

Research

SRE/AIW/3.5

17th December, 1973

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FOR FILING

Dear Eberhard,

Following my visit last week, I would like to confirm our discussions as set out below :

General

The reduction in staff necessitated by the decision by B-AT not to undertake further long-term skin painting experiments at Battelle was discussed with Dr. Sacherer. The number of assistants employed to smoke cigarettes has been reduced from 12 to 2. In one instance, this will result in a hearing in the Industrial Court in the New Year. The number of animal keepers and histology technicians has also been reduced.

The second batch of smoking machines (14) have been serviced and will be shipped to Southampton in the near future. Following discussions with the Administration and tax inspector approximately £1,000 has had to be paid in taxes to the German Government.

You informed me that you would like to present two papers on the basis of the inhalation study. The first, for the Annual Working Group of European Veterinary Pathologists, would be concerned almost entirely with some detailed aspects of the pathology. The second, which would cover all aspects of the work, you would like to present at the Battelle Conference in Seattle. I reminded you that it was essential that the proposed publications are submitted to B-AT for approval before they were submitted elsewhere. This requirement applied also to the submission of a title and an outline or summary of the proposed publications. I can see no reason why B-AT should wish to withhold such permission.

Mouse Skin Painting Experiments

A. Long-Term Experiments

The few mice alive in the B10 experiment died at the end of November, so this experiment reached its natural termination in week 174.

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The B11 experiment is continuing satisfactorily; the death rate is still (week 63) low relative to that found in the B10 and most other experiments.

The current position with earlier experiments is as follows :

B6 : Coding complete, masterfile being prepared
B7 : Histology complete, awaiting coding
B8 : Histology and coding complete for about 70% of animals
B9 : }
B10 : } approximately 10% of histology has been undertaken.

B. Promotion Experiments

The two promotion experiments on the B11 and D series were terminated in November at week 36. The histology is now in progress.

C. Hyperplasia Tests

A test with five samples was planned for January, 1974.

In general, it was established that, providing condensate deliveries are not abnormally low, it should be possible to undertake tests with eight samples including the B0 continuity control. The possibility of further tests was discussed. It is planned to examine the B12 samples in two tests when the cigarettes are available.

It was agreed that Battelle would submit a simplified cost proposal covering hyperplasia tests with from 4 - 8 samples.

Reports

The experimental and results sections of the report on experiment B3 had been prepared in advance. The report was considered and subsequently discussed in detail with all those concerned.

I indicated that the statistical analysis had been completed and it was expected that the report would be ready for issue very shortly. I agreed to obtain "top" copies of the computer print-outs on white paper so that these can be forwarded to the printers. You will send me a copy of the draft summary and conclusions as soon as these are available.

Inhalation Experiments

A. Effect of Dietary Levels of Vitamin A on Laryngeal Lesions Produced by Inhaled Smoke

This inhalation experiment is proceeding satisfactorily. At the high and intermediate dose levels of Vitamin A only, a small proportion (ca 10%) of the hamsters have died. In group 5 (target 200 IU/Kg), the control animals and those exposed to only one round (ie. 30 cigarettes) per day are surviving satisfactorily, but only one hamster is still alive in the group exposed to 2

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rounds per day. Only one animal in group 6 (zero IU/Kg) is alive. This pattern of mortality is consistent with that expected.

Since relatively few animals have died, it is difficult to obtain a clear picture of the progress of the severity of laryngeal lesions. Nevertheless, it has been observed that only grade 0 and grade 1 lesions occurred in the first 3 months; in this period, there was no indication of vitamin A deficiency. In the second three monthly period, vitamin A deficiency was found in animals of group 6, and to a smaller extent group 5, but not in those groups on higher dietary levels. Histological assessment of most animals which have died, has been undertaken, lesions up to grade 3 have been observed; the experiment is now in week 44. It was agreed that the assessment of the lesions would be kept up to date so that the results can be revised in February. At that time, it will be desirable to decide whether a proportion of the animals should be sacrificed to assess the development of lesions after approximately 1 year.

B. N.M.U. Promotion Experiment 1 Report

All the figures and photographs are now prepared for this report. Those sections of the report which had not been considered previously were discussed in detail. The draft of this report is now ready with the exception of the summary, a copy of which will be sent to Southampton. The final report should be ready early in the New Year.

An outline cost proposal will be submitted in January to cover the proposed promotion experiment with two of the B12 samples. I will advise you as soon as the samples are available subject to a satisfactory match in puff number.

C. Analysis of Inhalation Experiments.

A system definition for the analysis proposed by Dr. Labgein had been received in Southampton a few days prior to the visit. Although it was not possible to consider the paper in detail, a number of general points were raised.

From the system definition, it appeared that the programme had been changed, so that it would deal with non-sequential as well as sequential transitions between lesion classes. Although this type of analysis may be required eventually, I was concerned that this might complicate the analysis unduly at this stage and suggested that it might be more sensible to establish the analysis of sequential transitions, before proceeding to the more complicated case. I was assured that the method was such that the maximum likelihood values were obtained first for sequential transitions and only subsequently, did the program analyse the non-sequential transition rates.

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I also asked Dieter to explain how it could be asserted that some of the co-variances were vanishing or small before the data had been analysed. He assured me that this was quite possible in some cases, since it was inconceivable that, for example, the transition rate from class 4 to class 5 could have any effect on an earlier transition rate although the converse was to be expected. Finally, he explained that many of the equations were included in the document (eg. section 2) to explain the process of the analysis, but only those equations marked with a "+" would actually be used in the programme.

Miscellaneous

a) Reports

Apart from the reports on the inhalation promotion experiment and long-term experiment B3, which are referred to above, the report on the extended promotion experiment (skin painting) on samples B9/1 and B9/6 is nearing completion. Since the experiment was designed to examine the effects of both initiator and condensate dose-levels (and their possible interaction), this report cannot sensibly be finalised until the statistical analysis has been completed.

b) Coding and Data Transmission

The transmission of coded data from the revised mouse record cards (experiment B8 onwards) was discussed with Gerd. He confirmed that all the information pertaining to a particular animal and the histological findings are first recorded in script. The data is coded on the basis of the record. The problems of punching directly from these cards are probably less than we envisaged originally, since the punching will be undertaken by the Battelle Computer bureau and not by an outside commercial bureau. In these circumstances, it should be relatively easy for Gerd to ensure that the punching is undertaken with a minimum of errors.

As usual, I assume that you will write to me if I have omitted or misinterpreted any important points.

Thank you again for your kind hospitality.

With best wishes for Christmas and the New Year.

Yours sincerely,



S. R. EVELYN

cc: Dr. F. A. Sacherer
Dr. R. M. E. Sullivan

noo: Dr. S. J. Green ✓

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