

LH 75

PROPOSAL TO INTERNATIONAL LEAD ZINC ORGANIZATION FOR THE CONTINUATION, THROUGH THE YEAR 1965, OF THE FINANCIAL SUPPORT OF THE PROGRAM OF RESEARCH OF THE LEAD ZINC LABORATORY, IN THE DEPARTMENT OF PREVENTIVE MEDICINE AND INDUSTRIAL HEALTH OF THE COLLEGE OF MEDICINE OF THE UNIVERSITY OF CINCINNATI, ON THE PROJECT "EFFECTS OF INHALED PARTICULATE LEAD COMPOUNDS IN THE AIR UNDER EXPERIMENTAL CONDITIONS".*

Reference is made herein to our proposal made on October 3, 1962 in which the general experimental procedure, together with the details of a specific experiment to be carried out in 1963, were described in some detail. A further proposal, in relation to the continuation of the experimental program through 1964, was made on September 4, 1963.

The present proposal is concerned with the continuation of the program through the calendar year 1965.

It seems unnecessary to include the substance of earlier proposals in the present communication. Suffice it to say that a series of individual experiments has been designed to elucidate various features of the metabolism of lead, each of which is scheduled to extend over a period of months or years, according to a predetermined schedule, that is subject to alteration as the facts develop. For some 27 years systematic investigations of carefully chosen human subjects have been carried out in order to determine the course of events (in metabolic terms) associated with prolonged exposure to lead compounds in low (tolerable) levels of dosage. During the first thirteen years of the period, the responses of these subjects to lead taken by mouth were determined. Since that time (beginning in 1950), the fate of inhaled, particulate lead (in inorganic form) has been investigated, the purpose being to determine the influence (1) of dosage (concentration in the respired air), (2) of the size of the dispersed particles, (3) of the specific compounds of the dispersed lead, (4) of the

*The title of the project has been altered slightly at this time, in order to put it in somewhat more precise terms.

- 2 -

overall duration of the exposure, and (5) of the intermittency of the exposure, versus its continuity in time.

The original intention was to proceed with experiments in the sequence indicated above. However, after the completion of the initial experiments on dosage, and the partial investigation of the influence of the size of the particles on their fate in the respiratory system, a clamor arose in air-pollution circles for the consideration of a standard for the quality of the ambient air of cities, with respect to its lead content, and it was believed to be wise to revise the experimental schedule and to establish, experimentally, with all reasonable speed, the extent of the accumulation of lead in the human body during essentially constant (24 hours per day on 7 days per week) respiratory exposure, as contrasted with the presently known effects of such exposure to the same experimental conditions during an eight-hour, five-day schedule simulating that of industrial employment. The first experiment toward this objective was initiated in January 1959, and since that time, five* experimental subjects have been employed productively* in obtaining the necessary information. The experimental procedures and the results obtained up to a certain point in time, have been reported to the sponsors of this experimental program.

The full experimental program was supported initially and for ten years by Ethyl Corporation alone. Since 1949, part of the cost has been borne by E. I. duPont de Nemours and Company. In the year 1963, as the result of the interest of other organizations in the outcome of these experiments, and of a desire on the part of the Director of the Kettering Laboratory to spread and thus

*An additional subject, after serving for about 6 months, was found to be unsatisfactory, and was discharged, while another was discharged after a very short (10 day) trial period.

- 3 -

to stabilize the financial support of the experimental program over a period of years, the financial burden of this admittedly costly work was shared in substantially equal portions by four organizations, namely Ethyl Corporation, E. I. duPont de Nemours and Company, International Lead Zinc Research Organization, and the United States Public Health Service, thereby providing a budget of approximately \$100,000 per year. It is the purpose of this proposal to seek the continued support of International Lead Zinc Research Organization during the year 1965.

The Present Experiment

The experiment now in progress, which is to be continued into and probably throughout 1965, has been described in detail in our proposal dated September 4, 1963. A change in the procedure was introduced, however, as described in our progress report of April 19, 1964, in order to take advantage of the results obtained in the early part of the experiment and, hopefully, to expedite the experimental work for the convenience of the sponsors. In visualizing the logistics of the experimental design, the sequence of the observations is outlined briefly herein.

Subject M.K. entered upon his schedule of exposure to lead in the atmosphere of the chamber for the first time on October 7, 1963. He was subjected, for 3 hours, to the inhalation of air containing, approximately, 9 micrograms of lead, as the sesquioxide, per cubic meter. He followed this regimen on every other day until January 13, when the length of time spent in the chamber, under the same conditions, was 6 hours per day on alternate days. (The choice of lengthening the hours instead of increasing the concentration of lead was made for the reason that no demonstrable effect upon this Subject's output of lead in the urine (or upon the concentration of lead in his blood) was observed. No period of "recovery" was required therefore, and we could proceed to determine, experimentally, whether an effect could be obtained by merely lengthening the

- 4 -

period of exposure, this being the primary issue of these experiments.)

The exposure of Subject N.K. to air containing 9 micrograms of lead per cubic meter, for 6 hours per day on every other day, began on January 13 and continued until July 27, 1964 by which time, again, no evidence of an increase in the excretion of lead in his urine (or blood) had been obtained. (The duration of this phase of the experiment was extended, deliberately, beyond our earlier expectations in order to make sure that any minute effect could be found through a statistical analysis of the results of an adequate number of observations.)

On July 27, 1964, Subject N.K. was subjected to 9 hours of exposure in the respiratory chamber to the same conditions that had prevailed previously. He has continued since that time on this schedule. The data will be subjected to statistical analysis when a sufficient number are available.

The second Subject (S.S.), who had replaced the earlier, unsatisfactory subject, and whose schedule of otherwise parallel observations was initiated tardily and would therefore continue out of step in time, entered another respiratory chamber on March 2, 1964, where he was subjected, for 3 hours per day on every other day, to the inhalation of air containing 9 micrograms of lead (as sesquioxide). He, likewise, failed to show any response to the experimental exposure during the period of 24 weeks, and on August 17, 1964, his regimen was changed to 6 hours per day, on every other day. He continues at present on this schedule.

This experiment, involving the two subjects, N.K. and S.S., will continue into the year 1965, and after having gone through the cycle of 3, 6, 9 and 12 hours per day on every other day, over sufficient periods of time as determined by the outcome, each subject will go on into a similar cycle, involving a different (higher) level of lead concentration in the air of the chamber. By such means, basing each portion of the cycle of exposure on the results of the

- 5 -

previous portion, it should be possible to determine, clearly, by the extrapolation of these results to 24 hours per day on 7 days per week, the approximate degree of the physiological tolerance of healthy human subjects to readily absorbable, particulate lead in the atmosphere.

Completion of Present Experiment and Development of
Future Program

Results which will permit the termination of the experiments designed to test the influence of time (intermittency versus constancy) upon the metabolism of lead, may, with good fortune, be secured in 1965. (It is likely, however, that some further time will be required for bringing these observations to a definitive end. No experimental work of similar import is in progress, so far as is known, and it would be highly undesirable to discontinue the effort to obtain conclusive results.) If this should be the case, the next logical step in the program, from the aspect of the practical need for information, would seem to be that of investigating the ^Arole of the chemical and physical characteristics of specific compounds of lead dispersed in air upon the absorption, excretion and retention of lead in the body. (The sulfide, the sulfates and the silicates are of special interest in this connection.) Preliminary work in preparation for the initiation of these experiments can be made prior to the termination of the present cycle of experiments. There need be no loss of time, therefore, in the progress of the work, provided some of the sponsors agree to "the next step," and make financial provision for such an extension of the work. A detailed (supplementary) proposal will be made at the proper time, well in advance of the termination of the present experiment, so as to enable the developmental work (working out the method of obtaining and maintaining appropriate experimental conditions within the respiratory chambers) to be done.

- 6 -

Financial Considerations and Budget for 1965

Since the experimental program, as outlined above, has had much the same technical methodology for a number of years, it may be assumed that the cost of the conduct of the work will change little. However, certain new factors enter upon the scene within the year 1965, and all of the sponsors should be aware of them.

First, there will be a new Director of the Kettering Laboratory within the year, and since this experimental program has been developed and supervised in detail by the present Director, responsibility for its guidance will have to be put in other hands. It has been regarded as unwise to do this in advance of the appointment of a new Director, because of the need to fit this program into the structure and objectives of the new regime. Every effort will be made by the present Director to ensure its continuation in an effective manner, but there may be changes in direction or emphasis.

Second, the present grant of the Public Health Service will reach its termination in August 1965. There is reason to believe that it will be extended, but there is no guarantee, and here again, the situation will need to be examined by the individual sponsors, if the program is to be maintained.

Aside from these matters, which, admittedly, are crucial, but are not likely to be difficult of solution (the day to day work is in good hands, and no fundamentally different ideas or procedures will have to be applied or developed to carry it on, along presently productive lines). (There are ample opportunities for the development of new ideas, new techniques and new objectives, but the work of past years has served to pose certain specific questions to be answered and, at the same time, has provided methods whereby these answers can be obtained. The continuation of the program is in jeopardy, therefore, only because of financial uncertainties. It is to be hoped that this uncertainty will not prove to be serious,

- 7 -

since, in our view, the questions at issue are not only answerable, but also are in need of answers.)

On the basis of the expenditures accounted for thus far in 1964, and of those anticipated during the remainder of 1964, and on the assumption that some additional developmental work should be done in 1965 (to provide the means of dispersing one of the insoluble compounds of lead, as particles of uniform size, in the air of a respiratory chamber, in a known, stable and uniform concentration), the following budget for 1965 is recommended. It includes certain modest but essential increases in salaries, wages and other miscellaneous costs.

Personnel	\$ 55,000
Reagents, glassware, allowances to subjects for food, etc.	7,500
Overhead (all other costs prorated to salaries)	45,000

Total	\$107,500
-------	-----------

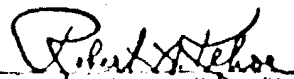
On the assumption that private funds will be forthcoming in the same amounts as in previous years, and that public funds may not be available after the termination of the present grant, it may be presumed that the financial outlook in 1965 will be as follows:

Ethyl Corporation	\$ 25,000
E. I. duPont de Nemours and Company	25,000
International Lead Zinc Research Organization	35,000
U.S. Public Health Service - AP 00220	17,500

Total	\$102,500
-------	-----------

Such funding of the project would be some \$5,000 less than the estimated requirements. Provision for this shortage could be made individually or jointly, prior to January 1965, by the private sponsors, or it may be postponed in favor of reviewing the situation within the year 1965.

Date: September 10, 1964


Robert A. Kehoe, M.D., Director,
Kettering Laboratory