

Meeting of Technical Sub-Committee of I.S.C. with Mr. E. Jacob
12th December, 1963 at 2.30 p.m.

Present:

- Mr. H.C.I. Rogers (Chairman, I.T.Co.)
- Mr. E.C. Fieldsend (I.T.Co.)
- Dr. H.R. Bentley (I.T.Co.)
- Dr. M.H. Hall (Gallaher)
- Dr. A.J. Lindsey (Carreras)
- Mr. G.W. Moore (Carreras)
- Mr. J. Gilmour (G. Phillips)
- Dr. I.W. Hughes (B-A.T.)
- Dr. D.G. Felton (B-A.T.)
- Sir Philip Rogers (Chairman, T.R.C.)
- Mr. G.F. Todd (Director, T.R.C.)
- Mr. H.B. Grice (Secretary, T.R.C.)
- Dr. T.D. Day (T.R.C.)
- Dr. A.K. Armitage (T.R.C.)
- Mr. A. Campbell-Johnson
- Mr. H. Bawden (Campbell-Johnson)
- Mr. Reppiatt (Solicitor, T.R.C.)
- Mr. B. Burnett (I.T.Co.)

Visitors:

- Mr. D.S.F. Hobson
- Mr. H.D. Anderson
- Mr. E. Jacob

The Chairman welcomed Mr. Jacob and invited him to give his views on the T.R.C. research programme and events in the U.S.

Mr. Jacob It was assumed that the Surgeon General's Advisory Committee would report unfavourably and that following this the Industry in the U.S. would be called upon to report in past, present and future research activities and to go over the whole of the health issue in front of Congressional Committees and Federal and State Regulatory Bodies. The latter two, in particular, could range widely over the whole field. Research in the U.K. would be one of the topics and they could be asked why they were not engaged on something similar in the U.S. (The T.I.R.C. and U.S. companies were appreciative of the T.R.C. consideration of their difficulties in the past).

He had visited Harrogate and had met T.D.D. and A.K.A. It was generally known, and by T.R.C., that Dr. Little disagreed with the Harrogate approach. He then gave a lawyer's view of the different U.S. and English approaches to research. The U.S. approach was that until it was possible to work on "whole smoke", there was no point in considering any portion or constituent of the smoke and therefore, instead, one concentrated on disease generally. He had understood Harrogate was working on Product Research, which he took to mean research into the biological characteristics of an altered smoke - altered by filtration, blending changes, etc. Such alterations were known to be possible - what was being done with such knowledge? Why not work on that? He found Harrogate was doing something different and had mentioned this at a meeting with B-A.T. at Millbank.

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He questioned whether it was not already well-enough established that smoke condensate was carcinogenic to mouse skin. Was it sufficient for Harrogate to refine this further and to establish an accurate dose-response curve for a particular strain of mouse? He understood that the next stage would be fractionation and establishment of a dose-response curve for the fractions. In the U.S., because of Wynder's activities, it was difficult to see any advance being made by fractionation. Wynder could not quantify his fractions and Wright believed that now more physiology of the cell was required. Wynder had established a crude dose-response curve for mice which showed a lower level without biological activity, but this did not fit epidemiological findings. What major purpose was served in repeating and resolving this work.

[At this point, E.J. was called to the telephone and it was decided that H.R.B. should reply].

H.R.B. explained that the whole of the Harrogate research was based on the hypothesis that cigarette smoke is carcinogenic. Following on from the old findings:-

1. Old smoke condensate is carcinogenic to mouse skin (Wynder and many others).
2. Smoke condensate is carcinogenic to rat lung tissue (Blacklock)

It was decided to refine skin painting as only one approach - another approach would be to use rat lung - with the aim of getting consistent results in all tests and on all tissues. If consistent results were not obtained then doubt would be thrown on the basic hypothesis.

Work on the dose-response curves starts where Wynder left off. He had studied old smoke condensate and neutral fraction. Harrogate would establish whether this biological activity is the whole or only part of that of fresh smoke condensate. So far, only 24-hour-old smoke condensate could be used but efforts were now in train to reduce this to seconds-old-smoke condensate.

A second approach was to find how much the activity of whole smoke condensate was due to neutral fraction and this required accurate measurement of dose-response, which required large numbers of mice in order to make sure that a 30% change in biological activity would be detectable. It was also intended to answer questions whether phenols, acids, bases, etc. were co-carcinogenic.

E.J. mentioned that the mouse-strain was not genetically pure and raised the question of synergism between fractions.

H.R.B. The mouse was used merely as a biological tool, which must be sensitive (which it was). The particular strain was also non-sensitive to nicotine toxicity. As it was an in-bred, and not a pure, strain different batches were being calibrated using known doses of two pure carcinogens.

He reiterated that this was only one of a series of animal tests - others now being planned concerned rat lung, where Blacklock had found

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carcinomata. [E.J. disagreed with the diagnosis, but H.R.B. remained firm on this] and fresh smoke by inhalation.

E.J. was reasonably aware of all this. He did not question whether to do mouse skin work, but could the problem the industry faced be met by this work. He suggested different mouse strains would show different responses and was not clear what the comparison with rat lung would show. [He misunderstood the reference to measuring a reduction of 30% in biological activity and this was later corrected]. He thought extrapolation from animal tests to humans would be different because human epidemiological results did not support the idea of a dose-response curve. There was a straight-line relationship from one cigarette up.

He pointed out that now it was possible to alter cigarettes by filters, etc. and therefore suggested that whole smoke should be looked at. This could be done in a number of ways and he instanced inhalation - viral infection followed by synthetic smog had produced lung cancers (Kotin) and viral infection with cigarette smoke had produced abnormal proliferation of lung tissue which was nearly, but not quite, cancer (Leuchtenberger). Vorwald had given mice one exposure to beryllium followed by exposure to aerosols and had got carcinogenic changes. This work, he felt, had a bearing on Dean's epidemiological studies which suggested men carried a focus of cancer with them from early life.

D.G.F. referred to E.J.'s mention of synergism and suggested that this might be merely an indication of the inaccuracies of Wynder's work, which a refined study would eliminate.

E.J. stated that the U.S. view was that such synergism was real and not simply due to inaccuracy.

D.G.F. went on to refer to the I.R.C./M.R.C. Planning Committee experiment with Mexican tobaccos, pointing out that Harris would be attempting to expose mice to different smokes following viral infection. This was only one attempt at inhalation work. Other attempts were under investigation with the aim of studying sequential changes in the bronchi which could be related through the bridging experiment by intratracheal instillation work to that with fresh smoke on mouse skin.

H.R.B. said that only large numbers of mice would reveal the truth about the lower end of the dose-response curve and stressed that this was an essential preliminary to other work.

E.J. returned to the point that a dose-response curve with one species of mouse would not be extrapolatable to another species, nor to rat lung.

H.R.B. replied that it was only to be used as a measuring tool for following qualitative changes in particular fractions.

E.J. enquired what would be able to be done if it was found that polycyclic hydrocarbons were the most important fraction.

A brief general discussion ensued on Wynder's work on polycyclic hydrocarbons, summed up by H.R.B. saying that Wynder had found that

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biological activity was not accounted for by the known hydrocarbons present.

E.J. then referred to Wynder's search for precursors and his suggestion that these were in the leaf waxes. Several U.S. tobacco companies had considered extraction processes but Wynder then reported that a safe smoke could not be made in this way. There were three sorts of substances: promoters, co-carcinogens and anti-carcinogens - and the waxes were anti-carcinogens. He then mentioned Wright's work on fractionation.

D.G.F. and A.J.L. pointed out that Wright's combustion conditions using a large drum as a "pipe" were unrealistic in terms of cigarette smoke.

H.R.B. asked why E.J. thought there was no dose-response curve in human epidemiology.

E.J. instanced a lack of threshold as shown by a linear response and an absence of time interval.

G.F.I. said that Hammond and Horn's results, which gave a straight line, could easily be transformed into a sigmoid curve by small errors in reporting cigarette consumption, and Hammond had told G.F.I. this verbally. Dean had figures to refute Passey's ideas about an absence of time interval.

E.J. said that U.S. hospital figures confirmed Passey's ideas - the lung cancer peak was at 55-60 years. He would like Hammond to state his views publically.

G.W.M. noted that in human epidemiology, dose was expressed on a cigarette basis only and this neglected factors such as amount of cigarette smoked, size of puff and depth of inhalation, which were valid considerations. He suggested the mouse dose-response was statistically more correct than the human epidemiology.

H.C.I.R. The Chairman recapitulated. E.J. argued against T.R.C. on the grounds that T.R.C. may believe mouse painting to be the answer, whereas T.R.C. believed that the research was a long-term affair, for which a datum line was required. T.R.C. do not expect to have solved the problem at the end of Stage 1. From there, T.R.C. will go on to intra-tracheal instillation and inhalation and, if these are consistent, can claim to be nearer the truth. What else might be done?

E.J. did not intend to be critical of Harrogate as a scientific exercise. He questioned whether this was the way to tackle product research. The work at Harrogate was being done by extremely competent people - but he would suggest work should be done on altered cigarettes at an accelerated rate and he mentioned catalysts and filters. At present, T.R.C. cannot answer the charge that such things are not being done, which might give qualitative differences.

H.C.I.R. suggested this was a case where 300 different things - phenols, aldehydes, etc. - might be removed and how to decide which to do? It was trying to pick a winner without a form book. If one made a change in a cigarette one either did it because one knew it made the cigarette safer, or one was a rogue.

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E.J. suggested that there were a small number of groups of substances which could be taken out, on the basis of biological tests and mentioned phenols, which were both irritants and co-carcinogens and which inhibited cilia.

D.G.F. asked whether E.J. knew of a test, other than cilia, which suggested phenols were irritant to human lungs. E.J. was aware that T.R.C. were investigating these tests which would ultimately be installed at Harrogate.

D.S.F.H. said that broadly we would agree with E.J. but it was a matter of timing.

G.F.I. said T.R.C. recognised the need for "ad hoc" testing and would have adopted it if it had been thought a reasonable basis. It was felt that a systematic approach would be quicker in the long run than a series of guesses.

E.J. agreed with this if:

1. The cigarette was a direct carcinogen in humans
2. Effects with animals were comparable to those in man

Opinion in the U.S. was against this approach. More and more, people believed, with Kotin, in the theory of a non-specific irritant acting on a chain of multicausation.

H.R.B. pointed out that cigarette smoke condensate was undeniably carcinogenic to animals.

E.J. said this was consistent with the hypothesis, but that it was not the sole action and returned to the argument of testing differences in cigarettes.

I.D.D. was asked for his views, but preferred not to enter the discussion other than to correct a wrong impression E.J. had obtained at Harrogate. The mice at Harrogate were not a heterogeneous strain, but were very homogeneous. I.C.I. tested this from time to time by tissue transplantation. Although they were not pure brother-sister matings, the breeding was within the strain and would make the mice more homogeneous rather than less.

H.R.B. enquired how E.J. would evaluate "ad hoc" changes without animal tests.

E.J. suggested examining human ciliary activity. He then digressed to say that in the current climate of opinion in the U.S., the companies were at a disadvantage in that through T.I.R.C. they had entrusted their research to the S.A.B. As the members of S.A.B. were all eminent and independent scientists, it would be unseemly for the companies to come before S.A.B. and tell them what to do. Therefore the companies could not direct the research effort and this created problems.

D.G.F. recalled that the only biological work which T.I.R.C. had sponsored directly, to his knowledge, was the investigation of differences between pipe, cigar and cigarette tobaccos, smoked as cigarettes, and this had been done by injecting beneath the skin of mice, as a bioassay.

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E.J. did not deny this - he only said it was insufficient. He was unhappy that they had not set up an institution like Harrogate in the U.S.A.

A.J.L. asked what E.J. would suggest T.R.C. did.

E.J. said that, personally, he would like to see a correlated series of experiments on inhalation and skin painting in which a series of modified cigarettes was compared. This would be done on a systematic basis - blend changes, filtration changes using selective filters. He did not like this called "ad hoc" investigation. It was a systematic quartering of the ground. What he would look for would be qualitative changes which could then be followed quantitatively.

D.G.F. asked for clarification of "qualitative". Did he mean ciliary inhibition?

E.J. That, and the Leuchtenberger work on cellular proliferation.

D.G.F. pointed out that the Leuchtenbergers had found similar proliferation in the controls and had stated that they were unable to draw quantitative deductions because of this.

E.J. said this was not true in their latest work and at G.F.I.'s request outlined what he had learnt from them.

1. There were no proliferative changes in the lung in the absence of bronchitis.
2. Muhlbock has increased the yield of adenomata by the administration of hormones.
3. The Leuchtenbergers now want to look at different kinds of cigarettes, effects of trace metals, etc. and are seeking T.I.R.C. support. T.I.R.C. have been loath in the past to support work outside the U.S.A.
4. They have kept samples of all their old experimental material which can be surveyed when required.
5. In their exposure of mice to smoke in a chamber, they have shown by fluorescence microscopy the penetration of smoke deep into the bronchioles.

E.J. went on to say that in the U.S. they expected that the S.G.A.C. would attack smoking as a cause of cardiovascular disease, emphysema and bronchitis.

H.R.B. said that E.J.'s suggestions were already in the T.R.C. programme. Was he suggesting T.R.C. should drop mouse skin painting?

E.J. replied that he wasn't but that the bulk of the effort, expense and time of the T.R.C. programme was devoted to mouse skin work, and that T.R.C. could not be defended against a charge of negligence in not considering the other approach and in neglecting the new for the old.

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D.G.F. asked if E.J. was suggesting that T.R.C. should drop an existing programme to follow a new approach whenever one was raised. This would mean that nothing would ever be accomplished.

E.J. replied that he didn't mean to suggest this. He pointed out that Product Research in the U.S.A. would be considered as commercial and no Government permission would be granted for co-operation between companies on this basis.

D.G.F. said he understood such a clearance had, in fact, been granted by the Attorney General of the U.S. at the time of the inception of T.I.R.C.

E.J. denied this, as regards Product Research. It was only true with respect to the setting up of T.I.R.C. Product Research carried an element of competition and joint work on this would be in restraint of trade. He went on to say there were three groups of opinion in the U.S.

1. One group believed in industry unity
2. A second believed an area of product research was necessary
3. The C.C. Little approach - no-one has yet shown whole smoke is harmful and therefore the disease itself was a topic for research.

H.D.A. proposed the hypothesis that a highly-efficient filter had been created which was to be tested on an "ad hoc" basis. What criteria would E.J. apply for test - as a lawyer.

E.J. replied that tests based on inhalation would be required.

H.D.A. said that T.R.C. were en route to just such a test.

E.C.F. remarked that E.J.'s visit was badly timed. In twelve months, Harrogate would be twice the size and would be working on inhalation projects and "ad hoc" research on altered cigarettes.

E.J. said he didn't like the words "ad hoc". He would prefer T.R.C. to say "systematic".

G.F.I. said it appeared that in the U.S., the direct carcinogenic effect of smoke had been discarded. He had noted it first in statements by Mr. Allen of the Tobacco Institute and had thought it was a Public Relations position. It now appeared to be the scientific and legal attitude also.

E.J. replied that it started with an editorial in the Lancet in 1961 to which Berkson had replied. There had been a general reorientation of the protagonists' approach along the lines of multicausation.

G.F.I. wondered if the present T.R.C./T.I.R.C. schism was not directly attributable to the abandonment by T.I.R.C. of the theory of direct carcinogenesis.

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The meeting ended around 5.0 p.m. with H.C.I.R. and E.J. both expressing thanks for the stimulating, informative and helpful discussion of the different approaches.

General Comments

Personally, I do not think E.J.'s charges were justified in the light of the whole T.R.C. programme. He tended to concentrate on what was in progress at Harrogate and to neglect what is being started elsewhere and will be carried on at Harrogate in the future. This point was made to him over and over again (by H.C.I.R., E.C.F., H.R.B. and D.G.F.), but he returned again and again to "Product Research". His use of "systematic" instead of "ad hoc" for this type of work would appear to be word-juggling - the approach and the aims are the same in both cases.

I suspect that E.J. was unconvinced by the arguments at the end of the meeting, but he was left in no doubt that the T.R.C. programme is designed to cover the various aspects he raised and is being developed in this way.

No one suggested to him that it was a little illogical to criticise T.R.C. because Harrogate was not yet able to resolve the American difficulties, when the opposition to the establishment of such a centre, for which the need was now apparently felt in the U.S., came to a large extent from T.I.R.C.

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