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TECHNICAL PROGRESS REPORT

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THE METABOLISM OF RARE EARTHS FOLLOWING
INHALATION: PATHOLOGIC AND BIOCHEMICAL RESPONSE
IN THE LUNG AND OTHER ORGANS

To

The Division of Biology and Medicine
Energy Commission
Washington, D.C.

From

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The short term inhalation studies of Scandium, Yttrium, Cerium, Europium and Ytterbium all in chloride form and contaminated with the appropriate radioisotope (^{46}Sc , ^{88}Y , ^{144}Ce , $^{152-154}\text{Eu}$, ^{169}Yb) have been completed and the data have appeared in previous reports.

Further work is being reported herein on an aerosolizer and its design. Oral intubation studies using europium were continued under varying conditions in order to verify data previously presented which indicated statistically insignificant absorption via the gastrointestinal tract. Some data on the long term inhalation of $^{152-154}\text{Eu}$ Europium were presented at Gatlinburg for a Conference on Inhalation Carcinogenesis and appear herein. Three preprints and four abstracts of papers to be given at various conferences are included.

A. Inhalation and Metabolism of Some Selected Rare Earths.

These data for the rat are being evaluated and will be available soon for Scandium, Yttrium, Cerium, Europium and Ytterbium. The physical characteristics (COO-1630-11) and protocols have been presented previously (COO-1630-1 and 2).

B. Repetitive Exposure of the Sprague-Dawley Rat to
¹⁵²⁻¹⁵⁴Europium.

These data were presented at the Inhalation Carcinogenesis Conference in Gatlinburg during the last contract period. The preprint, COO-1630-25, "Pathological Effects in the Rat After Repetitive Exposure to ¹⁵²⁻¹⁵⁴Europium" is appended to this report. The abstract appears below.

✓ Abstract:

Pathological Effects in the Rat After Repetitive
Exposure to ¹⁵²⁻¹⁵⁴Europium Chloride.
H. L. Berke and D. Deitch

Three groups of female Sprague-Dawley rats were exposed for 6 months (5 days a week) to aerosols of ¹⁵²⁻¹⁵⁴Europium Chloride at levels of 0.71, 1.9, and 31.0 X 10⁻⁶ μCi/ml of air; a fourth group received equivalent amounts of stable europium chloride, and others were maintained as controls, breathing room air only.

Cumulative pulmonary doses, based on lung activity concentrations, were calculated for a span of 2 years; they were about 3,000, 12,000, and 62,000 rads, respectively.

Pathologically, pneumonia, marked chronic inflammation, multiple abscesses, and bronchiectasis were more frequent in the animals exposed to the radionuclide, but no lung tumors were observed. Tabular pathological data will be available.

✓ C. Oral Intubation Studies Using Stable Europium.

The absorption of carrier-free radio-europium in chloride form has been shown to pass through the gastrointestinal tract without significant absorption (COO-1630-8). The absorption of larger doses of the stable nuclide was of interest to determine its contribution to body burdens following ingestion or inhalation in an industrial environment. Also, the effect of the presence or absence of food in the gastrointestinal tract was also studied. These data are presented in tabular form herein.

✓ D. Design and Operation of an Improved Aerosolizer.

For many years aerosol generator research has been a continuing preoccupation in our work for the purposes, specifically, of providing a stable aerosol in terms of its concentration and physical characteristics which would be suitable for discriminating long term repetitive inhalation studies. A generalized discussion of its design and operation is given below. A more detailed presentation is appended in the preprint (COO-1630-13).

Abstract:

An Improved Aerosol Generator

H. L. Berke and T. E. Hull

A device has been developed which automatically compensates for changes in the concentration and volume of a solution during

aerosolization with the production of an aerosol of unchanging characteristics. It represents the redesign of a generator previously used for short term inhalation exposures (1/2 hour to a few hours) where variability in solution concentration was not of great concern and solutions could be replenished daily. The original generator was quite inadequate, however, for production of aerosols over longer or repetitive time periods where a minimum of manipulation is required, viz., for radioactive materials, and where constant aerosol characteristics are desired.

The aerosolizer consists of two lucite tubes of different diameters set in a lucite base with a communicating port between them located so that the solution drains from a large reservoir tube by air displacement of the solution to a smaller generating tube (containing the air jet tube) when sufficient liquid volume is used up in the smaller tube. The air jet tube is made by drilling a #80 hole at a 15° angle upward in a plastic tube (5-6 mm in diameter) near one end which is sealed shut. Positioning lugs restrict movement of the air jet tube so that the distance to the impacting surface remains constant. The baffle plates and communicating orifices are so designed that air bubbles, unavoidably produced by the air jet, cannot enter the reservoir chamber to interfere with the gravity flow of solution regulated by the liquid level in the smaller plastic tube. (see COO-1630-10 for figures).

In order to prevent evaporation of solvent or condensation of water vapor from the air jet during aerosolization, the incoming air stream at 13.0 p. s. i. gauge pressure is saturated with water vapor before it enters the air jet tube at a temperature high enough to compensate for increments in the jet air volume at ambient at-

mospheric pressure. Thus, the air borne material should be unchanged in concentration or particle size.

With adequate control of all variables, the aerosol characteristics should in every respect be reproducible from day to day and data is available to indicate this constancy (COO-1630-13).

The aerosolizer should be valuable for long term or repetitive daily use since the concentration of the solution in the generator varies but little no more than 4-5 per cent in a five-day repetitive use. In addition, the generator requires no cleaning, merely refilling, and the reservoir volume can be made as small or large as experimental needs require. It should be particularly useful where correlations between the amount of deposition and aerosol characteristics are being studied.

E. Mucociliary Activity in the Rat.

An abstract for this study appeared in Report COO-1630-3 following oral presentation at an Industrial Hygiene Conference in 1968. A preprint is appended herein, COO-1630-6, "The Roentgenographic Determination of Tracheal Mucociliary Transport in the Rat", by H. L. Berke and L. M. Roslinski and will be submitted for publication soon.

F. Uranium Nitrate and the Lymphocyte Ratio.

In line with our interest in sensitive diagnostic procedures in toxicology, a study has been undertaken involving the complete separation of peripheral lymphocytes for purposes of facilitating sizing into large and small cells using the light microscope. The effect of Uranyl nitrate on the ratio of large to small lymphocytes indicated the feasibility of using this index in minimal uranium exposures, the changes attributable most probably to the biological response to the uranium rather than its very slight radioactivity. The abstract (COO-1630-23) to be presented at the Industrial Hygiene Conference this year appears below.

Abstract:

The Effects of Uranyl Nitrate on Peripheral Lymphocytes of the Rat Using a Micro Cell Separation Technique.

M. Palazzolo and H. L. Berke

A micro method using 100 μ l of blood has been developed for the separation and concentration of peripheral lymphocytes of the rat for the purpose of observing changes in these cells at very frequent intervals following exposure to various noxious agents without adverse effect on the animal. Briefly, whole blood is centrifuged in microhematocrit tubes containing fibrous

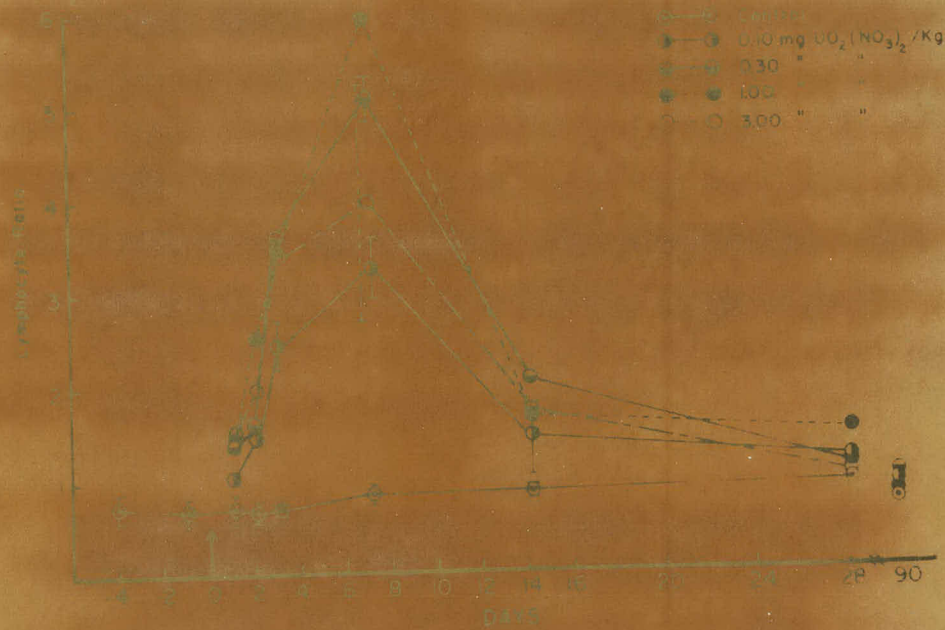


Fig. 1 - Changes in the lymphocyte size ratio following graded doses of Uranyl Nitrate using micro cell separation technique.

cotton threads permitting the isolation of non-phagocytic cells and their concentration in the buffy coat in excellent yield and with minimal manipulation. Optical sizing procedures at 1600x are greatly facilitated on the Leishmann stained smears by the densely deposited and homogeneous lymphocyte population which are also amenable to photographic recording and inspection. The ratio of large to small cells, i. e., larger or smaller than the median control diameter of separated lymphocytes was used as the index of size distribution changes and corresponded closely in value to direct blood smears taken in the usual manner indicating no sizing bias in the separation procedure itself. Preliminary trials in the uranium poisoned rat showed ratio increases in about a week, the maxima correlating roughly with dose. The changes in lymphocyte size may also be useful tentatively for the determination of dose response relationships not only for uranium but also following other toxicants as it is in the case of radiation exposure.

G. Occupational Effects of X-Irradiation in the Female Radiographic Technician.

A study was undertaken to elucidate the effect, if any, of prolonged exposure to low levels of scattered radiation in the young female technician. The experimental determination of more accurate values of radiological exposure by using the thermoluminescent dosimeter for comparison with film badges indicated wide errors in the latter. An epidemiologic approach

using questionnaires on general health and natal abnormalities represented an attempt to relate dose and effect. The abstract of this study, COO-1630-24, appears below.

Abstract:

Considerations in the Analysis of X-ray Technician
Exposure During Routine Diagnostic Roentgenography.
R. F. Dudek and H. L. Berke

This study was designed to define and evaluate more precisely the radiological dose to x-ray personnel from scattered radiation by comparing lithium fluoride (T. L. D.) dosimetry, an accurate measure of radiological dose, with that of the film badge generally used. These data could then be applied in retrospective epidemiological surveys to indicate the level of exposure eliciting an observable biological response in technicians. T. L. D. dosimeters were attached to film badges and both exposed in air to the scatter radiation from a phantom irradiated by a beam at 70 KVP, 100 ma and filtered by 2.5 mm Al for a total of 1306 ma minutes. The locations monitored were similar to those occupied by diagnostic x-ray technicians while working. Target to film distance was 36 inches with a field size of 10 x 11 inches. Low KVP techniques were used to allow comparison with accumulated film badge data. A limited spectral study of the scattered radiation was done as an aid in calculation of a meaningful exposure dose. An attempt to correlate the TLD-corrected film badge dose with the health of a small group of female

technicians (110) and their progeny as indicated in a survey by questionnaire will be presented as well as the comparative dosimetry observed in this study.

H. Metabolism and Pathology of Intratracheal Europium Chloride in the Dog.

The evaluation of this study is completed and the abstract, COO-1630-15, appears below. It is scheduled to be given at the IVth International Congress on Radiation Research in July, 1970.

Abstract:

Pulmonary Pathology in the Dog Following Intratracheal Injection of Europium Chloride.

H. L. Berke, D. Deitch, T. Hull and R. DuPraw

This study was designed to determine in the beagle dog the comparative pathological effect of intratracheally administered stable europium alone and in the presence of the radioisotopic europium. The animals were given either 5.0 milliliters of a stable europium chloride solution at pH 4.0 or one containing also 50 μ Ci of $^{152-154}\text{Eu}$ chloride. The instillation of the solution was very carefully done in each case in order to assure delivery to identical sites in the lung. In this way, the harmful sequelae attributable to each could be ascertained and tracer analysis of the radioisotope was also applicable to those animals receiving only the stable isotope. Dogs were necropsied at intervals up to one year following injection,

organs excised, weighed and assayed for activity where appropriate. Replicate and similarly located samples of large organs, etc., were obtained, weighed, assayed, and the tissue prepared for histopathological examination. An attempt was made to correlate the activity found with the pathological injuries observed assuming comparable distribution of the isotope in all animals. Urine and feces were also collected and assayed for activity. One of the most surprising observations was the very long retention time in lung tissue, only 10-15% of the activity being cleared in a one year period while absorption into soft tissue and bone was minimal. All significant lesions were confined to the lung tissue which showed minor degrees of emphysema, fibrosis, atelectasis and epithelial hyperplasia. Granulomatous lung lesions were a constant finding but the effect of the radio-europium was not clearly evident in terms of enhanced injury to the lung tissue.

I. Abstracts and Preprints

- 1) Roentgenographic Determination of Tracheal Mucociliary Transport in the Rat. H. L. Berke and L. M. Roslinski COO-1630-6
- 2) An Improved Aerosol Generator. H. L. Berke and T. Hull COO-1630-13
- 3) Pulmonary Pathology in the Dog Following Intratracheal Injection of Europium Chloride. H. L. Berke, D. Deitch, T. Hull and R. DuPraw COO-1630-15
- 4) Annual Report 1969-1970 H. L. Berke COO-1630-22

- 5) The Effects of Uranyl Nitrate on Peripheral Lymphocytes Using a Micro Cell Separation Technique. M. Palazzolo and H. L. Berke
COO-1630-23
- 6) Considerations in the Analysis of X-Ray Technician Exposure During Routine Diagnostic Roentgenography. R. F. Dudek and H. L. Berke
COO-1630-24
- 7) Pathological Effects in the Rat After Repetitive Exposure to ¹⁵²⁻¹⁵⁴Europium. H. L. Berke and D. Deitch
COO-1630-25

J. Addendum.

In the past year one of our technical personnel terminated to take a more lucrative position. We are again, however, liable to more attrition from army inductions but hope to lose little time in recruiting. Physical reshuffling of our faculty, installation of appropriate water supplies in new areas, resetting of experimental area pressure gradients and further required space partitioning was accomplished in the last period. One of our instruments, Packard Autogamma, developed an intermittent and its repair, finally accomplished, cost us considerable time loss. All appears, however, to be in order and hopefully will so continue.