PROCEDURE OF THE MEDICAL SCHOOL
AND THE UNIVERSITY
IN THE MATTER OF HUMAN EXPERIMENTATION

extrapolate so as to visualize the response of the subjects to 24 hours per day on 7 days of the week. Such a series of observations has been made at the level of 10 micrograms (0.010 mg.) per cubic meter of air, without obtaining a response, so that the next step in the experiment is that of increasing the concentration of lead in the air and repeating the observations through as many points (in time) as may be necessary to obtain a stable curve. (Obviously the threshold will lie somewhat below the slightest concentration that will induce a response.)

The full protocol of these related experiments is believed to be too extensive for presentation here. It is anticipated that these experiments will be continued for some additional years.

Purpose of Study

The primary purpose is to explore and reveal the physiological pattern of the metabolism of lead in the intact, healthy human organism under a variety of conditions. The practical objective is to relate the physiological behavior of lead to conditions of environmental exposure to lead, and to develop criteria for the differentiation of safe from dangerous human exposure. This has been done with respect to occupational exposure, and also in relation to the safe level of daily ingestion under basic conditions of respiratory exposure to lead.

The present experiments are intended to provide a standard of safety with respect to the concentration of lead in the air which will be applicable to the population of the urban centers in the United States, in which a combination of factors contribute to the dispersion of lead compounds in the air. (The issue in the eyes of public officials is, of course, the extent to which the lead compounds discharged from the exhausts of automobiles may be permitted to elevate the lead content of the atmosphere of streets, freeways and the community generally, on the somewhat dubious assumption that other sources, combined, are of negligible proportions.)

Potential Hazards

(a) The potential hazards borne by the subjects are negligible, especially in the present series of experiments, which are to be carried out at the lowest levels of concentration that will yield any physiological (excretory) response. (Previous experiments have been carried out under conditions of much more intensive exposure, but always below the threshold of danger, in terms of the concentrations of lead in the tissues, body fluids, and excreta which have been found in association with the mildest manifestations of plumbism. The present experiments do not approach threshold levels.)

(b) Despite the lack of hazard, and in order to collect further basic data, the subjects are maintained under the supervision (in a manner comparable to the best and most exacting medical regimen) of a physician who has no responsibility otherwise for the experimental regimen, and has the authority to terminate the experimental exposure to lead for any medical or hygienic reason that to him is valid. A medical examination is carried out, weekly, and the results recorded by this physician, and certain observations of the laboratory are made, some at daily, some at weekly intervals, for the purpose of a meticulous regard for the physiological status of the subjects, as well as for the gathering of pertinent data.

Previous Work Done in this Area

Two publications (reprints) which are little more than descriptions of methodology and the principal results, are submitted herewith.

Method of Procuring Subjects

All but two* of the subjects engaged for these experiments, who have numbered more than a score in the past thirty years, have been obtained by engaging them as non-academic members of the staff of the Kettering Laboratory, at basic salaries that are regarded as adequate, reimbursing them completely for out-of-pocket expense (food, special clothing, and certain medical expenditures), and covering

* These were members of the research staff during their activities as experimental subjects.

them with insurance under the Ohio Workmen's Compensation procedures. Insofar as it has been feasible and acceptable to these individuals, they have been retained within the staff in varying capacities after the completion of their stint as experimental subjects.)

Each subject has been selected after exhaustive medical examinations to determine his physiological fitness; each subject has had the appropriate prophylactic medical and dental care that has been indicated to maintain his fitness during the preliminary period of normal or basic metabolic observations and afterward if necessary.

Each subject has been interviewed by the principal investigator in the most thorough and informative manner, with respect to the objectives of the experiments, the potential risks involved (on the background of the extensive experience of the investigator in industrial practice in the lead trades). Only one subject in this entire period of time has failed to act in good faith in every respect, and, in this one instance, the subject became disenchanted with the somewhat exacting regimen after a few months, and wished to be released (perhaps some financial advantage was being exploited at this time, but that, if true, was not the primary consideration).

No written agreement or waiver has ever entered into these relationships, and with all due regard for the provision of a record to substantiate the action and position of the principal investigator and that of the University, should the facts be questioned and a claim made, it is our informed opinion that no waiver, on the part of the subject is worth, in law, the paper on which it is written, and also that no document can substitute for or guarantee the professional ethic that sees, first, the service to mankind that can be rendered by the subject, and in addition holds firmly in mind the plain duty not to compromise the health and well-being of the subject in any manner that is known or suspected. It is believed,

furthermore, that the legal position of the subject as an employee of the University, engaged in a theoretically hazardous occupation, and protected, economically, under the compensation laws of the State of Ohio, differs in no wise, from that of other employees of the University. It is believed, furthermore, that the liability of the University is defined and limited by this arrangement. It is recognized, however, that these legalistic considerations do not reduce, in the slightest degree, the direct professional responsibility of the principal investigator for the fulfillment of the most exacting ethical requirements for the immediate and ultimate safety and well-being of the subjects.

August 31, 1970

Evelyn V. Hess, M.D.
Chairman, Faculty Committee on Research
University of Cincinnati
Cincinnati General Hospital
Cincinnati, Ohio 45229

Dear Doctor Hess:

I am entirely willing to provide the information which you require, but I enclose, I hope, that which is necessary at this time.

I wish to make it quite clear that what is under way, at present, is not at all a "new project." It is rather the continuation of a systematic investigation, which began in 1939, to examine many aspects of the behavior of lead in the human organism. The general plan was interrupted some years ago (about 12 years) to look experimentally into the practical significance of lead in the ambient atmosphere, and to determine what level of the concentration of finely divided (particulate) lead might be found to be at, or near, the maximum concentration which would be tolerated physiologically by average people in the general population.

This interruption has come to an end with the completion of a series of experiments (which, we believe, have produced an answer to the question raised), and we are now taking up where we left off at the end of 1958, in the examination of the role of the dimensions of the dispersed particles of a specific compound of lead, the sesquioxide, Pb_2O_3, in the respired air, on the rate of accumulation of lead in the human body, and the rates of increase in the concentration of lead in the blood, and in the output of lead in the urine.

The level of exposure of a female subject is to be maintained so as not to exceed 0.15 mg. of Pb per cubic meter of air (the actual exposure of this subject to lead, under the experimental conditions to be described, has not begun, and will not begin until January of 1971 or thereabouts, dependent upon the pattern of the preliminary observations). The experiment then is to continue at the level of exposure indicated above, which is well within the limits of complete safety for an indefinite period of time, so long as the conditions of the exposure are limited to 40 hours or less per week (actually here 37.5 hours, which regimen corresponds to the usual cycle of industrial exposure, what with changing clothes just before going to work, and bathing and changing clothes afterward) as the latter regime is capable of being controlled within limits which are known to be harmless (with a fairly large factor of safety). In addition, this subject, in accord with our usual procedure, is under the surveillance of a physician whose sole function in the experiment is to see that she is free of any and all illness, including any deviations from a normal state which might be believed (or imagined by the subject or by others) to be due to experimental factors. He can require the discontinuance of the experimental regimen at any time which is advisable, in his judgment.

About two years (perhaps only 18 months) will be required to complete this experiment, after which the particle size will be reduced to about 0.2 micron in diameter (average size within a small range), a new subject will be obtained, and an additional experiment will be initiated. We shall notify you when this time comes.

In this manner, we shall determine the effects of particle size over a satisfactory range (particles of the size of 0.75, 1, and about 1.2 have been investigated prior to 1959, and these two experiments should provide the information required on this feature). Afterward, our intention is to examine the effects of the chemical compound (such as lead sulfide, the basic sulfate, and the silicate) on the rate and extent of the absorption. It would be useful to investigate the lead-chromium compounds in this regard, but I am unwilling to subject any human being to any concentration of a chromate or chromite in the respired air because of the apparent implication of these compounds (perhaps only one, but the evidence is not sufficient to differentiate between the several compounds) in the occupational causation of pulmonary malignancies.

I should point out to you that, because of the placement of these experiments within the framework of the original project, and because of our very long experience with all aspects of this matter, from the viewpoint of risks, we have not considered that any approval from any source was required for the continuation of this work. No formal report of our procedure has been made, therefore, except for the purposes of your information. This statement does not mean that we, or any of us, consider ourselves to be lacking in any way in our willingness to fulfill the requirements of the Public Health Service, the University of Cincinnati, or the constituted representatives of its faculty. We shall comply, fully, therefore, with your wishes. I would hope, however, that this does not mean that consent must be given to the continuation (into exposure) of an experiment which has now been under way since May of 1970. It is worthwhile, I think, to bear in mind that the principles of truly physiological experiments of this type, and the appropriate limitations of risk in their performance, were developed by ourselves many years before any such requirement were thought of in the Public Health Service or by the University. Our knowledge of the specific subject involved in this case, is such, I think, that we are justified ethically, among our colleagues, in the nature of their conduct. I do not say this defensively, as a matter of opposition to the present requirements of the faculty, but rather to clarify the issue of professional and scientific responsibility. In the long run, human experimentation, whether for therapeutic or preventive purposes, must be considered by an appropriate authority in the strictest ethical manner. One of the vital requirements of the precautions to be taken in the given instance, is that there be adequate knowledge on which to assess the potential risks of the experiment to be undertaken. As a senior member of this faculty (now in Emeritus status), I find it necessary to abide fully by the requirements of the faculty, after their due consideration of the issues involved in a type of human experimentation.

* I have given you something of the plans which I have had in mind (and have communicated to my present associates). It is apparent, however, that I am fairly full of years and cannot be expected to direct this work indefinitely. I have tried to develop, and I believe I have achieved, a degree of familiarity with the entire program of experimentation, so that it can be expected to continue long after I am no longer available to look after it. This means, I think, that there will be other phases of the program to be carried out and that there should be an understanding within the Medical Center as to how best to maintain the familiarity of key persons within the faculty with the work program, and also, on the other hand, an understanding as to what information should be supplied by the Laboratory to the Faculty of the Medical College. It is not possible to learn many of the facts concerned with the mineral metabolism in man (or for that matter, the facts relating to other substances than minerals) without investigating the behavior of the human subject (and outside

the area of illness and the availability of patients). In the field of Occupational and Environmental Medicine, it is absolutely essential to investigate human beings under stress, and while this can be done under the de facto situation of men at work or in other activities of life, it has come to be (and will be increasingly so) essential that observations ~~will have to~~ be made under the precise conditions of the laboratory, if they are to be sufficiently precise to be useful. This Laboratory can be expected to be engaged in many activities of this type in the years to come.

Some means will have to be developed to spare the principal investigators from the expenditure of undue effort and time in reporting and in other paper work inside the institution. It is also necessary, I think, to keep the responsibilities here within this institution. Not only will there be work done for which the Public Health Service has no responsibility, as in the present instance in which they have no sponsoring role to play. There is no good reason why experimental work in the University of Cincinnati, for example, experimental work which is not financed by the U.S.A., should require governmental consent to be done, unless the law of the land should so specify. It is wrong, I believe, to permit the precedent to be established in that direction. I think, therefore, in view of the situation, that it would be well if you (and perhaps others) were to meet and talk about this type of situation and plan to meet them, rather than to follow a procedure which was not designed to deal with matters of this type.

Yours sincerely,

Robert A. Kehoe, M.D.
Professor Emeritus of
Occupational Medicine

RAK:wb

July 22, 1969

Dear Mr. Curtin:

I missed seeing you before I left Cincinnati on a vacation which will continue (if it is not interrupted by something urgent) until August 24th, when I shall be back in Cincinnati .

I wanted to talk to you briefly to let you know that I am involved in two projects, with other people in the Laboratory, which will extend into next year.

The one is sponsored by Ethyl Corporation, and an appropriation of $25,000 has been made, to be drawn on at the end of the year (or far enough in advance, if we choose, so as to leave no sums due as of December 31). We shall not need the entire $25,000, I am sure, this year, and the work is to go on at an agreed upon pace in 1970. Dr. Pfitzer is initiating the work, in which the tissues of the Coroner's cases will be taken for analysis as they can be worked into the continuing stream of samples from other sources. Dr. Stanley Gross will assist Dr. Pfitzer. It seems likely that the cost can be assessed against this project on the basis of the number of samples which are analysed during 1969. However, I will confer with you about the means of accounting for our costs when I return from my vacation in August and get back to my desk on August 25. The money, in this instance, is available, but is to be paid in on a bill approved by me, with your advice and consent. I trust that this will be sufficient for your purposes. You can, of course, discuss it, if you wish, with Dr. Foulkes, but I had thought to take it up with Dr. Suskind, later, in view of the short interval before his arrival. Not that I was sidestepping Dr. Foulkes, but I saw no reason for complicating matters.

The other project has to do with the continuation of the work which I have been directing, in which Mr. Cholak, Mr. Schafer, Mr. Parkinson, Dr. Stemmer and Dr. Lerner are co-investigators with the technical assistance of several others. I have discussed the prospect for the future with the representative of the sponsors - Dr. Jerry Cole, of Lead Industries Association, acting also for Ethyl Corporation, E.I. du Pont de Nemours, and The Associated Octel Company of London. The specific part of this project which has been under investigation for the past eight years, is in effect a side issue of the main project. The main stream of the work began in 1939, and was interrupted by the practical problem of the level of lead in the general atmosphere which is compatible with public safety. This problem has been explored since 1960, and has now been brought to a point very near the solution.

It is planned now to return to the point in the original program from which we departed in 1960, and to resume the investigation for some time to come at an annual rate of expenditure of $75,000. I have made a proposal to Dr. Cole, for the consideration of the group of Sponsors, and this will be acted upon (with the anticipation of approval) between now and the end of the year.

I would suppose that the funds from this source have been made available quarterly in advance, but I am not sure that this is the case. It is what I shall be prepared to request, unless it is fully understood that this is and has been the procedure, or unless you wish me to make a different arrangement. Again, it is my assumption that you will consult Dr. Suskind on this matter if there is reason for doing so.

Sincerely yours,

RAK

Robert A. Kehoe, M.D.

P.S. I'll send you a copy of my proposal to Lead Industries Association for your use or for transmission to Dr. Suskind if you choose.

MEMORANDUM

TO: Sidney Lerner, M.D.

FROM: Robert A. Kehoe, M.D.

DATE: February 14, 1968

SUBJECT: Investigations Involving Human Subjects

In response to your memo of December 21, 1967, the material which I sent to the Research Committee of the Medical Faculty, is forwarded herewith.

I have not taken the trouble to reproduce the copies of these items that were in my files, but have sent the entire sheaf of information and exchanges of correspondence, in order that your Committee might be fully informed of what transpired. It may be that you will wish to have certain of these items of information in your files. If so, and if you will return these to me, I will provide what you require. I include the correspondence if only to illustrate the opportunities afforded for misunderstanding which arise out of this situation. I do not believe, however, that these exchanges have any proper place in your permanent file. You may not agree with this view, but I trust that you and the other members of your Committee will not make an arbitrary decision on the matter. In any case, I shall do my best to respond to your wishes, to the extent, if you choose, and as I suggested, of meeting with your Committee and discussing some aspects of this matter.

The issue here, I may say, is not a matter of form or a means of protecting investigators against unethical action, or accusations of such actions, but the genuine protection of human beings against any type of exploitation whether through ignorance or intention.

Sincerely yours,

Robert A. Kehoe, M.D.

wp

N13350.03

RE 0012374

Forwarded to Dr. Lerner:

Letter from Dean Grulee, dated May 4, 1966.

Dr. Kehoe's reply to Dean Grulee, dated May 6, 1966.

Letter from Dean Grulee, dated April 4, 1966.

Dr. Kehoe's reply to Dean Grulee, dated April 6, 1966.

Letter from Dean Grulee to Dr. Edward A. Gall, dated April 11, 1966.

Report to the Clinical Research Committee on the INVESTIGATION OF THE METABOLISM OF LEAD IN THE HUMAN SUBJECT (First Version)

Report to the Clinical Research Committee on the INVESTIGATION OF THE METABOLISM OF LEAD IN THE HUMAN SUBJECT (Dated June 7, 1966).

Letter to Dean Grulee and the Members of the Research Committee, dated June 7, 1966.

MEMORANDUM

TO: Robert A. Kehoe, M.D.

FROM: Sidney Lerner, M.D.

DATE: December 21, 1967

SUBJECT: Investigations Involving Human Subjects

The Committee on Ethics of Human Experimentation has reviewed the material you sent ~~to me~~ on October 9, 1967. The Committee would appreciate having this material supplemented with a copy of the information, including protocol, that was sent to the Faculty Committee on Research as well as their reply to it.

To facilitate the review of projects, individual members of the Committee will be assigned to function as liaison between principal investigators and the Committee. Dr. Carl Smith will be the representative for your project. Please feel free to talk with him or, if you prefer, with any other member of the Committee, about any questions you may have.

Thanks very much.

Sid Lerner

Sidney Lerner, M.D.

SL:rms

Answered January 12
Proposed meeting & future Committee

N13350.04

KE 0012376

April 6, 1966

Clifford G. Grulee, Jr., M.D.
Dean
College of Medicine
University of Cincinnati

Dear Bud:

I do not understand fully just what it is that the Research Committee desires, from the indications in your letter of April 4th, in relation to my memorandum on, "Investigation of the Metabolism of Lead in the Human Subject." I shall do my best, however, to provide additional information, in the hope that it may fill the bill. Perhaps, I expect the Committee to understand that I am somewhat more cautious in these matters than most people would be, and that I use any and all knowledge and skill that I may have, in avoiding any risk to the subjects. It is not easy to say more than just this, in connection with day by day observations.

First, with reference to the means by which the subjects are obtained, let me say that, conditional upon his being found acceptable, physically and psychologically, by the staff physicians who act for me (or for any other principal investigator who may be involved later), the subject is offered employment, and the financial terms of his employment are clearly defined in the business office of the Laboratory. The conditions with respect to potential risk are explained in the following terms: The principal investigator has been responsible for the development of the standards of safety that are now operative in the best circles of industrial employment in the lead trades, these having been worked out over the period of many years through clinical and physiological observations of the employees of industrial organizations. It has been found that no person is poisoned by lead unless he has absorbed quantities of lead which result in a specific degree of elevation of the urinary output of lead or the concentration of lead in his blood. The quantities of lead concerned in establishing these criteria have been viewed critically by many investigators and are now agreed upon in knowledgeable professional circles. It is believed that they are entirely sound. They are based on the most rigid clinical critique, in regarding as signs of lead intoxication such biochemical evidence as interferences with the porphyrin metabolism which cannot be explained otherwise. (It is fair to say within our own household, that these standards have been developed in the Kettering Laboratory, and that they are applied there more critically and consistently than they are anywhere else.) The experimental program of the Laboratory in this field is explained in detail to the potential subject, and he is promised the protection of the Laboratory against the slightest danger of being rendered ill or vulnerable to illness from the absorption of lead. Inasmuch as the program involves the investigation of the intake and output of lead day by day, it is possible at all times for the principal investigator and the responsible physician (the head of the Clinical Division of the Laboratory) to follow the physiological evidence of the rate of absorption and excretion of lead, while he is carrying out the clinical and laboratory investigation of the hygienic status of the subject week by week. There is no more informative regimen of medical supervision than that which is followed here.

Second, with respect to the toxicity of the lead to which the subject is exposed, the dosage from day to day is never in or near the range of actual danger, being

always within the limits of safety that have been set by experience. Far more importantly, however, the quantity absorbed by the subject over the period of time involved in any experiment, is never permitted to reach the range within which intoxication may occasionally be expected to occur. In this respect, the experiments, as conducted since 1939, have refined and verified the criteria of safety, so that if they could ever have been (in the earlier periods of experimentation) regarded as proceeding into regions of risk, they can no longer be so regarded.

Incidentally, it is not quite true that "no other measure than examination by a physician," for the purpose of determining the status of the subject, is mentioned in the original memo. Paragraph (b), page 3, points out that "the subjects are maintained under the supervision (in a manner comparable to the best and most exacting medical regimen) of a physician etc. etc." I realize that the members of the Research Committee may not know just what such a regimen involves, but members of the Clinical Staff of the Kettering Laboratory have such knowledge. It seems hardly necessary to set down the details of such a regimen and to document its adequacy, but it has been done, and the record can be supplied.

Finally, it is recognized that in the carrying out of human experimentation in many fields, a certain amount of real risk is involved. This must inevitably be the case in dealing with most medical problems that require elucidation. It so happens, however, that in the field of occupational medicine, the crucial experiments which have been productive of disease are often carried out by a society that is willing to subject workmen to unknown risks for the sake of the economic life of the community. It is not necessary, therefore, as a rule, to engage in such experiments blindly. One can easily, therefore, take the point of view that there must be no risk whatever in investigating the parameters of human physiology.

Sincerely yours,

Robert A. Kehoe, M.D.

RAK:wp