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UNIVERSITY OF CALIFORNIA, BERKELEY

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SANTA BARBARA • SANTA CRUZ

DONNER LABORATORY

BERKELEY, CALIFORNIA 94720

20 June 1980

Refer to 80RM269

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Buckley*

Dr. Adolf Pfefferbaum
Veterans Administration Medical Center
3801 Miranda Avenue
Palo Alto, CA 94304

Dear Dr. Pfefferbaum:

The project you propose for evaluating the distribution of metabolism in schizophrenic vs. normals fits in well with our neurobiology and neurochemistry program at Donner Laboratory. As you mention in your proposal, Dr. Sargent and I have been interested in experimental approaches using our 280-crystal dynamic positron tomograph. We are examining hypotheses regarding abnormal methylation, abnormal tyrosine metabolism, and altered dopamine pools in affective disorders. The study of glucose metabolism will complement these studies well and I envision a strong collaboration between your center and our group.

As I have discussed before, you and Drs. Berger and Roth provide the important ingredient of controlled diagnosis or "calibrated" patients as well as the neuropsychiatric expertise. Our strengths involve the methodology for brain blood flow and metabolism, particularly of bioamines and amino acids. Until recently we have emphasized methionine metabolism studies in the brain, rubidium-82 studies of brain blood volume, flow and permeability, and myocardial studies with our 280-crystal tomograph. As you know F-18-deoxyglucose studies are being pursued by Phelps, Kuhl and others at UCLA; Reivich, Wolf and colleagues at University of Pennsylvania and Brookhaven; and Raichle, Ter-Pogossian and others at Washington University. Our emphasis has been on amino acids and bioamine work. Six months ago we decided to incorporate some measures of glucose metabolism in our brain and heart studies. In addition to your interest, Professor Elwin Marg of our campus and Professor Robert Friedland from the Davis campus have approved protocols to pursue studies of F-18-deoxyglucose. Your approach with schizophrenics would not seriously overlap with their scientific objectives and in fact, as mentioned above, would be complementary to our present program. Thus, I am happy to see us embark on a collaboration.

I would like to take this opportunity to make a few scientific comments with regard to the proposal. First, I find the proposal a well written scholarly document. The unfortunate problem in affective disorders research is the

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Dr. Adolf Pfefferbaum
Page two
8ORM269

difficulty in pinpointing crisp experiments which will clearly answer biological questions. The biological question being asked in your proposal relative to our collaboration is: "Is there an abnormal pattern in the anatomical distribution of glucose metabolism in the schizophrenic vs. the normal patient?"

This would normally be a superficial question but is in fact supported by evidence that there is a decreased frontal flow in schizophrenic patients. The proposition that this decreased flow is associated with decreased metabolism is sound from my understanding of brain physiology and is supported by recent discussions I have had with Dr. David Ingvar and Dr. Niels Lassen. Though as indicated above I am enthusiastic about our collaboration, I am not enthusiastic about the validity of Ingvar's results. As you properly noted in your application, the patients who were studied received 200 mg of phenobarbital and .75 mg of atropine. There is, of course, strong evidence that this level of barbiturates will lower brain metabolism by more than 25%. My evidence is based on the circumstances of an experiment done at Mass. General Hospital and although my interpretation might be arguable, it is certainly well known as you have noted that barbiturates do change cerebral blood flow. Other evidence from our experiments in hyperthermia with monkeys and dogs corroborates this observation. Thus, one of the experimental protocols I feel we must pursue is the examination of the effects of that level of barbiturates on brain blood flow. I am not proposing this necessarily be part of your scientific proposal, but believe we should have an open mind about what we expect to see.

A few months ago I made arrangements with Dr. Ingvar to visit his lab in Lund on 3 July. I hope that Dr. Lassen will join us and that we can work out an agreed upon protocol for examining this question. Should they be enthusiastic about cleaning up their own experimental circumstances, then I think we can be satisfied that the hypoperfusion experiments will be redone. Should they not be interested, then we can approach the metabolism protocol without any strong preconception that decreased or increased flow might be found. I hope you will agree with this criticism and method of approach.

A second category of constructive comment involves the availability of a single photon tomograph for blood flow measurements in Dr. Lassen's laboratory. This device will allow blood flow measurements to be made without the limitation you mentioned in your application.

In terms of the number of patients we can accommodate, I previously mentioned that we could handle as many as 2 1/2 patients per month. This number might be greater or smaller by a factor of 2 during the first year. I suspect we can commence the studies in January 1981 and if the Davis cyclotron can deliver adequate amounts of F-18-deoxyglucose by January, then I believe we will be able to study a sufficient number of patients in the next year to meet your objectives. Just today I reconfirmed this with Professor John Jungerman at UC Davis.

In addition to the patient studies, we do need some capital support as I have indicated to you in order that the regular delivery of F-18 material can be assured. Our present objective is the fabrication of two complete target and delivery system units, one for use at the 88" cyclotron in Berkeley and the other at the Davis Crocker facility. Your budget reflects this initial investment.

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Carton No.	<i>33</i>
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Dr. Adolf Pfefferbaum
Page three
8ORM269

On my return from Sweden, I will contact you regarding the hypofrontal flow experiments.

Sincerely,



Thomas F. Budinger, M.D., Ph.D.
Henry Miller Professor of Medical Research
Donner Research Medicine Group Leader

TFB/11

cc Philip A. Berger, M.D.
Walton T. Roth, M.D.
John Jungerman, Ph.D., UC Davis
Yukio Yano, Chemist, Donner Laboratory
Thornton Sargent III, Ph.D.
✓ Laurie Graves, Donner Financial Officer

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