

M.H.S. - 18

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703044

United States Senate

COMMITTEE ON ARMED SERVICES
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July 8, 1968

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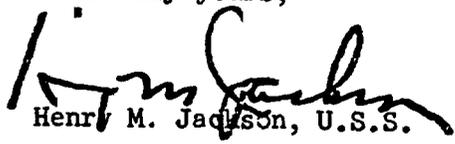
The Honorable Glenn T. Seaborg
Commissioner
The Atomic Energy Commission
Washington, D. C.

Dear Sir:

The enclosed is respectfully submitted to you
for every proper consideration.

Please provide me with a report in duplicate,
and return the enclosure to me with your response.

Sincerely yours,


Henry M. Jackson, U.S.S.

HMJ:cn
enc.

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7-8-68

0000298

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98105

Please return to
SENATOR HENRY M. JACKSON

College of Engineering
Nuclear Engineering Department
BENSON HALL

July 1, 1968

Dr. Leonard A. Sagan
Medical Research Branch
Division of Biology and Medicine
U.S. Atomic Energy Commission
Washington, D.C. 20545

Dear Dr. Sagan:

Dr. Woodruff has referred your letter dated June 21, 1968 (received on June 27) to me for reply because we both feel it is an unsatisfactory explanation of why our research proposal submitted in March, 1968 was not considered competitively with that from the group at Texas A & M. Please understand that the comments in this letter are not directed to you personally for we all feel that you have been trying to help us.

Ever since our first formal disclosure of the potential use of Neutron Activation Analysis (NAA) in the early diagnosis of cystic fibrosis in children (Transactions of the American Nuclear Society, 9, 591, November, 1966), we have been diligently seeking support from Federal Agencies with little success.

Prior to submitting our first proposal for funds we considered simultaneous submittals to AEC and NIH. In the spring of 1967 I called the Division of Biology and Medicine inquiring about their interest in this work and requested a brochure describing the procedure for submitting a research proposal. The doctor to whom I spoke was not very encouraging about the availability of support for new projects. Consequently, on May 15, 1967, we submitted a proposal to NIH which included both the NAA work to be done in this department plus clinical and biochemical studies to be carried out at Children's Orthopedic Hospital (COH) in Seattle.

On November 15, 1967, we received a note from Dr. James R. Weiseger of NIH telling us that our proposal was not approved.

We then learned that the Regional Medical Program of PHS might be interested in supporting part of our work particularly as it related to the clinical

0000299

DOE ARCHIVES

Dr. Leonard A. Sagan

-2-

July 1, 1968

follow up of the children sampled in our study. We then responded to this possibility with another proposal jointly with COH.

On January 15, 1968, you very kindly called Dr. Stamm of COH stating that you had received a proposal from a group at Texas A & M requesting funds for a study using NAA for mass screening children's nails for diagnosis of C.F. You went on to say that since our original work was referenced in the proposal - why hadn't we submitted a proposal? Dr. Stamm related to you our discouragement following my telephone call to your office but asked if there was time for us to submit a proposal and have it reviewed in competition with the Texas A & M proposal. You suggested that we write a summary of our proposal for staff review and that you would reply formally.

On January 16, I wrote to you (please see attachment A) outlining our proposed research program. Your reply dated January 25, 1968 (please see attachment B) stated explicitly that the DBM staff "would be happy to review a formal proposal from you."

We began work immediately to prepare a new research proposal incorporating several important new developments that had taken place since our submittal to NIH in May, 1967.

In order to keep you informed of our progress, Dr. Stamm visited your office on February 9, 1968. Dr. Stamm said that he was very well received by the DBM staff personnel as well as Dr. Seaborg. When Dr. Stamm returned to Seattle, he related to us that he was most encouraged by the response to his visit and felt that our proposal would receive favorable consideration. It was also his understanding that the Texas proposal had not been funded at that time. In all honesty, one of our reasons for optimism regarding this proposal has been the low esteem in which our competitors are apparently held by AEC staff members.

On March 8, 1968, advance copies of our research proposal were mailed, with the formal University approved copies being transmitted two weeks later.

To further follow up our submittal, Dr. Woodruff visited you on March 22, 1968. Dr. Woodruff was asked several questions about the budget and submitted a reply dated March 26, 1968 (please see attachment C). Dr. Woodruff was also told that the timing on our submittal was not an issue since no funds would be available until at least June, 1968. He further deduced that our proposal was being actively reviewed.

On June 25, Dr. Stamm learned that the Regional Medical Program had awarded funds to COH for clinical aspects of cystic fibrosis research and that \$20,000 was allocated for the Neutron Activation Analysis (NAA) studies to be carried out in this Department. Although this represented only 1/3 of

0000300

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Dr. Leonard A. Sagan

-3-

July 1, 1968

the funds we felt necessary to refine our diagnostic criteria for both children and newborns, we immediately revised the budget submitted with our proposal to AEC. On June 26 Dr. Stamm telephoned you to ask your opinion about submitting a revised budget on the order of \$27,000 for one year rather than the \$47,055 requested.

It was during this conversation that you indicated the research review committee had acted favorably upon the Texas proposal and therefore AEC could not support our proposal also. The implication is that our proposal was not reviewed at the same time by the same group that reviewed the Texas proposal and that our proposal was rejected on the basis of the time it was received rather than on its technical merits. If our conclusions are correct then we feel that either someone has been less than candid with us or Dr. Stamm, Dr. Woodruff, and myself misunderstood DBM's intentions. Moreover, it was not until we received your letter of June 21, 1968 (please see attachment D) that there was any intimations of prior commitments on the part of AEC.

After eighteen months of work following the conception of the idea, we have analyzed hair, finger and toe nail clippings from about 1,000 children referred to us not only locally but from around the United States. We have also made some progress with the analysis of nails from newborns. We have accumulated complete clinical data on all patients and are programming the data for computer sorting routines. We developed sampling procedures and made these available to physicians collaborating with us, including personnel at the Texas Regional C.F. Center. We are not "Johnny-come-lately" in medical applications of NAA and it is most discouraging to learn that despite our best efforts and contributions an award was made to a group that first heard of our work through the cited American Nuclear Society article with more details revealed in the Life magazine article of November 10, 1967 and a Master's thesis published in June, 1967.

On a technical basis, during their first year they will undoubtedly plow the same furrows that we have this past year. They also do not appear to have the close clinical affiliation with a large number of Regional Cystic Fibrosis Centers that has required us over a year to establish. In addition, in terms of the magnitude of AEC support to Texas A & M versus the amount of Neutron Activation Analysis research contributed to the scientific literature over the past few years we feel that our position compares quite favorably.

I would therefore appreciate receiving answers to the following questions:
(1) when was the research proposal submitted by the Texas group reviewed?
(2) when was the contract awarded to them? (3) when will a renewal proposal be submitted by them for a second year of research? (4) has there been an implied commitment by AEC that the Texas group will be supported for a second year? and (5) will we be able to submit a competitive proposal to be considered on technical grounds at the time the Texas group submits their renewal proposal?

0000301

Dr. Leonard A. Sagan

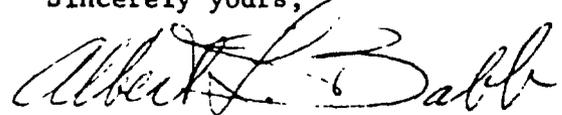
-4-

July 1, 1968

In these days of restricted Federal support of research it appears that every dollar invested needs to be carefully evaluated. If we lost the contest on technical grounds, so be it. However, in the event that this is not the case I want to go on record as registering a formal complaint about the manner in which our research proposal was handled by your office.

I intend to transmit copies of this letter and your reply to Dr. Seaborg, who mentioned this C.F. research in a recent speech, and to Senator Henry M. Jackson who has been interested in our quest for financial support.

Sincerely yours,



Albert L. Babb, Ph.D.
Professor and Chairman

ALB:bth

Enclosures (4)

cc: Dr. Stanley J. Stamm
Dr. Gene L. Woodruff
Dr. Jack M. Docter

0000302

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98105

ATTACHMENT A

College of Engineering
Nuclear Engineering Department
BENSON HALL

January 16, 1968

Dr. Leonard Sagan
Division of Biology and Medicine
U. S. Atomic Energy Commission
Washington, D. C. 20545

Dear Dr. Sagan:

Dr. S. J. Stamm indicated that we should send a letter to you immediately pursuant to your telephone call yesterday.

Since November 1966 when we presented our first results for the potential use of neutron activation analysis in the early diagnosis of CF in children, we have established guidelines for research and are actively seeking financial support. I did call a physician in the Division of Biology and Medicine about one year ago to see if there would be interest in supporting our work. However, at that time we included in our overall research proposal clinical studies and follow-up so it did not seem appropriate for submittal to the AEC. Consequently, we submitted the overall proposal to NIH and were advised last November that it would not be funded. We believe the reason for this is that the proposed research was not "basic" enough, namely, not strongly enough oriented toward the elucidation of biochemical mechanisms.

Since last fall we have been seeking alternate sources of support. The National Cystic Fibrosis Foundation has provided additional funding to Children's Orthopedic Hospital so this takes some pressure for funds off the clinical part of the research. Our primary need now is to secure funding for the research programs which would be largely carried out in this Department in collaboration with Children's Orthopedic Hospital. Our current thinking on the scope of this research is given below.

As you may know, cystic fibrosis is a disease that is both widespread and very little understood. Approximately one child in every thousand born in the U. S. has cystic fibrosis. To date, no cure has been found although considerable success has been attained in treating the disease. An important factor in a CF patient's prognosis is the age at which the disease is diagnosed. In spite of a very accurate and reliable diagnostic test, the sweat test, one-third of all children born with cystic fibrosis die in their first year. In the absence of a cure for this disease and most probably after a cure has been discovered as well, the pressing need is for a successful screening technique.

0000303

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The project which we propose involves measurements of the concentrations of trace elements in biological samples in a systematic study aimed at improving the diagnosis as well as the general understanding of cystic fibrosis. More specifically, the aims of this project are:

1. To demonstrate the feasibility of using neutron activation analysis to measure trace element concentrations for the purpose of screening large populations for the presence of cystic fibrosis,
2. To demonstrate that cystic fibrosis can be diagnosed in the newborn infant using neutron activation analysis,
3. To determine the feasibility of using measurements of trace element concentrations to identify carriers (heterozygotes) of cystic fibrosis,
4. To determine the relationship between the zinc metabolism in cystic fibrosis patients and that in normals,
5. To determine the feasibility of identifying cystic fibrosis in an animal model for CF research.

For the past 18 months, we have been cooperating closely with the Cystic Fibrosis Center at Children's Orthopedic Hospital in a series of preliminary studies. These studies have included the measurement of sodium concentrations in about 1500 nail and hair samples including about 300 from CF patients. Some of the results of these studies can be briefly summarized, especially as they relate to the objectives stated above.

1. The measurement of sodium alone is a useful supplemental diagnostic test for cystic fibrosis. It is possible to establish criteria such that the accuracy for the identification of CF subjects is approximately 90%. These results have, in a number of instances, had considerable significance when diagnosis was difficult, especially due to borderline sweat test results. On the other hand, the same criteria also produce almost a 50% inaccuracy in normals (i.e., almost half of the normals require follow-up sweat tests). Thus there remain unresolved problems in establishing a completely successful screening technique for use on a large scale. It appears that the most promising solution will be the measurement of other elements, especially potassium, in addition to sodium. This will require a supplementary β -counting technique since sodium interference will preclude a purely instrumental technique based on γ -spectroscopy. Radiochemical separation is unacceptable due to the time and expense involved. The transition from the sodium only approach to the multi-element approach is reflected in the sample data cards attached.

2. There are special problems in the analysis of nails from newborn infants. Sample procurement must fit into the framework of established procedures for the care of newborns in hospital nurseries. Such procedures customarily include frequent bathing in solutions that have a very high sodium content. Furthermore, although only a small amount of data have thus far been obtained, it is clear that sodium concentration is a strong function of age in the first few days of life. Much more data must be obtained to establish the significance of the parameters involved, and it is likely that additional elements are especially important in infant samples.
3. The results thus far also indicate that while values of sodium concentration in samples from CF heterozygotes are on the average higher than normal, there is too much overlap in the groups to permit reliable identification. Future plans include measurements of additional elements in heterozygote samples and also correlation of these results with those from the tests of Doctor Spock at Duke University. The latter test appears to have great reliability in identifying CF heterozygotes, but is far too complicated for use on a routine basis.
4. Dr. Clara Meuhlbacher of Children's Orthopedic Hospital has proposed the thesis that cystic fibrosis may be caused, at least in part, by a failure of the body to maintain a balanced level of carbonic anhydrase. Concurrent with biochemical studies at Children's Orthopedic Hospital, it is proposed to systematically measure zinc concentrations in a wide variety of biological samples supplied by the Cystic Fibrosis Center at Children's Orthopedic Hospital.
5. An animal model has long been sought for use in cystic fibrosis research. One of the major difficulties experienced in this search has been the lack of reliable diagnosis, especially since, for a variety of reasons, the sweat test is usually not useful. The techniques being developed in the present project may be quite applicable for this purpose. A few measurements have already been performed from samples provided by Doctor Warwick of the University of Minnesota, and the preliminary results are very promising. In fact, a copy of a letter sent recently to Doctor Warwick will indicate why we are excited about the animal model results to date. Sample E is the offspring of parents B and D.

We have been limping along on what funds I have been able to allocate from our State budget but these are inadequate for the research now needed.

Dr. Leonard Sagan

4

January 16, 1968

We will be glad to answer additional questions that you may have, and we would be grateful for your comments and suggestions regarding submission of a research proposal based on the further development of this project.

Sincerely yours,

Albert L. Babb, Ph.D.
Professor and Chairman

ALB/fn

Enclosures

cc: Dr. G. L. Woodruff
Dr. S. J. Stamm
Dr. J. M. Docter

Albert L. Babb

0000306



UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

January 25, 1968

ATTACHMENT B

RECEIVED
NUCLEAR ENG. UNIV. OF WASH.
SEATTLE, WASH.

JAN 29 1968

AM PM
7,8,9,10,11,12,1,2,3,4,5,6

Dr. Albert L. Babb
Professor and Chairman
Nuclear Engineering Department
University of Washington
College of Engineering
Seattle, Washington 98105

Dear Dr. Babb:

Thank you for your letter of January 16, 1968, describing your interest in neutron activation analysis of fingernail sodium as a diagnostic technique for children with cystic fibrosis.

Several of our staff members have seen your letter and have shown interest in this work. We would be happy to review a formal proposal from you, and I have enclosed a brochure describing the procedure for doing so.

Allow approximately four months for processing of your proposal.

Sincerely yours,

Leonard A. Sagan, M. D.
Medical Research Branch
Division of Biology and Medicine

Enclosure:
Guide for the Submission of
Research Proposals

0000307

ATTACHMENT C

March 26, 1968

Leonard A. Sagan, M.D.
Medical Research Branch
Division of Biology and Medicine
U.S. Atomic Energy Commission
Washington, D.C. 20545

Dear Dr. Sagan:

I would like to thank you for your kindness in meeting with me at your office last Thursday. I enjoyed the opportunity to get acquainted with you and to discuss our research proposal with you.

I also want to take this opportunity to make an additional comment regarding our discussion. At the time, when you asked about the item in our budget for secretarial assistance, I failed to recall the real motivation for this entry. Although routine correspondence would not require such assistance, there is a very substantial amount required in this project. This correspondence results from the fact that we normally make two contacts with individuals in obtaining samples - once beforehand, in which the sampling procedure is described and various information is requested, and again afterwards, when results are available. I have enclosed copies of the forms we are currently using for this purpose. At the present time, this work load is being carried by Dr. Stamm's secretary. It is anticipated, however, that as the number of samples processed is increased, the amount of work involved will be substantially increased and eventually correspond to at least half a secretary's total effort.

Thank you again, and please let me know if you have other questions about this or any other aspects of the project.

Sincerely yours,

Gene L. Woodruff
Assistant Professor

GLW:cjk
Enclosures

bcc: Dr. S. J. Stamm

0000308



UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

June 21, 1968

ATTACHMENT D

Dr. Gene Woodruff
Department of Nuclear
Engineering
University of Washington
College of Engineering
Seattle, Washington 98105

Dear Dr. Woodruff:

Your proposal, entitled "The Use of Neutron Activation Analysis in the Early Diagnosis of Cystic Fibrosis," has been reviewed by the Research Committee of the Division of Biology and Medicine. The proposed studies were considered to be of interest to the Atomic Energy Commission; however, in light of budgetary limitations and prior commitments, it was recommended that the proposal be rejected.

It was a pleasure to have had the opportunity to review the proposed work and if we can be of further assistance, do not hesitate to contact us.

Sincerely,

A handwritten signature in cursive script that reads "Leonard A. Sagan".

Leonard A. Sagan, M. D.
Medical Research Branch
Division of Biology and Medicine

0000309