May 23, 2003

Bernard Schwetz, D.V.M., Ph.D
Acting Director
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Dear Dr. Schwetz:

I am submitting the following report for the HHS Review of Research under 45 CFR 46.407 regarding the research proposal, Sleep Mechanisms in Children: Role of Metabolism, Gabriel Haddad, M.D., Principal Investigator pursuant to the panel meeting on May 6, 2003.

Dr. Gabriel Haddad and colleagues propose to measure cerebral glycogen, glutamate turnover rate and glutamate-glutamine cycling during wakefulness and sleep in children ages 13-17 years. The investigators hypothesize that the underlying metabolic regulation of sleep depends upon a functional coupling between glia and neurons and down regulation of synaptic activity during sleep, which allows for restoration of glial energy stores. Specifically, the investigators hypothesize that: 1) compared to wakefulness, stage III/IV sleep has a lower metabolic requirement and a lower glutamate turnover rate in neurons and glia; 2) in children, sleep deprivation prevents the lower rate of brain neuronal glutamate release and glial glutamate uptake; 3) brain glycogen content increases during sleep; and 4) sleep deprivation lowers the accumulation of glycogen during sleep.

The proposed research studies represent an important opportunity to address the paucity of information regarding the underlying metabolic mechanisms of sleep, particularly in children. The investigators indicate that a better understanding of the changes in cerebral glycogen storage and glutamate/glutamine cycling during sleep is needed for all ages, from infancy though adulthood. The investigators have chosen to begin the evaluation in adolescents for "practical and conceptual reasons." The proposed studies are novel and may lead to new information regarding the underlying mechanism of sleep. It is important to note, however, that no data are available regarding glycogen storage or glutamate/glutamine cycling in children or adults during sleep. Even though alterations in glucose metabolism have been demonstrated in adults with PET studies, it is entirely possible that differences in glycogen storage or glutamate/glutamine cycling during sleep will not be detectable with the magnetic resonance spectroscopy techniques proposed in this study. Furthermore, methodological considerations may make it difficult to detect differences in the adolescents, even if they exist. For instance, children, particularly the younger ones, may not be able to fully cooperate with the studies. The investigators have proposed evaluation of 5 adults "to perform some studies and then to focus on adolescents."

For the purpose of this review, it is important to decide whether the individuals that will participate in the study have a condition for which the research will lead to important benefit, or

do they represent a normal control group of children against whom other groups of children with specific conditions may be compared. The answer determines whether the proposal is considered under HHS regulations 45 CRF section 46.406 vs. section 46.407. The investigators propose inviting adolescents who are free of recognized medical conditions and sleep disturbances to participate in the research. Adolescence itself could be recognized as a specific condition that influences the health and development of the child. Under this assumption, adolescence is not simply an arbitrarily defined developmental stage, but rather it encompasses a distinct set of changes, physical, psychological and social, which have important influences on the individual's health and development. Sleep deprivation represents an important problem or condition for adolescents with implications for many aspects of their health and well-being. Aside from the wide range of medical conditions that influence sleep, a number of other factors and pressures contribute to sleep deprivation among adolescents. Even though the individuals being invited to participate in the program are free of sleep disturbance at the time of the study, this does not eliminate the possibility that they could have disturbance in sleep at a later time. As such, it is plausible to view the subjects being recruited for this study as having a general condition for which this research is likely to yield generalizable knowledge for that condition, although of no direct benefit to the subject. That is, the research could be considered under section 46.406. Conversely, these research participants could be viewed as typically developing children without any identified condition, but in whom baseline data on cerebral metabolism and during sleep is desired. In the latter situation, the proposal would need to be considered under section 46.407. While it may be desirable to consider adolescence as a condition for the purposes of this proposal, the investigators do not clearly propose any hypotheses regarding the effect of adolescence, per se, on brain metabolism. Therefore, this proposal is best considered under section 46.407.

The research proposal is moderately complex and it involves multiple visits, two of which involve an extended stay in the sleep center, as well as multiple procedures. The risks of the procedures used in this study need to be considered individually, but also in the aggregate. The cumulative effects of the various procedures, particularly in the context of the stress of sleep deprivation, may pose a greater risk that the sum of any of the procedures performed individually.

Risks of the procedures:

1. **Magnetic Resonance Spectroscopy (MRS) in a 4 Tesla magnet.** With appropriate precautions outlined in the proposal, performance of the MRS presents minimal risk to the subjects.

2. **Polysomnographic monitoring**. The routine polysomnographic studies pose minimal risk to the research subjects. Recording of the studies within the magnet, however, presents potential risks due to the theoretical possibility that coiled electrode leads might produce conducting currents within the magnet. The specific procedures regarding how polysomnographic monitoring would be performed in the magnet were not included with the material available for this review. Under the Human Subjects section of the proposal, however, the investigators twice mention that metallic conductors and electronic circuits can become thermally heated when exposed to fluctuating magnetic fields. The specific reason this risk was

noted and whether it was intended to apply to the electrophysiological monitoring is not clear from the proposal. Furthermore, this risk is not mentioned in the consent forms. Dr. Haddad addressed this risk in a separate letter indicating that the studies will be performed with carbon fiber leads and a MAG-Link system obtained from Neuroscan. With these appropriate precautions, the electrophysiological recording within the scanner likely poses minimal risk.

3. **Sleep deprivation**. Sleep deprivation is a condition likely to be experienced by children during adolescence and may present minimal risk to children under most circumstances. Problems will arise if the sleep deprivation interferes with school, work or driving. The investigators indicate that the sleep deprivation studies will not be performed prior to a school day, but similar protection is needed with regard to employment. Any number of work related activities could present a greater risk of injury after sleep deprivation. While it may be true that many adolescents may attempt to engage in work after staying up all night on their own, the investigators bear an added responsibility to warn the research participants not to work after a night of sleep deprivation associated with this protocol. Even for work that does not seem to pose risks of injury, the participants could be subject to disciplinary action at work if they were not able to perform well because of the sleep deprivation.

4. **Blood drawing**. Two different procedures are proposed. At the time of the original screening, a blood sample will be obtained. This procedure presents minimal risk. With visits 2 and 3, however, an indwelling catheter will be placed so that blood samples may be drawn every 15-20 minutes. The indwelling catheter and repeated blood drawing may be considered minimal risk, although the duration of the insertion raises the question of whether this procedure is a minor increase over minimal risk. Furthermore, the consequences of a catheter becoming non-functional are not addressed within the proposal. In this situation, the catheter would need to be replaced, or the study would be ended. The need for restarting additional indwelling catheters may make the procedure a minor increase over minimal risk.

5. **Indwelling catheters with continuous infusion of acetate and glucose**. This procedure represents at least a minor increase over minimal risk for several reasons. First, two intravenous lines will be placed for each subject. While the placement of one indwelling line could be broadly construed as minimal risk, the placement of two lines is beyond the experience of the overwhelming majority of healthy individual presenting for a routine physician's evaluation. Second, the lines may be kept in place for up to 12 hours. Again, the probability that a complication will occur in any given individual is low, but the risk of inflammation or thrombosis may be enhanced by the continuous infusion of glucose. Finally, even though the infusion of glucose or acetate appears to be a safe procedure as described in the protocol, both are outside the range of daily experience. The investigators indicate that the elevation of glucose with the infusions would be similar to postprandial levels; however, the risk of hyperglycemia with intravenous glucose infusion, say due to errors of infusion rate, is greater than after a meal. As such, the infusions, whether glucose or acetate, represent a minor increase over minimal risk.

6. **Payment of research participants**. Overall, the compensation arrangement is appropriate for the participants, both children and parents; however, the higher amount paid to parents or guardians, poses a potential risk for coercion to participate in the study. The payment provided for the parents or guardians may seem appropriate compensation for their time and

effort; however, the children may feel undue pressure to participate in the study or continue against their wishes so that their parents or guardians receive compensation. The younger children in this study are more likely to be influenced by the pressures to complete the study than the older adolescents. While an alternative distribution of payment could be considered, it is not entirely clear that this would remove the potential for coercion and the best solution is likely with careful attention to the potential for coercion.

Adequate measures are also necessary to mitigate the psychological effect on the child of not being able to participate in the study. Aside from the disappointment of not being compensated, the children, particularly the younger ones, may feel a sense of failure about not being invited to participate after the screening procedure. When children screened for study do not qualify for continuation in the protocol, the investigators should be clear that the children may not be able to participate because of the narrowly defined entry requirements of the protocol rather than because of some failure on the child's part. In this regard, the line in the consent form, "If you do not pass the screening test, you will not be able to participate in the study" poses a risk of conveying a sense of fault to the participant. Furthermore, the children need protection from pressure to participate for confidential reasons that they do not want to share with their parents or guardian.

In summary, the research proposal to evaluate brain metabolism during sleep presents an important opportunity to develop a greater understanding of the underlying mechanism of sleep. This information is clearly lacking in children and requires further study. The studies, as proposed, have a reasonable chance of providing new information regarding the underlying mechanism of cerebral metabolism during sleep. While this information may be of particular interest in children, the adolescent group suggested for study in this proposal does not seem to represent a special group or condition that can be singled out as for study compared to another age. The risks of the procedures proposed in the study present varying amounts of risk. Most are minimal risk but a few procedures present at least a minor increase over minimal risk. The investigator's proposal and the Clinical Investigations Committee review per the minutes of November 13, 2002 indicate that the research will be conducted in accordance with sound ethical principles. The investigators have described in detail the protection of subjects. I agree with the Committee on Clinical Investigations report that review should occur 6 months after the start of the protocol. In general, adequate provisions have been made for soliciting the consent of the parents or guardians and assent of the children. I agree with the recommendations of the Committee on Clinical Investigations regarding informed consent. The investigators made the suggested recommendations.

Therefore, I agree with the findings of the Clinical Investigations Committee of the Albert Einstein College of Medicine that the proposed research is best considered to represent a reasonable opportunity to understand a serious problem affecting the health or welfare of children under Section 46.407. Furthermore, I agree with most of the recommendations of the Clinical Investigations Committee as outlined in the Minutes of November 13, 2002. I would recommend that the research proposal be approved under section 46.407 with the following recommendations:

1. The five adult volunteers should be fully studied before enrollment of the adolescents. These studies should include 2-3 individuals who undergo sleep deprivation. Complete analysis and review of the data should be performed before beginning the studies with adolescents.

2. The investigators should make adequate provisions that the children are not coerced to participate so that the parents or guardians can be compensated. This could include provisions for a confidential interview with the child to assess for any reluctance to participate.

3. The investigators should make adequate provision for confidentiality for the child with regards to other reasons for not participating, particularly related to a history of drug use, chance of pregnancy, or other causes.

4. The investigators should clarify and define how many attempts will be made for IV line insertion. What will happen if a IV catheter becomes dislodged or is non-functional? Will the child be compensated for that visit even if the study cannot be completed for technical reasons.

5. The investigators should consider changing the line in the consent that reads, "If you do not pass the screening test . . ." to a more neutral statement.

6. The investigators should discuss the procedure for electrophysiological monitoring in the magnet and incorporate this procedure in the consent.

7. The investigators should advise the children about the risks of working after a night of sleep deprivation, similar to the already included warning about use of machinery and driving.

Sincerely,

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