

VISIT TO T.I.R.C., NEW YORK CITYTUESDAY, 11TH OCTOBER, 1960

FILE COPY

Present: Dr. R. C. Hockett
Mr. W. T. Hoyt
Dr. J. Morrison Brady
D.G.I.F.

The purpose of the visit was to explain in detail the thinking behind the T.M.S.C. decision to undertake biological research and to eliminate any misunderstandings which might otherwise have arisen.

Dr. Little was unable to be present, but he had been fully appraised of T.M.S.C.'s aims and thinking by Mr. A. D. McCormick, during the Lartigue hearings at New Orleans. He had already spoken on the telephone with Dr. Hockett.

It was clear at the outset that Mr. Hoyt had reservations about the T.M.S.C. approach, fearing that T.M.S.C. had accepted that there existed a causal connexion between smoking and lung cancer and that mouse skin painting tests were, in fact, a demonstration of this. Dr. Hockett, who had discussed the matter earlier with Sir Charles Ellis, was much less perturbed and throughout the discussion which ensued, nodded agreement with me.

The line of argument, stemming from the T.M.S.C. mission to the U.S. in May 1958, was gone over in detail. It was emphasised at the outset that in order to follow biological activity of any form whatsoever, and without any underlying implication, it was necessary to have a biological test of known and proven precision. Biological activity could then be

100159319

measured just as, for example, ultra violet absorption spectra and might be employed to study non-additive effects of smoke condensate fractions, possibly indicative of co-carcinogenesis. Since it was known that skin painting could be employed to give positive results with mice, this had been selected for the initial study and the first part of the work was a large scale experiment designed to define the precision of the method within reasonable limits. A subsidiary aim was to determine whether storage of condensate was an important factor in these investigations. Additionally, the opportunity would be taken to compare the activity of the neutral fraction with that of whole condensate.

The difficulties and dangers inherent in animal husbandry on the scale proposed were discussed and Dr. Hockett expressed approval of the intention to work with carefully segregated sub-colonies.

The future extension of work was then discussed and the aim of using two, and preferably more, distinctly different tests with several species of animal was mentioned, with emphasis being given to a test involving lung tissue. The meeting with the Drs. Leuchtenberger in London was mentioned as possibly providing leads for future work.

The negotiations with various bodies, e.g. I.C.I., B.E.C.C., M.R.C., were then touched on, culminating in the recent decision by T.M.S.C. to go ahead with the proposal with the location of the Research Unit in Harrogate and the appointment of Dr. Day. Mr. Hoyt was particularly pleased that it was the intention of T.M.S.C. to handle the location in such a discreet fashion.

The possible appointment of a panel of advisers, whose function would be to assure T.M.S.C. that the suggested programme was scientifically sound

100159320

and to prevent overlapping with existing biological work was welcomed by Dr. Hockett, who was sure it was a wise move. The point was made that the advisers would not have any executive authority in the matter and that they would undoubtedly be of great value in bringing new approaches to the attention of T.M.S.C.

Having dealt in some detail with the matter, I then enquired whether my exposition had satisfied those present and whether I had allayed any fears they might have had. Both Dr. Hockett and Mr. Hoyt assured me that I had. Mr. Hoyt added that, of course, T.M.S.C. were aware of the undoubted problems in Public Relations which could arise should unwanted publicity be given to the project. In turn, I assured him that T.M.S.C. were aware of this and that it was, partly, because of possible misinterpretation by T.I.R.C. of T.M.S.C.'s intentions as outlined in the memorandum on the Research Unit that I had been asked to call.

Dr. Hockett then went on to tell me of several rather similar projects which were being directly sponsored by T.I.R.C. These were:-

(a) Dr. Freddie Homburger (Biological Research, Inc. Boston) was attempting to utilise sub-cutaneous implantation of condensates to elicit quantitative responses, rather along the lines proposed by T.M.S.C. Stage one of the project was devoted to comparing the effects of cigarette, cigar and pipe tobaccos when smoked in the form of cigarettes, with the aim of establishing whether there was anything in the concept quâ cigarette. Stage two would be to compare the same tobaccos when smoked in a pipe.

100159321

Dr. Homburger has a contract to supply the Sloan Kettering with 14,000 animals bearing tumours. By injecting one shot of 3:4:9:10- dibenzpyrene subcutaneously, he elicits an 80% response, and although the eventual incidence is the same, he finds an earlier development of tumours with male, as compared to female, animals. When injection is made into the endometrium of female animals, no tumours develop, and on following this up by injecting a mixture of endometrial extract with dibenzpyrene, it was again found that no tumours developed. Dr. Hockett thought this a particularly intriguing result.

(b) Dr. Boutwell (Wisconsin) has developed a supersensitive strain of animals by careful selection and breeding. By passage through eight or nine generations, only crossing those animals which develop papillomata with similar animals, he has succeeded in producing a substrain with a 9:1 quicker response and greatly increased susceptibility.

(c) Dr. Benjamin Rubin (formerly Houston Texas, who has now joined Wyeth Ltd., Philadelphia) has been studying skin transplants and the effect on these of very pure polycyclic hydrocarbons. Normally a skin transplant from one animal to another sloughs off fairly rapidly. Rubin has found that either by painting the hydrocarbon on the skin or by administering it in the diet at very low dosage before a transplant is made, it is possible to keep a transplant going. By varying the interval between treatment and application of the transplant, he has shown that the effect wears off. He suggests that antibodies are interfered with, in some way involving the reticulo-endothelial system.

Dr. Hockett mentioned here that both he and Rubin thought highly of

100159322

Prof. Nicol's work and that he was glad to see T.M.S.C. were supporting it.

(d) Dr. Sonneborn (Zoologist - Indiana U.) was studying the effect of polycyclic hydrocarbons on the photo toxicity for paramecia - the technique adopted by Dr. Stephano (Philadelphia) and reported on earlier by Mr. Mason.

Pure polycyclic hydrocarbons, produced by Dr. Becker (a Physical Chemist, Houston, Texas) were distributed as coded samples (with warnings as to photo decomposition, etc.) to Drs. Boutwell, Rubin and Sonneborn, to see whether the three tests gave similar ratings for biological activity. However, the technician employed by Sonneborn on this work, and trained by Stephano, had become excessively worried about working with hydrocarbons and the latter approach was virtually at a standstill, much to Rubin's disgust.

Dr. Hockett hoped that Dr. Rubin would be able to continue his approach, although he was now employed by a commercial firm, and there was the possibility of future collaboration with Stephano. Dr. Hockett explained that Stephano's work was an adaptation of work originally carried out in the U.K. by Doniach. He had attempted to get it published earlier but had had the paper rejected as too polemical. It now seems that it will appear in the first issue (in December) of a new periodical, Microchemical Journal, under the title "A Tentative Microbiological Test for Carcinogens in Submicrogram Amounts". Stephano had applied the test to smoke and claimed that the response was negative when applied to "normal" smoke ("normal" smoke in Stephano's nomenclature is smoke issuing from a cigarette butt at a temperature below body temperature).

10015932

The result for "abnormal" smoke was not indicated. Dr. Hockett added that Stephano had rated five hydrocarbons correctly using the paramecium technique.

OTHER TOPICS DISCUSSED

Nickel Carbonyl

Dr. Hockett mentioned that two doctors in Philadelphia had suggested the presence of nickel carbonyl in cigarette smoke because they had been successful in promoting the growth of lung tumours in rats by exposing them to nickel carbonyl at a dose of 1900 μg . per annum. These workers had disregarded the difficulties in producing nickel carbonyl, however, under the conditions of cigarette smoking.

I enquired whether beryllium had been mentioned in this connexion, but Dr. Hockett was unaware of it. At the Tobacco Chemists' Research Conference later that week, Williams and Garman (Liggett & Myers Tobacco Co.) reported that using a sensitive fluorometric technique (limit of detection 0.004 μg .) they were able to demonstrate the presence of beryllium in tobaccos.

	<u>Beryllium ppm.</u>
Bright	0.015
Burley	0.05
Turkish	0.07
Maryland	0.075

When cigarettes of a cased blend were smoked, no beryllium was transferred to the smoke, the whole being accounted for in the ash and unsmoked butt.

100159324

Arsenic

Dr. Hockett mentioned a comparison of chemical analytical methods with physical (activation) analysis being made on behalf of T.I.R.C. This showed that the values of arsenic reported by Holland (Texas) were probably incorrect. Nevertheless, it would be difficult to refute this work.

Tissue Culture Studies

The study of lung tissue culture is being carried on under T.I.R.C. grants by Drs. Pomerat, Pace, Gye and Philip Cooper, but the results are still difficult to interpret. Dr. Cooper has isolated a single cell, the descendants of which have then been subcultured for numerous generations. On injection into animals, some of the subcultures have been carcinogenic, while others are not. This illustrates the complexities of this approach and Dr. Hockett was not very hopeful of a successful breakthrough.

Ions

Dr. Hockett called attention to the work of Krueger in California on the effect of gaseous ions on ciliary activity. He stated that workers from the General Electric Company had shown that inhalation by animals of electrically charged dusts produced the same bronchitic changes noted by Dr. Cecilie Leuchtenberger. He added that a company in California claimed to have a cigarette filter capable of injecting negative ions into smoke, but had no further information on this.

I enquired whether Dr. Hockett had discussed this approach with Kotin as perhaps it went some way to explaining the ciliary inhibition studied by the latter. However, he had had no opportunity, so far.

100159325