

PROGRAM REVIEW  
OF  
THE LOVELACE FOUNDATION FISSION PRODUCT  
INHALATION PROGRAM

AEC CONTRACT NUMBER AT (29-2) - 1013

January 11-13, 1971

REPOSITORY Germanstown RC  
COLLECTION 6793  
BOX No. 3/5 Loc #2194  
FOLDER M, H.S.-21 (1971)  
Lovelace Foundation

Robert E. Anderson, M.D.  
\*A. J. Breslin, M. E.  
John Doull, Ph.D., M.D.  
R.J. Garner, D.V.S.C.  
Walter S. Snyder, Ph.D.  
John B. Storer, M.D.

\* Unable to attend scheduled site visit due to illness in family:  
visited subsequently and report will be submitted separately.

## I. GENERAL COMMENTS

Dr. McClellan and his associates continue to administer an outstanding laboratory investigating a problem of considerable applied interest. The staff is generally young, competent and enthusiastic with an appropriate admixture of more seasoned investigators to lend a proper balance. The following comments are offered with the hope that a small increment can be added to an obviously quality performance.

## II. SPECIFIC COMMENTS

### A. Nature of radioactive aerosol

One of the strengths of the Lovelace Fission Product Inhalation Program (FPIP) is the fact that most of the inhalation experiments have been carried out with careful attention to the physical-chemical properties of the aerosol. This basic approach seems to offer the only reasonable hope for bringing into a manageable schema the wide diversity of aerosols that are found in real exposure situations and the site visit team recommends that these studies continue until the accumulated information begins to approximate the demands of actual or strongly anticipated situations. It is important, therefore, that some attempts be made toward applying the experience gained by the use of these special aerosols, both to demonstrate to what degree the behavior of the more complex aerosols can be reasonably synthesized on the basis of the present experience and to discover whether certain important factors may have been overlooked.

In discussions with the staff, there was some evidence of a desire to undertake extensive studies of aerosols produced in various types of existing plants. While this might lead to better knowledge of the diversity existing at present and has some value for FPIP as noted above, we think such aerosol surveys should not be more than a small fraction of the total effort in this regard. It would be surprising if the basic information now in hand enables one to model more than the simplest situations, e.g., a highly soluble radionuclide such as  $^{131}\text{I}$  in its usual forms.

It was most encouraging to hear about the in vitro solubility studies and the extent with which they cross-check with the biological behavior. We urge that this effort be continued, perhaps expanded, and that at some stage of the work comparisons with animal exposure data be undertaken.

1098786

This may not be entirely possible by using data from the long term retention and effect studies because of the infrequency of sacrifice in those studies. However, the early data (one to two weeks) would be of greatest interest for the initial comparisons of in vitro and in vivo methods, and perhaps a few short-term studies could be initiated without unduly delaying the chronic studies.

RECOMMENDATION:

CONTINUED EMPHASIS ON IN VITRO SOLUBILITY STUDIES AND PARTICULARLY COMPARISONS BETWEEN SUCH EVALUATION AND BIOLOGICAL BEHAVIOR.

B. Radiation dose patterns from inhaled nuclides

The present dosimetry is excellent by present standards but may need future modification. It now appears that dose estimates to subregions of the lung will be considered in radiation protection work of the future, although probably not as the primary standard. A research program such as FPIP should apply dosimetry which will elucidate the extent to which particular doses correlate with hazard, e.g., dose to lymph nodes (individual nodes?), dose to bronchial epithelium or adjacent tissue, etc. The current program contains a certain amount of this finer dosimetry but the latter is apparently not being used systematically in interpreting effects. The same criticism applies to bone (endosteal cells vs. red bone marrow, etc.). Dose to lung is obviously of primary concern for FPIP but if relative hazard to lungs vs. liver or skeleton is to be assessed, then one needs fine dosimetry in these organs as well.

The models for retention are good but may need to include more identification for purposes of a meaningful dosimetry. The "rapid exchange" and "slow exchange" compartments of the skeleton as well as of the lung model (see Fig. 6, page 97, of LF-43, UC-48), come to mind in this regard; the latter shows no clearance pathway from the pulmonary region to the GI tract. Such a model may be adequate for reproducing the retention data on the dog but this is probably not the main purpose of modeling. Since one has the data on the dog, merely reproducing the data is of peripheral value. Of primary interest in modeling are (1) to provide a basis for dosimetry and, ultimately, (2) to indicate so far as possible what the corresponding human model might be. Of course, it is far more

1098787

difficult to construct a model which would identify more closely the regions of bone involved or the various pathways from the lung; yet the staff should have in mind the above two objectives in constructing models.

There may be value in using a common model for the different nuclides employed precisely because it may help in judging the relative importance of the various pathways as related to solubility, chemical and physical properties of the aerosol, and metabolism or transfer of the material in the body. When a different model is used for each it probably would be more difficult to make such comparisons than if a common model is used. We realize such detailed modeling often may encounter difficulties due to a paucity of data, but feel that it is important that it be attempted. The foregoing should not be interpreted as criticism of the work that has been done to date in modeling or dosimetry, as it is in the best traditions of the past, i.e., the practice of averaging doses over organs and using retention functions of a few components which frequently are not identified as to the tissue involved. However, there are signs that radiation protection of the future will demand more than this, and FPIP should be leading the applied field.

#### RECOMMENDATION:

INCREASED EMPHASIS UPON OBTAINING MORE DETAILED DOSIMETRY WHICH EMPHASIZES SUBREGIONS OF COMPLEX TISSUES INSTEAD OF AVERAGE DOSES OVER ORGAN.

#### C. Dose-response studies

When further studies of this kind are designed, the review team would strongly urge consideration of the inclusion of a substantial number of dogs available for sacrifice. The functional tests employed thus far appeared to be insensitive and the results have, to date, been disappointing. Thus, to adequately examine the pathogenesis of a particular impairment it will be necessary to fall back on careful biochemical, morphologic, etc. examination of sacrificed animals. In retrospect, the disappointing results of the previous sacrifice program are understandable but now with a considerable reservoir of relevant data such a program might well be re-instituted.

A watchful eye still needs to be kept on the number of procedures performed routinely (blood chemistries, hematologic

parameters, EKGs, blood pressure determinations, etc.). The value of these examinations as diagnostic aids is unquestionable but as adjuncts to the dose-response studies the value is doubtful. It is deceptively easy to collect data, but it is equally easy to forget that the analysis of these data cost time and money. The purpose of each individual test should therefore be clearly defined.

RECOMMENDATION:

- 1) FUTURE INCLUSION OF DOGS FOR PERIODIC SACRIFICE:
- 2) CONTINUED RE-EVALUATION OF THE RELATIVE IMPORTANCE OF "ROUTINE CLINICAL TESTS".

D. Pathogenesis of radiation-induced disease

1. Pulmonary function tests. The above comments on blood chemistries apply equally to pulmonary function tests. It is appreciated that an inhalation toxicology program would seem incomplete without work on pulmonary function but now that the initial developmental stages have been completed, it is necessary to take a hard look at the role such studies should play in the overall program.

All the evidence available suggests that these parameters are of little value in the early detection of pulmonary impairment so that, in this context, they can be regarded only as a costly way of confirming and quantitating clinical observations. Their sensitivity may be improved by looking at function under stress as is proposed, but the site visit team is skeptical that even this approach will prove to be particularly fruitful. These tests may be useful in following the development of pulmonary damage, but this will necessitate correlation of functional, morphological and possibly also, biochemical changes. Nevertheless, it seems to us to be doubtful if the routine application of conventional techniques as presently proposed is worthwhile. Techniques using radioactive gases are said to be more sensitive and, of course, are of great value in examining regional function. However, it is recommended that such methods should be carefully evaluated in the context of the current program and possible future program with  $\alpha$ -emitters.

Now that the conventional techniques have been successfully adapted to the beagle, there may be a temptation for the pulmonary function laboratory to revert largely to a service role. If the full potential of this lab is to be utilized,

1098789

the involved personnel need to be encouraged to explore and to devise novel methods of approach.

2. Biochemical studies. These fall into two categories: a) work with surfactants; b) connective tissue studies. From discussions with the involved persons, it seems that, on the one hand, much of the research in these areas, although of considerable academic interest, has little application to the overall program and that, on the other, some fundamental problems have not been approached. For example, it is proposed to examine the relative importance of two synthetic pathways for surfactant lecithins and yet no method exists for estimating the overall production of surfactants by the lungs. Work on surfactants is thought to be relevant, if only because they offer a means of studying serial changes in one aspect of lung metabolism, but a somewhat more structural program needs to be developed. Most importantly, some effort needs to be directed towards a method of characterizing surfactants to allow them to be distinguished from other lung components. Interdisciplinary collaboration could be fruitful in ongoing connective tissue studies with histochemical techniques being used to supplement the more conventional biochemical methods. The purpose underlying this work should be to establish the mechanisms promoting fibrosis - this does not, of course, preclude more fundamental studies.

3. Studies concerned with synergistic infectious agents. This work is thought to be of great practical importance and we strongly encourage continued effort in this area, initially with "tracer" bacteria and, later, with pathogenic organisms (perhaps as part of a more widely based combined insult program).

RECOMMENDATION:

1) CAREFUL REAPPRAISAL OF THE ROLE OF ROUTINE PULMONARY FUNCTION TESTS (WITH AND WITHOUT STRESS) AND CONSIDERATION OF A MORE EXPERIMENTAL APPROACH IN THIS REGARD WITH PRIMARY EMPHASIS ON DEVELOPMENT OF NEW AND MORE SENSITIVE TECHNIQUES; 2) CAREFUL INTEGRATION OF BIOCHEMISTS INTO DOSE-RESPONSE STUDIES WITH ATTENDANT EMPHASIS UPON CORRELATION BETWEEN CHEMISTRY, FUNCTION AND MORPHOLOGY; 3) RE-EXAMINATION OF PRESENT APPROACH TO METABOLISM OF SURFACTANTS.

E. Therapy for inhaled radionuclides

Toxicology programs generally have three major goals: 1) characterization of the hazard associated with exposure to the

1098790

toxic agent; 2) elucidation of the mechanism(s) by which injury occurs; and 3) development of methods for the prevention and treatment of such injury. Although each of these three goals is represented in the FPIP it is evident that the current major effort is in those areas which relate to hazard evaluation. The second goal is also being pursued actively in studies designed to detect functional impairment, morphological changes and pathogenesis. The third goal (prophylaxis and therapy) is the most recent addition to the program and is therefore more restricted in scope (pulmonary lavage as a means for removing inhaled radionuclides). Any attempt to evaluate this area of the total program requires consideration of the current level of emphasis and whether there should be any shift in direction of the present effort.

Basic to any decision concerning the emphasis that should be placed on the prophylaxis and therapy area of the fission product inhalation program is the question of whether short term and long range objectives for this area can be clearly delineated. Although one does not need to know what causes a disease to find a cure, the chances of success are improved if we have a good understanding of what we are specifically trying to prevent or treat. Thus, the first need is to decide whether there are satisfactory answers to questions such as the following:

1) What are the major toxic effects of inhaled radionuclides? Are these effects grossly different for different radionuclides and for different patterns of lung distribution?

2) Are we concerned primarily about the local effects of these toxic agents in the lung or effects elsewhere in the body?

3) Is the total toxic effect of the inhaled radionuclides due to radiation or are there other aspects which need to be considered (metal toxicity, for example)?

4) Are there any acute symptoms which require treatment? If not, does the immediate post-exposure therapy have any purpose other than to reduce the body burden and delayed toxic effects of the radionuclides?

5) How predictive are the results obtained in the animal studies carried out thus far for the effects which have been observed to occur in humans?

Assuming that we have adequate answers for these and other related questions, it would appear appropriate to distinguish between the therapeutic measures which could be used immediately after or close to the time of exposure from those which might be beneficial at a later stage of injury. In one sense, the pulmonary lavage therapy which is currently being investigated is not therapy but is prophylaxis against the delayed toxic effects (pulmonary and bone cancer) of the radionuclides. In this respect, one might speculate as to how the efficacy of the procedure could be improved (use of chelators, adjuvants or fluid combinations to increase the solubility of particles, use of bronchodilators and other drugs to increase penetration and recovery of the lavaging fluid, etc.). An alternate approach would be to look for other types of post-exposure therapy which might be capable of reducing the radionuclide body burden. In the present radionuclide inhalation program there is virtually no effort directed towards therapy of the delayed toxicity manifestations. The program appears to have developed to the point where the research team should consider the types of therapy that might be used in select exposed dogs. In this regard, it is appropriate to point out that the inhalation of radioactive materials has been recognized as a cause of pulmonary cancer in man for over fifty years and in animals for over twenty-five years. One might, therefore, ask how much longer we need to spend defining the problem before beginning to seek solutions to the problem of radionuclide exposure.

RECOMMENDATION:

THE CURRENT PROPHYLAXIS AND THERAPY PROGRAM OF THE FISSION PRODUCT INHALATION PROGRAM BE CONTINUED AND THAT THE PROGRAM BE EXPANDED TO INCLUDE OTHER TYPES OF THERAPY.

III. SUMMARY

Remarkable progress has transpired since the site visit of one year ago. Most of the recommendations made at that time have been implemented. Continued dialogue with other inhalation laboratories is strongly encouraged in an attempt to establish correspondence of aerosol data. Most of the recommendations made by the present site visit team involve questions of relative emphasis and do not imply a change in course (more detailed dosimetry, relative importance of "routine" determinations, greater emphasis upon structure-function correlative studies, etc.). A possible exception to the foregoing involves the suggestion that

1048 742 ifice program be reinstated.



UNITED STATES  
ATOMIC ENERGY COMMISSION  
HEALTH AND SAFETY LABORATORY-NY  
376 HUDSON STREET  
NEW YORK, N. Y. 10014

212 989-1000

March 30, 1971

Dr. R. E. Anderson  
Professor and Chairman  
Department of Pathology  
School of Medicine  
University of New Mexico  
Albuquerque, New Mexico 87106

Dear Dr. Anderson:

I'm writing to give you some impressions from a two-day visit to Lovelace earlier this month. This visit was intended to substitute for my absence from the program review in January. Therefore, the comments are intended to supplement the deliberations of the review panel although I realize they are quite tardy with respect to your report to Dr. McClellan. Please excuse my preoccupation with the aerosol segment of the Lovelace program.

My strongest impression concerns the high caliber and enthusiasm of the staff and their solid accomplishments. The capability for recognition and prompt resolution of problems is remarkable. I have the feeling that the sense of teamwork evident on the interdepartmental level permeates within departments as well. The results are commendable, whatever the reason.

With regard to action on recommendations submitted by last year's panel, the attainment of homogeneous 0.5 AMAD plutonium aerosols seems virtually assured. At the time of my visit, the first run was under way to produce insoluble plutonium particles in several narrow size ranges down to about 0.5 AMAD by means of the "spinning spiral", an adaptation of Stober's aerosol spectrometer. The process had been piloted successfully with a number of other materials and there was good reason to anticipate success with plutonium. Incidentally, I believe this process for producing monodisperse aerosols is an important advance in the field that undoubtedly will be utilized by other groups after it is published. I was also gratified to note promising efforts to generate even smaller monodisperse aerosols (as had been recommended) although attainment remains some distance ahead.

1098793

March 30, 1971

Unless I misunderstood the situation, the recommendation that Lovelace take the lead in establishing correspondence of aerosol data among the various inhalation laboratories has been implemented only to the extent of holding ad hoc discussions with representatives of other facilities. This step is necessary but far short of what the review panel visualized last year. It may be that Lovelace, having justifiable confidence in its own excellent aerosol group, has little motivation to push this matter. However, it is most certainly to the advantage of all parties that inhalation studies performed by different groups be interpretable without the complication of uncertain aerosol characteristics. I believe it is worthwhile to reaffirm the panel's position in this regard.

The effort to survey sources and nature of airborne particles (rec. B.3.a.) seems not as vigorous as it might be although I concede that the task is formidable. However, the present plan to study samples of plutonium-contaminated soil from the Nevada Test Site and to collect plutonium air samples at Dow, Rocky Flats is a practical, if limited, approach and I believe that Lovelace should be encouraged to pursue this kind of data acquisition at a moderate level of effort.

The basis for that earlier recommendation, of course, was an attempt to establish a bridge between the results of rigidly controlled exposures in the laboratory and exposures that occur in real circumstances. This, to my mind, remains a very important, difficult problem that quite possibly is beyond the scope of the Lovelace mission. Nonetheless, I think that Lovelace can make useful contributions.

For example, the Lovelace studies seem to be confirming that knowledge of both particle size and solubility is needed to predict the biological effect of an inhaled radionuclide. Looking ahead, then, the practicing industrial hygienist will require simple, reliable methods for measuring these properties of radioactive contaminants in the occupational environment. Development of such methods is well within the capabilities of the Lovelace staff and would seem to be a logical extension of their laboratory technology.

Gaining a broad base of information about the characteristics of aerosols released in accidents (which is vital, in my judgement, for preparation of hazards analyses, determining siting criteria, etc) is indeed a large problem that warrants general consideration, probably most notably by the AEC. But the Lovelace staff is in a unique position to determine the quality and extent

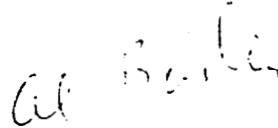
1098794

March 30, 1971

of data that are needed and to suggest approaches, possibly to be undertaken by other groups, that might best fill the need. I think the Lovelace staff should keep this under consideration and also be alert to situations such as destructive tests at NRTS that can be exploited, with either their participation or advice, to yield suitable data.

A final point that comes to mind is a question rather than a suggestion because of my circumscribed view of the overall program. I'm wondering to what extent the data being developed for acute exposures can be applied to the chronic exposure situation which is probably the more typical in industrial facilities. I believe this is a proper matter for consideration by the panel, especially in light of the reference to increasing industrial utilization in last year's recommendation to undertake plutonium studies. One might argue that industrial exposures consist of periodic, low-level, acute episodes amenable to treatment as summations. Actually, this may accurately characterize exposures in a plutonium facility. But I believe this matter warrants some study.

Sincerely,



A. J. Breslin, Director  
Health Protection Engineering Division

1098795