CCI has determined for other devices.

7. **DEVICE NOT APPROVED FOR GENERAL MARKETING:**
Has the device been classified by HCFA/FDA as:
☐ Category A (experimental)
☒ Category B (non-experimental)

IF CATEGORY A, has this study received administrative clearance from the applicable hospital or clinical site? Yes ☐ No ☐

8. **DEVICE WITH COMPONENTS:**
Is the same configuration of components approved by the FDA for general marketing being used? Yes ☒ No ☐
Has the device received the IDE and/or Category B status? Yes ☐ No ☐

If **NO**, explain:

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS

USE OF RADIOISOTOPES OR IONIZING RADIATION

RESEARCH INVOLVING THE USE OF IONIZATION RADIATION MAY **NOT** BE INITIATED UNTIL APPROVED BY THE RADIATION SAFETY COMMITTEE

This form must be completed if radioisotopes or other sources of ionizing radiation are used.

Principal Investigator Name: _____ Date: _____

Address: _____ Phone: _____

Title of Protocol: _____

1. Will this study involve the use of internally administered radioisotopes? ☐ Yes ☐ No
   If Yes, complete the following items:

   (a) Isotope(s) to be administered _____

   (b) Chemical form(s) _____

   (c) Total dose administered per patient in mc or mg for each isotope: _____

   (d) Will more than one study be performed per patient? ☐ Yes ☐ No

   (e) Dosimetry (include major organ, gonadal and total body dose): _____

2. Will this study involve the use of external radioisotopes or other sources of ionizing radiation (e.g., x-ray)? ☐ Yes ☐ No
   If Yes, specify sources of radiation and include dosimetry calculations. _____

COMMENTS:

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY
COMMITTEE ON CLINICAL INVESTIGATIONS
IND EXEMPTION REQUEST (WAIVER) FORM

Under FDA regulations, an IND exemption for investigational use of marketed drugs may be granted to an investigator provided the following criteria are met:

1. The investigation is not intended to be reported to the FDA as a well controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling of the drug;
2. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

For each drug for which you are requesting a waiver, check **all** applicable categories below and **specify** the difference(s) from the FDA approved usage (drug label).

Drug Name: 13C-glucose

☒ Different indication, Specify: to be able to examine turnover rates in brain tissue using MR

☐ Different population,(e.g., children or pregnant women, etc.) Specify: _____

☐ Different dose, Specify: _____

☐ Different route of administration, Specify: _____

Drug Name: 13C-acetate

☒ Different indication, Specify: to be able to determine glutamine-glutamate cycling between neurons and glia

☐ Different population,(e.g., children or pregnant women, etc.) Specify: _____

☐ Different dose, Specify: _____

☐ Different route of administration, Specify: _____

Drug Name: _____

☐ Different indication, Specify: _____

☐ Different population,(e.g., children or pregnant women, etc.) Specify: _____

☐ Different dose, Specify: _____

☐ Different route of administration, Specify: _____

Drug Name: _____

☐ Different indication, Specify: _____

☐ Different population,(e.g., children or pregnant women, etc.) Specify: _____

☐ Different dose, Specify: _____

☐ Different route of administration, Specify: _____

REQUEST FOR WAIVER:

I, , am requesting an IND exemption for the following drug or drug combination listed above under the criteria stated above.

_____ _____
Signature of PI Date

II. DESCRIPTION OF STUDY

Purpose

The purpose of this project is to measure glycogen, glutamate turnover rate and glutamate-glutamine cycling in wakefulness and sleep in adolescent children (13-17). We will also study a subset of children in the same way except after sleep deprivation. These measurements will be made using MR spectroscopy. None of the studies proposed have been done in adults or children. Indeed, only a small part of what is proposed here has been done in animals with the use of invasive techniques. Our long-term goals include the study of children of various ages, from the very young infant to the adult. For simplicity and for practical and safety reasons, we are starting with this protocol which calls for the study of the older child or adolescent, ie, 13-17 years of age. Hence these studies have not been done in the adult or child and the metabolic processes that occur in sleep are very poorly defined. Furthermore, we and others have shown in the past that sleep processes are very different in the child when compared to the adult. Depending on the age, from infancy to adolescence and adulthood, sleep architecture and patterns are different, and the amount of sleep is different. It is also likely that brain processes are very different during sleep at various ages since sleep may have different roles and functions at various ages. In the future, we intend to study other age groups such as infants and adults.

Background

Sleep and the neurobiological mechanisms controlling sleep/wakefulness have been an enigma in spite of important recent advances in the field. Although it is well known now that sleep affects a variety of systems, including the cardio-respiratory, endocrine and autonomic systems, we still do not understand why we sleep and the mechanisms that control sleep. For example, we do not have a good understanding of the mechanisms that induce or maintain sleep or those mechanisms that are activated with sleep deprivation.

One of the potentially important areas that have started to develop is the role of brain metabolism in sleep. Although metabolic studies during sleep have been done in the past few decades, new developments in brain imaging have made it possible only recently to examine the importance of metabolism in sleep research. Positron emission tomography (PET) studies have shown that there are major differences in the activation of certain parts of the brain between slow-wave sleep and REM sleep. In addition, there was a large difference in the pCO_2-corrected cerebral blood flow between the wake state and slow-wave sleep. The link between metabolism and sleep is very well illustrated also in the Benington and Heller's working model in which decreases in glycogen and ATP lead to alterations in released adenosine which, in turn, play an important role in neuronal excitability and sleep induction. Furthermore, and of major interest, is the growing evidence that O_2 consumption and metabolic rate in brain tissue is not only dependent on nerve cell function and excitability but also on the functional coupling between nerve and glial cells. Hence, glycogen metabolism, glucose oxidation and glutamate turnover are linked in that both glial and neuronal elements are apparently involved. Hence, in order to understand sleep and its mechanisms, it becomes important to study the functional integrity and coupling of both neurons and glia and their relationship as a function of state. Such studies have not been done in wakefulness and sleep in the adult or the child. Clearly the importance of the proposed studies stem from the following: a) The understanding of the induction and maintenance of sleep would allow us to understand better the function of sleep, which is about, on average, a third of our lives! b) The study of normative processes will allow us to better understand diseases related to sleep such as narcolepsy, obstructive sleep apnea, circadian rhythm problems, and the effects of sleep deprivation. c) The study of adolescent children in particular is important since the above mentioned diseases and conditions appear and occur specifically in adolescent children. For example, although narcolepsy can occur at an earlier age, the peak incidence is in adolescence.

Although a handful of studies have been done on the adult human brain to decipher the link between metabolism and sleep/wakefulness, none of them have looked at glutamate-glutamine cycling, glutamate turnover rate or glycogen. These are now feasible and should be helpful in allowing to understand the importance of sleep in what has been termed the "restorative" metabolic function of sleep. In the child, there have been no studies on the brain during sleep or wakefulness to examine any metabolic pathways. Clearly, there is considerable evidence that brain maturation indeed continues to take place with age through adolescence and adulthood. Since sleep patterns also continue to change (e.g. consider sleep patterns in the first few months as compared with older children), it is likely therefore that sleep mechanisms also mature

with age. In this application, we will focus on adolescent children for the practical and conceptual reasons mentioned above.

It has been clear for many years that sleep, like wakefulness, is not a homogeneous state. Sleep states have their electroencephalographic, autonomic, behavioral and cardio-respiratory signatures. For conceptual reasons and in order not to complicate the experimental matrix, we will focus this application on stage IV sleep (deep sleep) and will address our questions comparing this sleep stage to a well defined state of wakefulness. Furthermore, since previous studies have taught us about sleep and its mechanisms by studying sleep deprivation, we will, in a subset of our children, address the same questions after sleep deprivation.

Our laboratory has had a long-standing interest in sleep in children, especially as it pertains to the control of respiration and obstructive sleep apnea. For the past 2 decades, we have engaged in clinical and basic research in the control of respiration, consequences of tissue hypoxia and the mechanisms that lead to cell adaptation or injury. In addition, the Nuclear Magnetic Resonance and Imaging Center at this institution is endowed with the talent needed for the proposal and with state-of-the art approaches and techniques that have been developed in the Center and which are essential to the proposal. Hence the integration of our two groups will be exciting and will allow us to address questions of importance in sleep research in children, an area of research that, at present, is very fertile. *Our* *specific hypotheses* are as follows:

1. **Stage IV sleep, as compared to wakefulness, has a lower brain metabolic activity in children; this is reflected by a reduced glutamate turnover rate and this reduction is prevented by sleep deprivation.**
2. **Control mechanisms of glial glucose oxidation play an important role in glutamate/glutamine cycling and represent an important checkpoint in mechanisms of sleep deprivation.**
3. **Brain glycogen content increases during the course of sleep in children and sleep deprivation markedly lowers glycogen content.**

References:

a) **Buchsbaum, MS, et al. Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. Life Sci, 1989,45:1349-56.**
b) **Maquet, P, et al. Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method. Brain Res, 1990,513:136-43.**
c) **Madsen,PL, et al. Cerebral blood flow and metabolism during sleep. Cerebrovasc Brain Metab Rev, 1991,3:281-96.**
d) **Wu, JC, et al. The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. Sleep, 1991,14:155-62.**
e) **McCormick, DA, et al. Sleep and arousal: thalamocortical mechanisms. Ann Rev Neurosc, 1997, 20:185-215.**
f) **Rothman, DL, et al. In vivo nuclear magnetic resonance spectroscopy studies of the relationship between the glutamate-glutamine neurotransmitter cycle and functional energetics. Philos Trans R Soc Lond B Biol Sci, 1999, 354:1165-77.**
g) **Magistretti, PJ, at al. The astrocyte-mediated coupling between synaptic activity and energy metaboilsm operates through volume transmission. Prog Brain Res, 2000, 125:229-40.**
h) **Thomas, M, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res, 2000, 9:335-52.**
i) **Maquet, P. Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res, 2000, 9:207-31.**
j) **Shulman, RG, et al. 13C MR of intermediary metaboilsm: implications for systemic physiology. Ann Rev Physiol, 2001, 63:15-48.**
k) **De Graaf, RA, et al. Differentiation of glucose transport in human brain gray and white matter. J Cereb blood flow and metab, 2001, 21:483-92.**

l) **Netchiporouk, L, et al. Brain extracellular glucose assessed by voltametry throughout the rat sleep-wake cycle. Eur J Neurosc, 2001, 13:1429-34.**
m) **Rothman, DL, et al. The role of glia in controlling the synaptic pool of the transmitter glutamate via the glutamate-glutamine cycle: relation to glucose utilization and interpretation of the functional imaging signal. In press.**
n) **Carskadon, MA, et al. Sleepiness in the normal adolescent. In Sleep and Its disorders in Children, Edited by C. Guilleminault, Raven Press, NY, 1987.**

Specific Location of Study

The Sleep laboratory in the Children's Clinical Research Center and the Magnetic Resonance Center

A. Probable Duration of Project

4 years

B. Research Plan

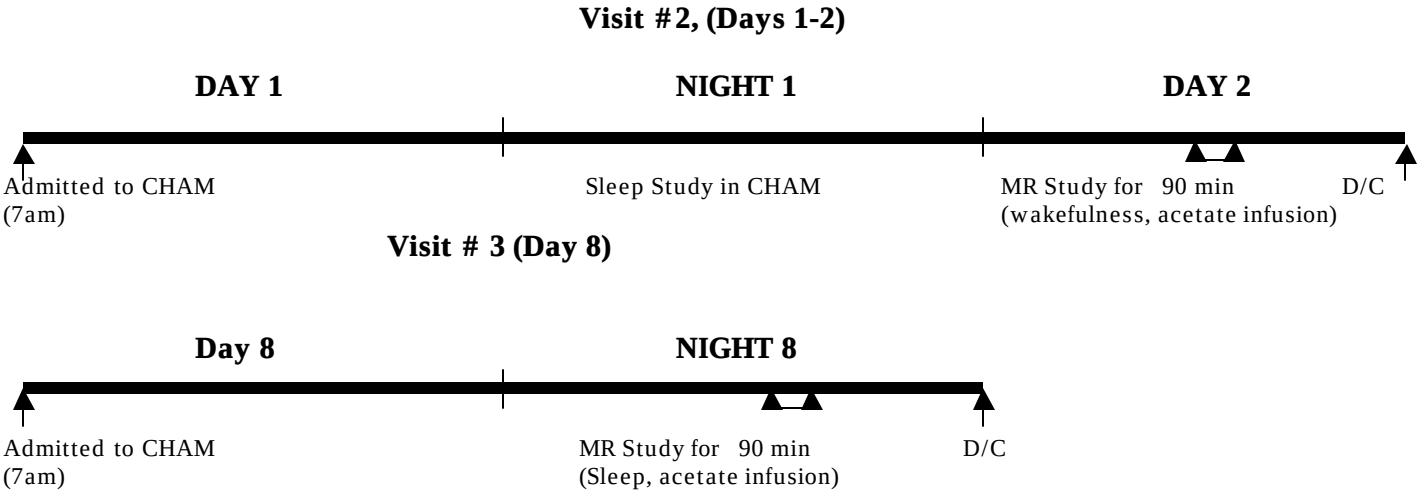
I. Objectives: The objectives of these studies are four-fold: a) To determine glutamate-glutamine cycling between neurons and glia in both wakefulness and quiet sleep in adolescent children. b) To determine the neuronal and glial TCA cycle rate in quiet sleep and wakefulness in these same subjects. c) To determine glycogen content during quiet sleep and wakefulness and d) to study the effect of sleep deprivation on neuronal and glial TCA cycle rate, glutamate-glutamine cycling and glycogen content.

II. Paradigm and Measurements: The study will involve 3 visits to the Children's Hospital (CHAM) under the observation of Drs. Lewis Kass or Gabriel Haddad. Visit # 1 is a screening Specialty Clinic visit during which a physical exam, a history with blood tests will be performed. Blood tests will be taken in the Clinic to test for potential factors that would exclude the volunteer from the study, specifically elevated blood glucose, elevated liver function tests, low hematocrit, and impaired renal function. Visits #2 and 3 will be visits to the CHAM and Nuclear Magnetic Resonance (MR) visits. ***Screening Clinic Visit (Visit #1) for all children:*** Before the child can be part of the study, the child will come to the Specialty Pediatric Clinic (2^{nd} floor of the Children's Hospital) for a screening visit of approximately 1 hour. During this visit, the PI or co-investigators who will perform a physical examination and ask about the medical history will explain the procedures of the study. During this visit a set of blood (15cc) and urine tests will be done. One week later, after the results of the first screening visit have been evaluated, Dr. Kass or Haddad will set up a date for the next visits as described below. ***There are 4 groups of adolescent children*** participating and these will be randomly assigned. Two groups will be studied with an infusion containing ^{13}C-acetate (A1, with normal activities, and A2, with sleep deprivation) and the other two groups with an infusion containing ^{13}C-glucose (G1, with normal activities, and G2, with sleep deprivation). One group receiving the acetate infusion will be studied during wakefulness or sleep after normal daily activities and another group will be studied after sleep deprivation of one whole night. Similarly, each of the two groups receiving the glucose infusion will be studied in the same way as for the groups receiving acetate, that is one group will be studied after normal activities during the previous day and the other after one night without sleep. The protocols of these groups are detailed below.

A. GROUPS A1 and A2 (Acetate)

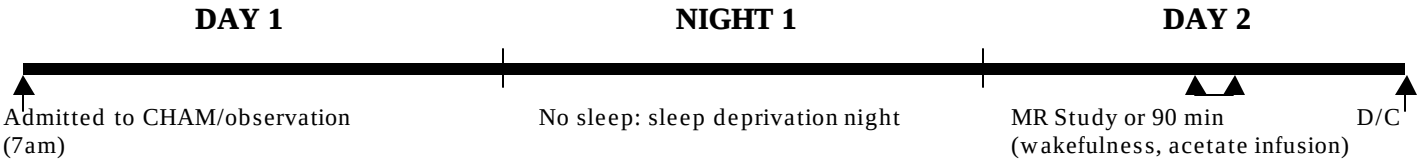
CHAM and MR Visit (Visit #2), Group Acetate infusion, normal activities (A1): Day 1. The child in this group A1 will be admitted to the C
CHAM in the morning (7-8am) (see chart below). The child will have normal activities during the day until the evening when the child will have a sleep study in the Sleep laboratory of the CHAM. Each study will involve the recordings of EEG, EOG, EMG, respi-bands for chest and abdominal movements, O_2 saturation, end-tidal CO_2, EKG, leg movements, snoring using a microphone placed on the neck, and a video camera to monitor behavioral aspects during sleep. This will involve placing surface electrodes like those used for the

electrocardiogram on the head, forehead and chest. If this study shows that the sleep architecture is normal for the age group, and that there is no medical problem such as snoring, then we will continue with the study, as described below. Otherwise the child will not be eligible for any subsequent part of the study and no additional visits will be required. Day 2. If the child is eligible for the rest of the study, day 2 will be spent in the CHAM until mid-day (at about 12-1 pm) when the child is transported to the MR Center and studied there. During this study, an intravenous infusion of acetate will be given for over 90 min during which MR spectra will be collected. The acetate infusion will be given at a rate of 3mg/kg-min. A blood sample (3 cc) will be taken every 15-20 min. This infusion rate will raise blood acetate levels to approximately 2 mM which well within what is tolerated. During the acetate infusion, a blood sample will be taken every 15-20 min and a total of about 15cc will be taken. Furthermore, the child will have to be **awake during the 90-min period of study**. When finished the child can be discharged home (D/C). Every child who is eligible to be studied in the magnet can, for purposes of acclimatization to the magnet, spend a certain time (for a few hours if needed) in a "mock" magnet. This will allow children to acclimate themselves and be prepared for the study the day or night before. ***CHAM and MR Visit (Visit #3), Group Acetate infusion, normal activities (A1):*** Day 8. This is the last part of the study for this A1 group (see chart below). On Day 8, the child will be admitted to the CHAM in the morning (6-7am) to be observed. In early evening (7-8pm), the child will be taken to the MR Center to have a study similar to the one performed on Day 2. The child will be prepared at that time but may not sleep until later on. However, during this study in the MR center, we will also monitor the sleep stage using EEG and EOG while in the magnet. We will start the same intravenous infusion of acetate and will sample blood (15 cc) over the 90 min period, much like we did on Day 2. The infusion and blood sampling will take place only after the child had **fallen asleep since this study, unlike that on Day 2, is done during sleep**. We will start the infusion only when the child is in the first cycle of Stage III-IV sleep. Sleep state will be monitored continuously during the infusion. After we finish the 90 min MR study measuring glutamate turnover and glutamate-glutamine cycling (see techniques), the child can be transported to the CHAM and discharged the following morning.

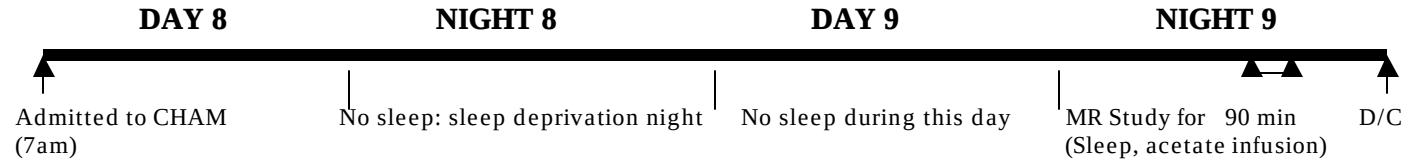


CHAM and MR Visits, Group Acetate infusion, sleep deprivation (Visits #2,3) (A2). This protocol is exactly the same as for the normal activity group (A1) except that on Day 2 when admitted, the child will not sleep the night that follows the morning of admission (see graph below). The child will be admitted that day before the sleep deprivation night in order to ascertain that the child will have normal activities during the day and that during the night children will be kept awake. They will be able to listen to music, watch TV, read, but they will not be allowed to go to sleep. For adolescent children, this will not, in all likelihood, be difficult. During the following day, children will be studied like the other group on Day 2 at around 12-1pm (see graph below). Since this a **wakeful study**, the child will be awake in the magnet during the infusion and the blood sampling. The MR **sleep study** will also, like in the previous group, be done on Day 8. Therefore, the child will be admitted in the morning, stay up that night in the CHAM, stay awake during the day that follows that night and then be studied on the second night when the child will be allowed to go to sleep. The study again will take place in Stage 3 or 4 NREM sleep during the first cycle.

Visit #2, (Days 1-2)



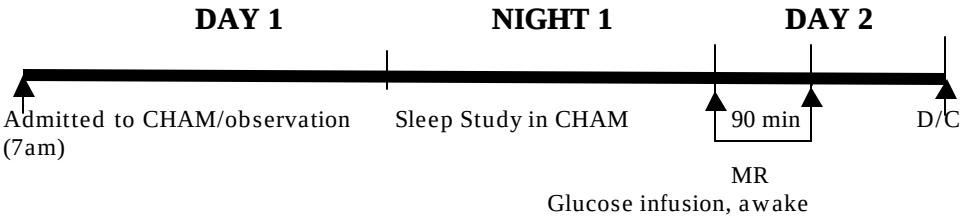
Visit # 3 (Days 8-9)



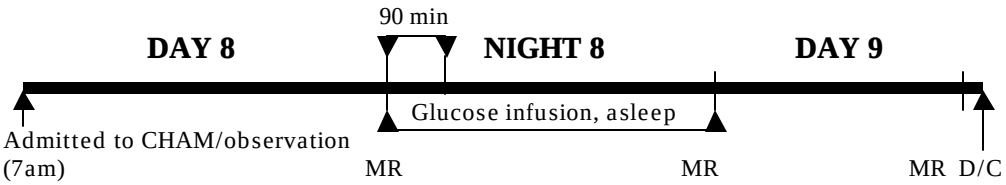
B. GROUPS G1 and G2 (Glucose)

CHAM and MR Visit (Visit #2), Group Glucose infusion, Normal Activities (G1): Day 1: This first day will be the same as for the Acetate groups (A1/A2) (see graph below). Essentially, the child will be studied during the first day in the CHAM and Sleep laboratory to determine the sleep architecture. Day 2: During the 12 hours (6am to 6pm) that follow the sleep study in the CHAM, the subject will carry normal activities but will have a glucose infusion for only 90 min during the day, when the **child is awake** (see graph below). ^{13}C glucose will be infused and blood will be sampled during the infusion every 10-15 min to increase the fractional enrichment and maintain it at a constant level. This coincides with an initial hyperglycemia which is similar to that observed postprandially. The total amount of blood taken will also be about 15 cc. MR studies will be performed during the infusion in the MR Center in order to determine glutamate turnover rate. The reason for the use of glucose here is mostly to determine the TCA cycle in a short period. This will complement the acetate infusion since glucose and acetate isotopes label ***first*** the neuronal glutamate and the glial glutamine pools respectively. Hence we will be able to obtain in the first 20-30 min the initial phase of labeling in the neuronal and glial pools respectively. On this second day, the subject will be discharged home after finishing the glucose infusion. ***CHAM and MR Visit (Visit #3), Group Glucose infusion, Normal Activities (G1):*** Day 8: On Day 8, the subject will be admitted to the CHAM in the morning and will be asked to maintain daily activities (see graph below). In late evening (10-11pm), an infusion of glucose will be started and this will last for 12 hours, **throughout the night, when the child is asleep**. The glucose infusion will be started when the patient is asleep, in the MR facility. The glucose infusion will be done as described under Techniques for 90 min in order to perform the MR turnover rate studies that are similar to those done in the wake state on Day 2. However, in order to obtain information for glycogen synthesis and metabolism, we will keep this glucose infusion going for the rest of the night at euglycemia (5mM). The child will spend only the first 90 min in the MR Center but then will spend the night in the CHAM. MR spectra will be obtained not only at the beginning, but also at the end and 12 hours after the infusion of glucose had stopped. The reason we will examine glycogen 12 hours after the glucose had stopped is to be able to look at the washout of the label and understand what happens during sleep and wakefulness. Also, like on Day 2, blood will be sampled during the infusion, totaling about 15 cc over the entire infusion. After the MR studies, the subject can be discharged from the hospital and children in G1 group would have completed the study. The patient will be discharged from the hospital in the morning after he/she has had the studies completed.

Visit #2, (Days 1-2)

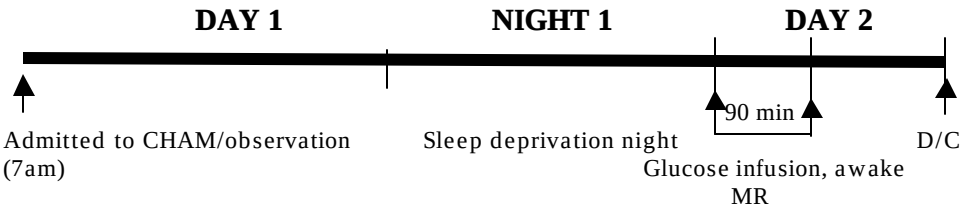


Visit # 3 (Days 8-9)

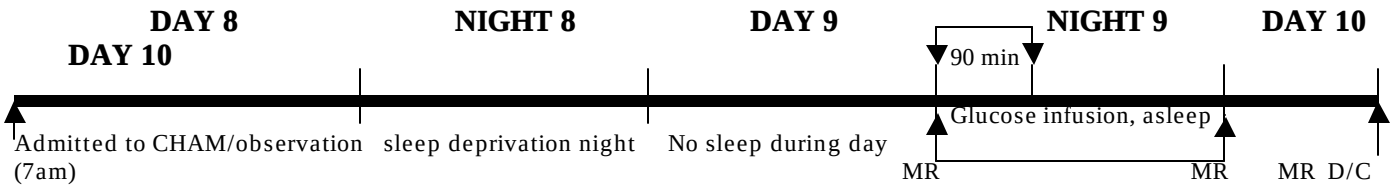


CHAM and MR Visits, Group Glucose infusion, <u>Sleep Deprivation</u> (<u>Visits #2, 3</u>) (G2): This protocol is exactly the same as for the G1 group except on Day 2 when admitted, the child will not sleep that night which follows the morning of admission, as we have done with group A2 (see graph below). During the following day, after one night of sleep deprivation, the child will be studied **awake in the magnet** and the protocol is like that of G1 except that the subject has spent the previous night awake in the CHAM. Therefore, an infusion is given after sleep deprivation and the same MR studies are performed as stated above for the G1 group. The study of Day 8 in this G2 group will be done as follows: The subject will be admitted on Day 8, will stay awake that night on the day of admission in the CHAM, stay awake during the day that follows that night of sleep deprivation and then be studied on the second night when the **child is allowed to go to sleep**, in exactly the same way as we did for the G1 group (see graph below). Hence, the subject will have the infusion during the second night when the subject is allowed to sleep, with the MR studies and protocol (see graph below). Blood sampling is done as on day 8 for the G1 group. The child can be discharged after the MR studies.

Visit #2, (Days 1-2)



Visit # 3 (Days 8-10)



C. Statistical Considerations

The steady state and flux rates will be calculated using ^{13}C isotopic turnover of glutamine, and glutamate from specifically ^{13}C labeled acetate. The number of patients selected for each protocol is determined from the variance of the measurement and the criteria that the above mentioned rates be determined with a 95% confidence interval of better than 10%. We also anticipate that 20% of children may not be able to finish the protocol. This is due to either not being able to continue with a particular study because of disconfort in the magnet or inability to pursue the studies because of time constraints. It should be noted however that the inability to continue these studies is not because these studies are not minimal risk. We estimate therefore that we will need 12 children studied in each of the 4 groups (total of about 48 children). With this in mind, we will have 96 visits and CHAM/MR studies over the course of the application. Analysis of individual data will be done using rather straightforward parametric (t-testing, ANOVA) or non-parametric statistics (e.g., Wilcoxon Rank Sum) with computations of means and SDs.

D. Economic Considerations

In order to defray the costs incurred in each visit, we will compensate the parent and child for their time and expenses. This is estimated to be about $50 for the clinic visit (screen), $100 for the sleep architecture visit (no MR study done during that visit) and $150each for each of the 2 MR visits. Volunteers who finish all 3 phases will be compensated for a total of $450.

III. HUMAN SUBJECTS

A. Subject Population, Recruitment

Subjects will be recruited by Drs. Kass and Haddad. Volunteers will be recruited from the NY area by advertisements in local newspapers and posters in the area (we will show the CCI these before we send them). Inclusion criteria include the age group of 13-17 years adolescent children and include Tanner Stage II-III. All studies will be performed after a clinic screening visit. *Exclusion criteria* include any known metabolic, endocrine, neurologic, cardiac, GI or respiratory disease, a hemoglobin <10 g/dl and hematocrit <30%, implanted magnetic material, trauma, history of HIV infection, hepatitis or drug abuse. Venous blood will be drawn during the infusion of labeled glucose and acetate. The maximum blood drawn as described in the Consent form and will be no more than 40 cc during a 9-day period. MR spectra will be obtained at various intervals as described below.

To participate in the MRS study, patients will have a face to face interview with one of the project investigators where the nature of the project, the risks and the benefits of participation in the projects are discussed with the subject. A focused history will be taken and a checklist of hazards will be reviewed with the subject. If following these discussions, the subject continues to be interested in the project, informed written consent will be obtained on the consent form approved by the Committee on clinical investigation (CCI). Both child and parent will sign. Thereafter, clinical responsibility for the subject care is assumed by the investigators.

All measurements will be made using MR spectroscopy during wakefulness or sleep after patients have been screened and studied in the Sleep center. None of the studies proposed have been done in adults or children. Indeed, only a small part of what is proposed here has been done in animals with the use of invasive techniques. Our long-term goals include the study of children of various ages, from the very young infant to the adult. For simplicity, for practical and safety reasons, we are starting with this protocol which calls for the study of the older child or adolescent, ie, 13-17 years of age (Tanner II-III). Hence these studies have not been done in the adult or child and the metabolic processes that occur in sleep are very poorly defined. Furthermore, we and others have shown in the past that sleep processes are very different in the child and especially the adolescent, when compared to the adult .

B. Source of Research Material

Venous blood will be drawn during the infusion of labeled glucose and acetate. The maximum blood drawn as described above is 40-45cc during a 9-day period. This is the total amount of blood required of a teenager across all studies and the whole period. MR spectra will be obtained at various intervals as described above.

Consent Procedures

Patients will be recruited by Drs. Kass or Haddad at CHAM. Healthy volunteers will be recruited from the NY area by advertisements in local newspapers and posters in the area. To participate in the MRS study, patients will have a face to face interview with one of the project investigators where the nature of the project, the risks and the benefits of participation in the projects are discussed with the subject. A focused history will be taken and a checklist of hazards will be reviewed with the subject. If following these discussions, the subject continues to be interested in the project, informed written consent will be obtained on the consent form approved by AECOM CCI. An assent form will also be read and signed by the child. Thereafter, clinical responsibility for the care of the subject is assumed by the project investigators.

Risks

The risks of this study are minimal. The approximate blood loss will be 40cc maximum over 9 day period. Intravenous catheters used during the glucose or acetate infusion are associated with a mild to moderate degree of pain upon insertion, and a small risk of localized bruise, hematoma and/or infection. Other than the needle stick for the local numbing (anesthesia) of your skin before the infusion is started, this is a painless procedure. On rare occasions a bruise may occur at the infusion site. On very rare occasions inflammation of the vein may occur at the same site. Such complications usually disappear spontaneously or with local heat. Hence the risks in this whole study are minimal.
These risks will be also minimized by the use of the smallest possible catheter and sterile technique. In addition, we will only raise the glucose level minimally (to what usually coincide with a postprandial level), there will be no danger of hypoglycemia at the end of the infusion. Acetate will increase the acidity (lactate) and the Na^+ load in the blood but at the concentration and duration we are giving the acetate, the amount of lactate and salt given will be a small fraction of the amount of Na^+ and acidity present in the lactated Ringers solution given to children with dehydration.

Patient discomfort /passing out in magnet –During each study the subject will be monitored by EEG, EOG and EKG and by the nurse who will be in the magnet room with the patient at all times. If at any point the patient complains of discomfort the study will be halted and the subject removed from the magnet. If the subject passes out during the procedure, the subject will be removed from the magnet on the mobile patient bed and taken out of the room. Once outside the room the patient will be assessed by an MD who will be present throughout the procedure. If necessary resuscitation procedures will be performed and an ambulance called to the MR Center to take the patient to the emergency room of CHAM.

In the very unlikely event of a patient being injured in the magnet, the patient will immediately be removed and brought to the hallway in the mobile patient bed. The MD present will evaluate the severity of the injury. Depending on the severity the patient will either be wheeled to the emergency room on the patient bed or an ambulance will be called to the MRC. If necessary first aid will be applied to stop any bleeding. If the patient is pinned to the magnet by a metal object the spectroscopist running the scan will enter the room and assess whether the object can be safely removed. If it can, the object will be removed from the patient and the procedures outlined above followed. If the object cannot be removed the magnet will be de-energized in order to eliminate the magnetic field. The de-energization procedure will take on the order of 1 minute.

Magnetic resonance spectroscopy will be performed at AECOM Magnetic Resonance Center on a 4 Tesla magnet with a 72 cm clear bore and Bruker Avance electronics. Ionizing radiation is not used, and there are no known side effects of the procedure. Some subjects who undergo MRS feel anxious from being in an enclosed space. If this occurs, the procedure will be stopped. The most significant hazard concerns magnetic objects. If brought in the magnet room they may be drawn forcefully in to the magnet and many cause injury. Metallic conductor and electronic circuits can become thermally heated when exposed to fluctuating magnetic fields. ^{13}C MRS spectroscopy will be performed within the FDA guidelines for regional specific absorption rate of rf power (4.0 W/kg locally) and gradient switching rate (400mT/m-sec). Adherence to these guidelines are insured by the safety circuitry of the spectrometer which will shut down the system if either the power deposition or gradient switching rate exceeds safe levels. In addition the gradient coil/amplifier is physically incapable of exceeding FDA guidelines.

Protection of Subjects

Subjects will be closely followed by an experienced clinical research team (they all be identified and will have human subjects training). All of the information obtained from subjects participating in this study will be coded by numbers and kept in locked files in the research unit which ensures confidentiality. One member of the two to three person team will watch the subjects while in the magnet room. Patients who experience distress in the magnetic room for any reason including claustrophobia will be removed from the magnet room in accordance with well-established procedures developed for the Magnetic Resonance Center. All members will be thoroughly familiar with the established emergency plan. A non-magnetic stretcher will be on standby next to the entrance to the magnet. Non magnetic oral airways, an Ambubag and a stethoscope are stored with the emergency stretcher in the magnet room. Should an emergency arise, one member of the spectroscopy team will telephone the emergency operator to notify the CHAM ambulance team of the emergency in the Magnetic Resonance Center. The other members will remove the patient via stretcher from the magnet room taking the patient to the part of the Magnetic Resonance Center designated for cardiopulmonary resuscitation.

Data and Safety Monitoring Plan

Patients undergoing these studies will be monitored very carefully. First, during the studies, patients will be monitored in the Magnet using electrophysiologic measures (EEG and EOG) and EKG. All data will be acquired using computerized techniques and will be saved on disc files. No personnel other than those listed will be involved with the data at any time and data will be stored in databases that are password-protected, only known to this group of investigators. It is also important to realize that the studies proposed with glucose or acetate infusions have been done in the MR Center and no new drugs or agents are used in this study. All isotopes used are stable and have been used numerously as part of studies done in the MR Center previously. One member of the two to three person team will watch the subjects while in the magnet room. Patients who experience distress in the magnetic room for any reason including claustrophobia will be removed from the magnet room in accordance with well-established procedures developed for the Magnetic Resonance Center. All members will be thoroughly familiar with the established emergency plan (see above). The assessment of risk is as follows:

1. **Attribution of** adverse effects**: Unrelated to the investigational agents. It is possible however that a hematoma or a bruise occurs as a result of an IV.**
2. **Plan for** grading **adverse events: No adverse effects or mild adverse effects anticipated.**
3. **Plans for** reporting **unanticipated and anticipated** adverse **events: Serious unanticipated adverse effects will be reported immediately to the CCI and any appropriate funding and regulatory agencies.**
4. **Plans for** reviewing and reporting non-serious **anticipated or non-anticipated adverse events: The PI will conduct a review of all adverse effects at least quarterly. The PI will evaluate the frequency and severity of these effects and determine if modifications to the protocol or consent form are required. A chart accompanying the quarterly summary will be sent to the CCI.**
5. Safety review**: The PI is responsible for monitoring the data and conducting performance of safety reviews every 3 months. Either the PI or the CCI has the authority to stop or modify the study. The CCI will review all safety data at least once a year.**
6. **Although the type of studies proposed using the CHAM or the MR center are performed every day at AECOM,** teaching **of key personnel about equipment used in the CHAM, in the MR center will be continued and emphasized. Also, teaching everyone involved with the children in this study about subject confidentiality will be very important.**

Confidentiality

All data will be acquired using computerized techniques and will be saved on disc files as coded data. No personnel other than those listed will be involved with the data at any time and data will be stored in databases that are password-protected, only known to this group of investigators.

Potential Benefits

The patients will not directly benefit from participation in this study. However, the benefits to society may be considerable. Better understanding of human brain mechanisms involved in sleep and wakefulness and the role of the glutamate/glutamine neurotransmitter

cycle should further our efforts designed to develop treatments for several disorders involved in sleep such as narcolepsy, obstructive sleep apnea, and sleep deprivation.

The Risk-Benefit Ratio

The risks are very small as outlined above (see above). There are no direct benefits to individual subjects. The potential implications to a number of clinical problems involving sleep are significant (see above).

Project Title: Sleep mechanisms in children: role of metabolism

Invitation to Participate:

You are invited to participate in a study that will examine the levels of certain chemical substances in the brain during wakefulness and during sleep and how the brain functions during sleep. We are studying the conversion of acetate and glucose (blood sugar) in the brain to the chemicals glutamate and glutamine. You have been asked to participate in this study because you are a normal healthy person with no disease and would therefore be representative of a healthy person's response.

This study is not designed to provide you with any direct benefit. Rather, we hope that the results of this research will provide a better understanding of the way the brain metabolizes chemical substances under normal wakeful and sleep conditions.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study which a member of the research team will discuss with you. This discussion should go over *all* aspects of this research: its purpose, the procedures that will be performed, risks of the procedures and possible benefits. Once you understand the study, you will be asked whether you wish to sign this form or not.

Description of Project:

The study will involve 3 visits to the Children's Hospital (CHAM) under the observation of Drs. Lewis Kass or Gabriel Haddad. Visit # 1 is a screening Specialty Clinic visit during which a physical exam, a history with blood tests will be performed. Blood tests will be taken in the Clinic to test for potential factors that would exclude you from the study, specifically elevated blood glucose, elevated liver function tests, low hematocrit, and markers of impaired renal function. Visits #2 and 3 will be visits to the CHAM and magnetic resonance (MR) visits. Visits and procedures are described below as follows:

Screening Clinic Visit (Visit #1):

Before you can be part of the study, you will come to the Specialty Pediatric Clinic (2nd floor of the Children's Hospital) for a screening visit of approximately 1 hour. During this visit, the procedures of the study will be explained to you by a doctor who also will perform a physical examination and ask about your medical history. During this visit a set of blood and urine tests will be done. The amount of blood taken will be 1/2 ounce. One week later, after the results of the first screening visit have been evaluated by the study investigators, Dr. Kass, or Haddad will call you on the phone, to set up a date for the next visits as described below. There are 4 groups of adolescent children participating and you will be randomly assigned to one of these groups, as described below.

Groups of children participating:

There are 4 groups of children in this study. Two groups will be studied with an infusion into a vein containing ^{13}C-acetate and the other two groups with an infusion containing ^{13}C-glucose. Both acetate and glucose are chemicals that are present in the body and therefore these are not drugs that are being given to you. Carbon 13 (^{13}C) is a stable (non-radioactive) carbon that is present as part of the glucose or acetate, and we use them regularly to study metabolism. These infusions will allow us to study the chemicals in your brain. The studies will be done in a magnet in the Nuclear Magnetic Resonance (MR) Center. One group receiving the acetate infusion will be studied once during wakefulness and a second time during sleep after normal daily activities and another group will be studied during wakefulness and during sleep, after sleep deprivation of one whole night. That is, if you are chosen to be in the sleep deprivation group, you will be studied during the following day or night, after you have not slept one whole night prior to the day study or one whole night plus the following day prior to the night study. Similarly, each of the two groups receiving the glucose infusion will be studied in the same way as for the groups receiving acetate, that is one group will be studied after normal activities during the previous day and the other after one night without sleep. These groups are separated and their protocols detailed below.

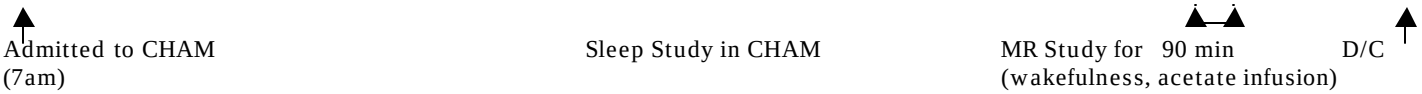
ACETATE INFUSION, NORMAL ACTIVITIES

Day 1. You will be admitted to the CHAM in the morning (7-8am). During this part of the study you will have normal activities during the day until evening when you will have a sleep study in the CHAM in our Sleep laboratory. The study will start when you fall asleep normally but we will place the electrodes and the bands on you in early evening. This will involve placing surface electrodes like those used for the electrocardiogram on the head, forehead and chest. In addition, we will monitor your breathing using cloth bands on your belly and chest as well as your oxygen saturation in your body by placing a band around your finger. If this study shows us that your sleep is normal, you do not have any medical problem such as snoring, and that your sleep states are normal in duration, then you will be able to continue with the study, as described below. Otherwise you will not be eligible for any subsequent part of the study and no additional visits will be required.

Day 2. If you are then eligible for the rest of the study, you will stay in the CHAM during this visit for another 12 hours, until late afternoon. During these 12 hours, from 6am to 6pm, you will have normal activities, until mid-day (at about 12-1 pm) when you will be transported to the MR Center and studied there. During this study, you will have a catheter placed into a vein. Through the catheter, there will be an intravenous infusion of acetate for about 90 min during which we will monitor the concentrations of a number of chemicals such as glutamate and glutamine and how fast they increase or decrease in the brain. During the acetate infusion, a blood sample will be taken every 15-20 min from your vein (same vein used for the infusion) and obtain a total amount of blood of about 1/2 ounce. This will be performed while you lie within a whole-body magnetic resonance (MR) scanner that consists of a large doughnut shaped magnet. You will be asked to place your head between two plastic plates that will hold your head still during the scanning because movements will disturb the measurements. Your head will be resting on a plastic plate under which a coil (antenna) is placed. As part of the study, an image (picture) of your brain will be taken to make sure that the coil is placed at the right position. You will be given earplugs to reduce the effects of the loud noise produced by the MR scanner. Neither you nor the MR scanner will move during the study. There will be someone with you in the room all the time. You can listen to music but you have to be **awake during the 90 min when you are being studied**. There are no known side effects with this procedure. If at any time you become frightened or overly nervous and can't continue to lie still, we will take you out of the MR scanner for a break. If you do well in the magnet, you will be finished after these 90 minutes and will be discharged home.

Day 8: If you do well on Day 2 in the magnet, then you will need to come back on Day 8 to finish completely your study. On Day 8, you will be admitted to the CHAM in the morning (6-7am) and maintain your daily activities as usual. In early evening (7-8pm), you will be taken to the MR Center to have the same types of electrodes placed on you that you had on Day 1. We place these on you to be able to monitor your sleep stage when you fall asleep. Also, we will start an intravenous infusion of acetate at a later time during that night, much like we did on Day 2 when you were previously in the magnet. Also, like on Day 2, we will sample blood from you during the infusion just as on Day 2, a total of about ½ ounce over the 90 minute study. We will start the infusion and sample blood only after you have been comfortable in the magnet and **fallen asleep since this study that we do on Day 8 is during sleep**. We will start the infusion only when we see from the recording that we are performing on you, that you are in Quiet or Non-REM sleep. Also, as on Day 2, you will be in the magnet during the infusion and we will repeat exactly what we did on Day 2 except that you will be asleep (Quiet sleep). After we finish the 90 min study in the magnet, you can be discharged to the CHAM and discharged from the hospital in the morning. You would have completed all the study.

Visit #2, (Days 1-2)



Visit # 3 (Day 8)

ACETATE INFUSION, SLEEP DEPRIVATION

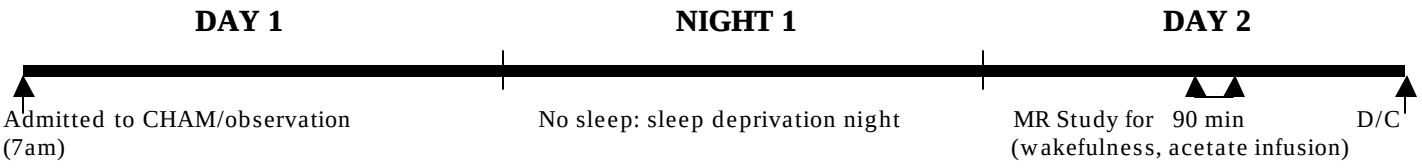
Day 1. You will be admitted to the CHAM in the morning (7-8am). During this part of the study you will have normal activities during the day until evening when you will have a sleep study in the CHAM in our Sleep laboratory. The study will start when you fall asleep normally but we will place the electrodes and the bands on you in early evening. This will involve placing surface electrodes like those used for the electrocardiogram on the head, forehead and chest. In addition, we will monitor your breathing using cloth bands on your belly and chest as well as your oxygen saturation in your body by placing a band around your finger. If this study shows us that your sleep is normal, you do not have any medical problem such as snoring, and that your sleep states are normal in duration, then you will be able to continue with the study, as described below. Otherwise you will not be eligible for any subsequent part of the study and no additional visits will be required.

Day 2. If you are then eligible for the rest of the study, you will stay in the CHAM during this visit for another 36 hours, until late afternoon the following day. You will not sleep during the night that followed the night of your sleep study. You can listen to music, watch TV, read, but you cannot go to sleep and you will need to stay awake during that night. During the following day, from 6am to 6pm, you will have normal activities, until mid-day (at about 12-1 pm) when you will be transported to the MR Center and studied there. During this study, you will have a catheter placed into a vein. Through the catheter there will be an intravenous infusion

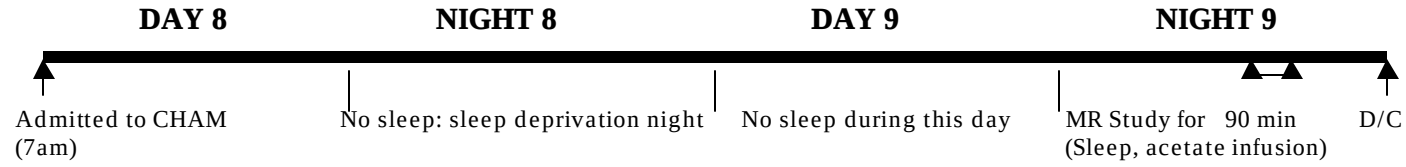
of acetate for about 90 min during which we will monitor the concentrations of a number of chemicals such as glutamate and glutamine and how fast they increase or decrease in the brain. During the acetate infusion, a blood sample will be taken every 15-20 min from your vein (same vein used for the infusion) and obtain a total amount of blood of about 1/2 ounce. This will be performed while you lie within a whole-body magnetic resonance (MR) scanner that consists of a large doughnut shaped magnet. You will be asked to place your head between two plastic plates that will hold your head still during the scanning because movements will disturb the measurements. Your head will be resting on a plastic plate under which a coil (antenna) is placed. As part of the study, an image (picture) of your brain will be taken to make sure that the coil is placed at the right position. You will be given earplugs to reduce the effects of the loud noise produced by the MR scanner. Neither you nor the MR scanner will move during the study. There will be someone with you in the room all the time. You can listen to music but you have to be **awake during the 90 min when you are being studied**. There are no known side effects with this procedure. If at any time you become frightened or overly nervous and can't continue to lie still, we will take you out of the MR scanner for a break. If you do well in the magnet, you will be finished after these 90 minutes and will be discharged home.

Day 8: If you do well on Day 2 in the magnet, then you will need to come back on Day 8 to finish completely your study. On Day 8, you will be admitted to the CHAM in the morning (6-7am) and maintain your daily activities as usual but you will need to stay awake that night that follows the day of admission. Therefore, you will be admitted in the morning, stay up that night in the CHAM, stay awake during the day that follows and then be studied on the second night when you will be allowed to go to sleep and then studied. Therefore, what will happen is that in early evening (7-8pm), you will be taken to the MR Center to have the same types of electrodes placed on you that you had on Day 1. We place these on you to be able to monitor your sleep stage when you fall asleep. Also, we will start an intravenous infusion of acetate at a later time during that night, much like we did on Day 2 when you were previously in the magnet. Also, like on Day 2, we will sample blood from you during the infusion just as on Day 2, a total of about ½ ounce over the 90 minute study. We will start the infusion and sample blood only after you have been comfortable in the magnet and **fallen asleep since this study that we do on Day 8 is during sleep**. We will start the infusion only when we see from the recording that we are performing on you, that you are in Quiet or Non-REM sleep. Also, as on Day 2, you will be in the magnet during the infusion and we will repeat exactly what we did on Day 2 except that you will be asleep (Quiet sleep). After we finish the 90 min study in the magnet, you can be discharged to the CHAM and discharged from the hospital in the morning. You would have completed all the study.

Visit #2, (Days 1-2)



Visit # 3 (Days 8-9)



GLUCOSE INFUSION, NORMAL ACTIVITIES

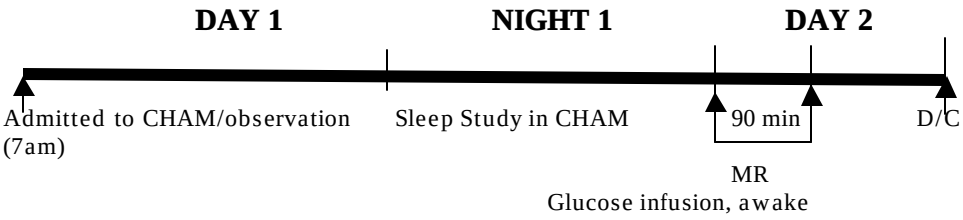
Day 1. You will be admitted to the CHAM in the morning (7-8am). During this part of the study you will have normal activities during the day until evening when you will have a sleep study in the CHAM in our Sleep laboratory. The study will start when you fall asleep normally but we will place the electrodes and the bands on you in early evening. This will involve placing surface electrodes like those used for the electrocardiogram on the head, forehead and chest. In addition, we will monitor your breathing using cloth bands on your belly and chest as well as your oxygen saturation in your body by placing a band around your finger. If this study shows us that your sleep is normal, you do not have any medical problem such as snoring, and that your sleep states are normal in duration, then you will be able to continue with the study, as described below. Otherwise you will not be eligible for any subsequent part of the study and no additional visits will be required.

Day 2: During the 12 hours (6am to 6pm) that follow your sleep study in the CHAM, you will be carrying normal activities but you will have a catheter placed in a vein. Through the catheter there will be a ^{13}C glucose infusion for 90min during the day, when the child is awake. For this infusion, glucose will be infused through this catheter. During the infusion, blood will be sampled every 10-15min. The total amount of blood will also be about 1/2 ounce. The MR studies that you will have will be performed while you lie within a whole-body magnetic resonance (MR) scanner that consists of a large doughnut shaped magnet. You will be asked to place your head between two plastic plates that will hold your head still during the scanning because movements will disturb the measurements. Your head will be resting on a plastic plate under which a coil (antenna) is placed. As part of the study, an image (picture) of your brain will be taken to make sure that the coil is placed at the right position. You will be given earplugs to reduce the effects of the loud noise produced

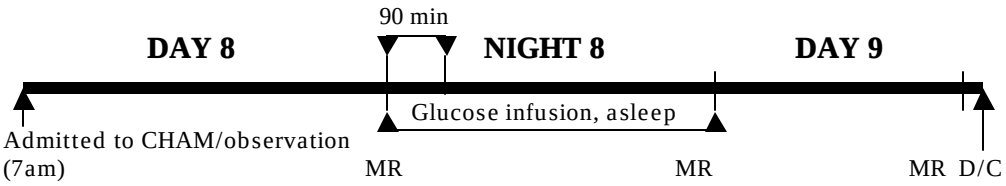
by the MR scanner. Neither you nor the MR scanner will move during the study. There will be someone with you in the room all the time. You can listen to music **but you have to be awake during the study**. There are no known side effects with this procedure. If at any time you become frightened or overly nervous and can't continue to lie still, we will take you out of the MR scanner for a break. You will be discharged home after finishing the glucose infusion.

Day 8: If you do well on Day 2 in the magnet, then you will need to come back on Day 8 to finish completely your study. On Day 8, you will be admitted to the CHAM in the morning and maintain your daily activity as usual. During this visit there will be three 90 min MR studies. In early evening, you will have an infusion of glucose which will last for 12 hours throughout the night. The glucose infusion will be done like on day 2 but it will be continued throughout the night. You will spend however only 90min in the MR Center for initial studies and then have the rest of the night in the CHAM. MR studies will be performed at the beginning, at the end and 12 hours after the infusion of glucose. Also, like on Day 2, we will sample blood from you during the infusion, a total of about ½ ounce over the entire infusion. After we perform the MR studies, you can be discharged from the hospital and you would have completed all the study.

Visit #2, (Days 1-2)



Visit # 3 (Days 8-9)



GLUCOSE INFUSION, SLEEP DEPRIVATION

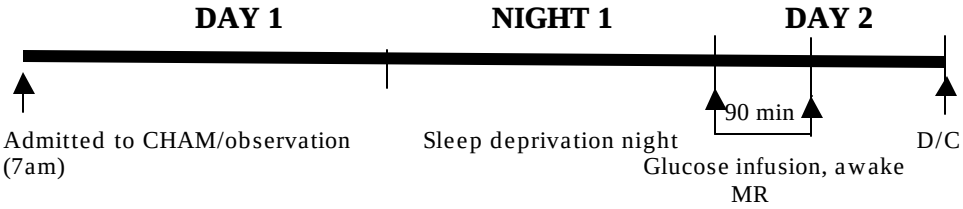
Day 1. You will be admitted to the CHAM in the morning (7-8am). During this part of the study you will have normal activities during the day until evening when you will have a sleep study in the CHAM in our Sleep laboratory. The study will start when you fall asleep normally but we will place the electrodes and the bands on you in early evening. This will involve placing surface electrodes like those used for the electrocardiogram on the head, forehead and chest. In addition, we will monitor your breathing using cloth bands on your belly and chest as well as your O_2 saturation in your body by placing a band around your finger. If this study shows us that your sleep is normal, you do not have any medical problem such as snoring, and that your sleep states are normal in duration, then you will be able to continue with the study, as described below. Otherwise you will not be eligible for any subsequent part of the study and no additional visits will be required.

Day 2: During the 12 hours (6am to 6pm) that follow your sleep study in the CHAM, you will be carrying out normal activities but you will not sleep the night that follows the night of your sleep study. You can listen to music, watch TV, read, but you cannot go to sleep and you will need to stay awake during that night. During the following day, you will be studied in the magnet and an infusion is given. A catheter will be placed in one of your veins. The infusion will be given after this catheter is placed in one of your veins. Three short MR studies are performed. You will have a ^{13}C glucose infusion during that day for 90min. Blood will be sampled every about 10-15 min. The total amount of blood will be about 1/2 ounce. The MR study will be performed while you will lie within a whole-body magnetic resonance (MR) scanner that consists of a large doughnut shaped magnet. You will be asked to place your head between two plastic plates that will hold your head still during the scanning because movements will disturb the measurements. Your head will be resting on a plastic plate under which a coil (antenna) is placed. As part of the study, an image (picture) of your brain will be taken to make sure that the coil is placed at the right position. You will be given earplugs to reduce the

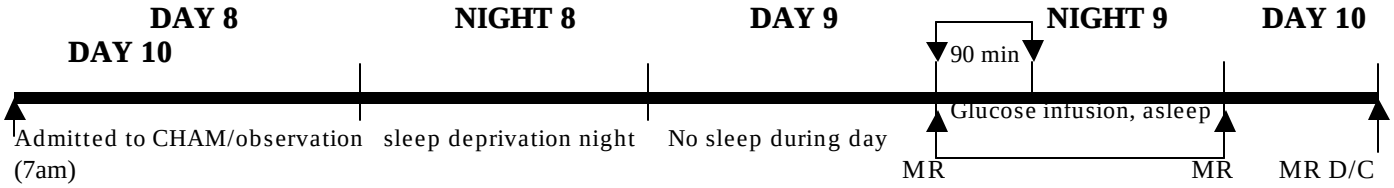
effects of the loud noise produced by the MR scanner. Neither you nor the MR scanner will move during the study. There will be someone with you in the room all the time. You can listen to music **but you have to be awake during the short study**. There are no known side effects with this procedure. If at any time you become frightened or overly nervous and can't continue to lie still, we will take you out of the MR scanner for a break. You will be discharged home after you finish with the infusion.

Day 8: You will be admitted in the morning, stay up that night in the CHAM, stay awake during the day that follows that night and then be studied on the second night when you will be allowed to go to sleep. You will have the infusion during the second night when you are allowed to sleep, with MR studies at the beginning, end of the 12 hour infusion and 12 hours after the end of the infusion. Blood sampling is done as on day 2. You can be discharged after the 3 MR studies.

Visit #2, (Days 1-2)



Visit # 3 (Days 8-10)



Risks and Inconveniences:

1) Catheter Placement:
Other than the needle stick for the local numbing (anesthesia) of your skin before the infusion is started, this has almost no pain. On rare occasions a bruise may occur at the infusion site. On very rare occasions inflammation of the vein may occur at the same site. Such complications usually disappear spontaneously or with local heat.

2) Blood Loss:
The amount of hemoglobin in your blood will be tested prior to the study and if it is low you will be excluded from the study. The total blood loss for the study will not exceed 1.5 ounces, a volume which is safe to take and which is only a small fraction of the amount of blood taken during a normal blood donation.

3) Carbon ^{13}glucose and carbon ^{13}acetate:
Glucose and acetate are naturally occurring substances in your body. Carbon 13 is an isotope of carbon, it is not radioactive and has no known harmful effects. It exists in nature and it is the form of carbon that can be measured with MR spectroscopy.

4) MR:

The MR scanner uses a large magnet and magnetism and radio waves to obtain chemical (MR) information from your body. If you have a pacemaker or some type of metallic implant, you will be excluded from this study due to possible effects of magnetic fields on the pacemaker or implant. Be sure and tell us if you know or think you have a pacemaker or metallic implant (such as an aneurysm clip, heart valve, etc.). When you fill out the attached safety questionnaire make sure that there is no hazard to you from one of the devices mentioned on the form. There are no known side effects associated with these procedures. A few people become anxious from being in an enclosed space (claustrophobic) while lying in the MR scanner. If you think or know that you feel that way, let us know. If you feel anxious or uncomfortable during the study and wish to stop at any time, tell us immediately and we will take you out of the magnet.

Benefit:

This study offers no direct benefits to you. However, it is hoped that the results of this study will give more insight into how the brain uses glucose (sugar) and acetate in healthy individuals during wakefulness, during sleep and after people are deprived of sleep.

Economic Consideration:

In order to help defray the costs you have incurred in each visit, we will compensate you as follows: $50 for the clinic visit (screen), $100 for the sleep visit and $150 for each of the 2 MR studies. If you finish all 3 phases, you will be compensated a total of $450. If you finish 1-2 phases, you will be compensated for those.

Confidentiality:

In all records of this study a number will identify you and your name is going to be known only to the researcher and your clinic team. Your name will not be used in any scientific reports of the study.

In Case of Injury:

If you are physically injured as a result of your participation in this research, acute medical care will be provided at no cost to you. No other financial compensation is available.

Voluntary Participation:

You are free to choose not to participate and if you do become a subject you are free to withdraw from this study at any time during its course. If you choose not to participate or if you withdraw, it will not adversely affect your relationship with the doctors or this hospital.

Questions:

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider the consent form carefully - as long as you feel is necessary - before you make a decision.