

123

Exh 304

TSC 21

REPORT ON VISIT TO U.S.A. AND CANADA

17th APRIL - 12th MAY 1958

by

H. R. BENTLEY

D.G.I. FELTON

H. W. REID



105408490

BAT Co LTD - MINNESOTA TOBACCO LITIGATION

TIOK 0034790

ITINERARY

April 17th	American Tobacco Co., Richmond	Mr. H. R. Harner Dr. F. E. Harlan Mr. E. S. Harlow
" 18th	Medical College of Virginia, Richmond	Prof. P. S. Larson Prof. H. B. Haag
" 22nd	Duke University, Durham	Prof. F. Bernheim
" 23rd	Liggett & Myers, Durham	Dr. E. R. Darkie Dr. W. T. Patca
" 24th	Philip Morris, Richmond	Mr. A. E. O'Keefe Mr. R. D. Seligman
" 25th	A. D. Little, Inc. Cambridge.	Mr. U. W. Bass Dr. C. J. Kenalar
" 28th	T.I.R.C., New York.	Mr. E. T. Hoyt Mr. Carl Thomson (Hill & Knowlton)
" 29th-30th	Roswell Park Memorial Institute, Buffalo	Mr. F. G. Bock
" 29th	Yale University, New Haven	Dr. E. S. N. Greene
" 30th	Biological Research Institute, Inc., Cambridge.	Dr. F. Hoesburger
May 1st-2nd	Roscoe Jackson Laboratory, Bar Harbor	Dr. W. S. Murray Dr. Murphy Dr. Gwynn
" 5th	Industry Technical Committee of T.I.R.C., Richmond	Mr. H. R. Harner, Chairman Mr. W. T. Hoyt Dr. R. C. Hockett
" 6th	National Cancer Institute, Bethesda.	Dr. G. B. Nider Dr. M. J. Sbar Dr. E. B. Andervont Dr. W. C. Husper Dr. H. L. Stewart
" 7th	Johns Hopkins Hospital, Baltimore	Dr. George Gay
" 8th	New York University, New York.	Dr. A. Kosak
" 8th	T.I.R.C. New York.	Dr. C. C. Little Dr. R. C. Hockett
" 9th	Sloan-Kettering Institute, New York.	Dr. E. L. Wynder Dr. J. Spranger
" 10th	T.I.R.C., New York.	Scientific Advisory Board of T.I.R.C.
" 12th	Montreal	Dr. G. Wright (University of Toronto)

.....

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

TIOK 0034791

105408491

### INTRODUCTION

From our contacts in U.S.A. and Canada we sought information on the following :-

1. the extent to which it is accepted that cigarette smoke "causes" lung cancer,
  2. up to date evidence as to the carcinogenicity of smoke condensates to animal tissues,
  3. the extent to which extrapolation from animals to man is justified,
  4. the relative usefulness of different biological tests,
  5. the progress made towards identifying any active fraction in smoke condensates,
  6. the attitude of the tobacco industry in U.S.A. and Canada to biological research,
  7. the extent to which T.M.S.C. would be justified in doing biological research and the form which this should take,
- and
8. the practical methodology of biological testing.

In what follows a general discussion of these points is given together with a section on filtration and related problems and recommendations for action by T.M.S.C.

Detailed notes of the day-by-day discussions are available for further reading.

### "CAUSATION" OF LUNG CANCER

With one exception (H.S.N. Greene) the individuals whom we met believed that smoking causes lung cancer if by "causation" we mean any chain of events which leads finally to lung cancer and which involves smoking as an indispensable link. In the U.S.A. only Berkson, apparently, is now prepared to doubt the statistical evidence and his reasoning is nowhere thought to be sound. Hueper of the National Cancer Institute accepts that cigarette smoke is capable of causing lung cancer but believes that as compared with other environmental carcinogens the contribution of smoking to the total mortality from lung cancer is being greatly exaggerated.

There is no support for the view that in the same individual the tendency to smoke and to be susceptible to lung cancer are each independently an outward expression of some third unknown factor.

Greene of Yale still says that his repeated failure to produce carcinoma by implanting lung tissue along with tobacco smoke condensate into the muscles of mice is conclusive evidence that smoke cannot cause lung cancer. His experiments were not done quantitatively, however, and on these grounds alone the conclusion which he draws is certainly not justified.

We found disagreement however as to the likely mechanism by which smoking may cause lung cancer.

The S.A.B. of T.I.R.C. and the group we met at the National Cancer Institute, Bethesda, broadly take the view that causation is likely to be indirect. Several hypothetical means by which this could occur were proposed but with no experimental evidence to support any of them.

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

105408492

TIOK 0034792

Otherwise we found general acceptance of the view that the most likely means of causation is that tobacco smoke contains carcinogenic substances present in sufficient quantity to provide lung cancer when acting for a long time in a sensitive individual. It was argued that the only positive experimental evidence to date, using animal tissues sensitive to carcinogens, is at the very least entirely consistent with this view as is the fact that several known carcinogens have already been found to be present in smoke condensates. It is generally accepted that tobacco smoke is only feebly carcinogenic.

The main effort outside T.I.R.C. therefore has switched from trying to confirm the direct causal hypothesis to trying to find biological test systems which will allow active substances in smoke to be identified.

#### CARCINOGENICITY OF SMOKE TO ANIMALS

No possible doubt now remains that Wynder's results using mouse skin painting are entirely genuine. Using whole smoke condensate and fractions separated from it Bock at Buffalo, Kensler at A.D. Little and Kosak and Nelson, New York University, have each independently confirmed Wynder's earlier work qualitatively. Quantitatively there remain differences in the level of activity detected in smoke but this is not thought to detract from the general value of the results.

We must conclude therefore that the failure of workers in the U.K. to reproduce Wynder's results is due to faulty technique or the use of much lower dose levels.

#### EXTRAPOLATION FROM ANIMAL TESTS TO MAN

Without exception no single individual whom we met was prepared to extrapolate unambiguously from any single animal test to man. At the same time there was general agreement that in the field of smoking and lung cancer no biological test wholly free from criticism is available at the present time or is likely to become available in the foreseeable future.

Those individuals and groups engaged in biological testing whom we met (Wynder, Bock, Liggett & Myers - A.D. Little, Homburger, Roscoe Jackson Laboratory) justify their animal research programmes roughly on the following lines :-

1. The human epidemiological data add up to a reasonably convincing case that tobacco smoke is weakly carcinogenic to the human lung.
2. In dealing experimentally with a material possessing biological activity a biological screening test is essential; in the absence of this, purely chemical work is meaningless.
3. Although it undoubtedly differs in detail the mechanism of carcinogenesis is likely to be basically similar for all tissues in all animals.
4. For study of tobacco smoke it is therefore justifiable to use any animal tissue which will give cancers and for practical purposes to choose the most sensitive tissue or animal available. Rapid screening tests which stop short of cancer (e.g. sebaceous glands) are justified if they correlate closely with tests producing cancers but in the end they must be confirmed by full scale tests producing cancers.

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

TIOK 0034793

105408493

5. Dose-response relationships can be established in animals which parallel those deduced from human epidemiology and therefore it is justifiable to base practical remedial measures on these relationships.
6. If two or more animal tests can be shown to correlate closely, the case for extrapolation to man may be strengthened. Dr. C.C. Little agreed with this with the reservation that the tests which are shown to correlate should have been done on widely different species.
7. The use of animals as a screening medium for man has proved its practical value over a very long time in the fields of pathology, pharmacology and cancer and unless strong evidence to the contrary were to be discovered it is reasonable to believe that this will hold for smoking and health.

Each of these points can be criticised in detail but in the absence of anything better we found no individual prepared to dissent strongly from the general line of argument.

#### CHOICE OF A BIOLOGICAL TEST

Skin painting with mice combined with sebaceous gland suppression as a screening test has given consistently useful results in hands of Wynder, Kensler and Bock. Kensler claims that a negative sebaceous gland reaction is unambiguous, false positives are occasionally found. Wynder confirmed this for polycyclic hydrocarbons and cigarette smoke fractions. Bock has observed an occasional false negative but with substances which are not polycyclic hydrocarbons. Kensler has found rabbit skin more sensitive than mouse skin for some fractions; isolated rabbit intestine *in vitro* is a useful screening test. According to Hockett Pomerat has found that cigarette smoke condensate induces suggestive changes in kitten or human lung tissue cultured *in vitro* but the general opinion of tissue culture methods was that they are unlikely to be useful for some considerable time, if at all. Eshburger hopes to be able to produce tumours by subcutaneous injection of smoke fractions; this is capable of being made quantitative much more easily than skin painting but whole smoke condensate is too toxic. Gwynn at the Roscoe Jackson Laboratory has confirmed the usefulness of sebaceous gland suppression and is working on a possible chemical method for detecting early changes in skin.

#### RESULTS OF SCREENING TESTS ON SMOKE FRACTIONS

One of the main objectives of the visit was to discover whether there were any experimental grounds for believing that cigarette smoke condensate contains only one principal carcinogen which is quantitatively responsible for a large proportion of the biological activity as measured by animal tests (a "super carcinogen" in Wright's terminology).

On the evidence available to date in U.S.A. and Canada this is most unlikely to be so.

Liggett & Myers have so far found that the biological activity of whole smoke is distributed between four different fractions of it.

Bock has found that the specific activity of smoke neutral fraction accompanies the polycyclic hydrocarbon sub-fraction and increases as this is purified. However, the specific activity is much greater than can be attributed to the known amounts of these

105403494

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

TIOK 0034794

carcinogenic hydrocarbons reported by Neukam and Bonnet. Further fractionation at first leads to a splitting of the activity but beyond a certain point the activity of these sub-fractions disappeared and was not regained on recombination.

Wright, working with Wynder, agrees that whereas a fraction rich in polycyclic hydrocarbons can be isolated which is highly active, this activity disappears when the fraction is further subdivided.

The prospects of our being able to identify a single active carcinogen, quantitatively responsible for the activity of smoke condensate in animals, are therefore remote.

Wynder remains convinced that the biological activity of smoke condensate resides principally in a small group of mixed polycyclic hydrocarbons (his "1.5%" fraction) in which several new compounds have been identified; these are being tested separately for carcinogenicity. Benzopyrene is a useful index of the concentration of this fraction and although the amount of benzopyrene itself in the fraction is too small to account for more than one-thirtieth of its activity any method which will reduce the amount of benzopyrene will also reduce the amounts of the other more active polycyclics which are formed along with benzopyrene. Wright does not agree with this view.

#### ATTITUDE OF U.S. INDUSTRY TO BIOLOGICAL TESTING

Liggett & Myers stayed out of T.I.R.C. originally because they doubted the sincerity of T.I.R.C. motives and believed that the organization was too unwieldy to work efficiently. They remain convinced that their misgivings were justified. In their opinion T.I.R.C. has done little if anything constructive, the constantly re-iterated "not proven" statements in the face of mounting contrary evidence has thoroughly discredited T.I.R.C., and the S.A.B. of T.I.R.C. is supporting almost without exception projects which are not related directly to smoking and lung cancer. Liggetts felt that the problem was sufficiently serious to justify large-scale investment by the Company directly in experimental research on smoke and cancer, accepting privately that a strong case against tobacco had been made out and avoiding any public comment until their own research had provided something concrete to offer.

After consulting the A.D. Little Organisation and others they concluded that access to biological testing facilities was essential and the outcome of this was the collaborative project with A.D. Little. We were told that Liggetts have already invested considerably more in this work than the combined donations of the rest of the industry to T.I.R.C. The object is to eliminate or reduce considerably the carcinogenicity of cigarette smoke as revealed by a series of animal tests and the results to date are considered to justify the investment. If anything useful finally comes to light Liggetts will publish only after they have first secured full commercial advantage for themselves, including patent protection if appropriate. Their daily production of about 150 g. of smoke fractions for testing is an index of the considerable scale on which Liggetts are operating.

It was clear from talks we had that, probably, member companies of T.I.R.C. had all at one time or another considered using biological testing in conjunction with chemical fractionation. Hammer of A.T.Co. had prepared a comprehensive scheme for biological research several years ago but action on this had been deferred. We were told that Phillip Morris were now considering a biological research project and we discovered that Lorillard have retained Wynder as a consultant and are collaborating with him.

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

105408495

TIOK 0034795

Hoyt told us that he did not know whether or not individual member companies of T.I.R.C. were doing biological research. He said it was generally assumed by scientists outside the industry that in fact the tobacco companies were doing this sort of work and that these scientists would be shocked if they thought that this was not so. At the meeting of the I.T.C. of T.I.R.C. which we attended we were unable to obtain any first hand information as to whether or not individual companies were engaged in biological research. It is probably safe to assume that at least A.T.Co. are not involved although they do support a considerable amount of biological research by Larson at Medical College of Virginia which is not related to lung cancer.

It is perhaps significant of the trend of thought in T.I.R.C. that we were told by Hockett that, in addition to work supported by grants which can be freely published the S.A.B. is now considering contracting out biological work on a commercial basis. This at first would be exploratory work on quantitative carcinogenicity but the change of principle is that for the first time the line of research and publication policy would be completely in the hands of the S.A.B.

#### T.M.S.C. POLICY ON BIOLOGICAL RESEARCH

We tried to confine discussion of this problem to the area of attempting to decide on purely scientific grounds what was possible or desirable in the present state of knowledge. Inevitably, however, policy and public relations considerations obtruded to some extent.

There was general agreement that on purely scientific grounds T.M.S.C. would be fully justified in extending its research activities into the fields of biology and animal experimentation. Since the whole subject of smoking and health is biological it seemed to the majority of our contacts to be axiomatic that the tobacco industry should have biological facilities at its disposal.

Opinions differed considerably, however, as to what type and scale of biological work would be most profitable and as to whether or not anything of immediate practical value to the industry could be expected to result from it.

The majority of individuals whom we met accepted that beyond all reasonable doubt cigarette smoke most probably acts as a direct though very weak carcinogen on the human lung. The opinion was given that in view of its chemical composition it would indeed be surprising if cigarette smoke were not carcinogenic. This undoubtedly represents the majority but by no means the unanimous opinion of scientists in U.S.A. These individuals advised us that although it is not possible to predict unambiguously the effect of any substance on man from its effect on experimental animals the generally successful use of animals in other fields as a model for man fully justifies their use in our problem. These workers do not recognise any need to face the extrapolation problem at the outset of this sort of research. They reason that the first essential is to discover what substances in cigarette smoke are quantitatively capable of causing cancer in animals and whether it is possible to modify cigarettes to make the smoke harmless to test animal tissues. Only later on, if this proves to be possible, would it become necessary to decide whether the evidence from animal tests justifies extrapolation to human lung cancer. In the meantime the greater the number of groups working in this field the faster can progress be expected to be made. This provides all the justification needed for T.M.S.C. to embark on such work.

Others, including the S.A.B. of T.I.R.C. and a group at the National Cancer Institute, do not accept that a case has yet been

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

TIOK 0034796

made that tobacco smoke is directly carcinogenic to the human lung. While accepting broadly that cigarette smoking may be said to be capable of "causing" lung cancer they argue that the evidence favours some indirect mechanism of causation. If this is so, of course, cancers produced by skin painting, and even more so, cell changes produced by short-term screening tests are misleading artefacts. Unfortunately so long as the basic problems underlying the transformation of a normal to a cancerous cell remain unsolved, theories of indirect causation must be largely speculative and almost without exception incapable of being tested experimentally. The advice we had from this group, which includes Dr. Little, was that T.M.S.C. should concern itself less with direct testing of cigarette smoke on animals than with fundamental work on carcinogenesis. An idea which we frequently encountered was that of an institute financed say by T.M.S.C. which would support a number of dedicated individuals of proved calibre who would devote their time to long range basic research on cancer without being distracted by administrative duties or financial worries. No short or medium-term solution to the problems facing the industry could be expected from such an institute, which would necessarily have to have no strings attached, but very long-term beneficial results might be expected.

The group at the National Cancer Institute despite their lack of conviction of a direct causal relationship nevertheless advised that the tobacco industry must concern itself permanently with the problem of the biological effects of smoking.

Finally our attention was drawn to some of the very real policy and public relations problems which might arise if the industry was seen to be engaged in biological testing. In the U.S.A. medical opinion on the likely role of smoking in the causation of lung cancer has not become consolidated to anything like the extent to which it has in the U.K. and T.I.R.C. is very much concerned not to encourage any such consolidation or to do anything which might reduce any further its degree of freedom to criticise and comment. For this reason alone it is improbable that T.I.R.C. would engage overtly in biological research with tobacco smoke.

Some of our colleagues in T.I.R.C. did, however, make the point that official opinion in the U.K. being what it is, with direct causation regarded as fully proven, the situation for the U.K. industry could hardly be made worse by T.M.S.C. engaging in biological research provided we were satisfied on purely scientific grounds that on balance such work could be expected to be useful to the industry.

#### METHODOLOGY OF BIOLOGICAL TESTING

We were given first hand information on the purely practical problems of animal work by the Roscoe Jackson Laboratory, the A.D. Little Organisation, F. Homburger and Wynder.

For a unit to carry out skin painting with mice and supporting short-term tests, estimates of the likely cost ranged from £10,000 to £100,000 per annum. £10,000 p.a. is Wynder's estimate for a unit like his own which has the minimum of essential facilities, certainly no "trimmings", and which is conveniently housed in converted old property near the Sloan-Kettering Institute. £100,000 p.a. was the maximum figure quoted by A.D. Little for a large-scale unit like their own which is lavishly housed and staffed within the A.D. Little laboratories.

We were advised by the Roscoe Jackson laboratory not to try to set up an animal breeding unit. Pure strain mice are shipped from Bar Harbor all over the world and, given adequate notice, they see no difficulty in supplying us with any number of mice at a cost of £0.70

105408497

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

TIOK 0034797



each plus cost of air transport. They estimate that this would be considerably less than the cost to us of breeding our own animals and ensuring purity of strain.

If necessary T.M.S.C. could contract out any necessary biological testing on a confidential commercial basis in U.S.A. Homburger of the Biological Research Institute Inc., Cambridge, is already doing this sort of work for European sponsors and agreed to send for our consideration a draft proposal giving some idea of the likely cost of a suitable project.

#### FILTRATION AND RELATED PROBLEMS

Research on smoking and health during the last few years has certainly convinced the majority of scientific opinion in U.S.A. that cigarette smoke is capable of causing lung cancer in man, without defining exactly what is meant by "causation" except that cigarette smoke itself is an indispensable link in the chain of events leading to cancer. It is also generally accepted that the carcinogenic effect of cigarette smoke, fortunately, is very weak and the overall effect on man therefore marginal. Wynder and many others, therefore, take the view that a practical remedy is to hand pending discovery of exactly what the mechanism of "causation" may be, which may not in any case be possible in the present state of knowledge of cancer.

The view is that since propaganda against the smoking habit is unlikely to be effective, practicable means should be found of reducing the overall amount of smoke produced per unit weight of cigarette. Wynder said if cigarettes can be altered so that on average the smoker absorbs 50% less smoke per cigarette than he did say five years ago then a significant reduction of lung cancer mortality will become apparent in U.S.A. within the next two decades.

Although T.I.R.C. officially still takes the view that "causation" is not proven, in practice the industry in U.S.A. has found here a good deal of common ground with the opposition. Unfortunately, however, this has taken the form of a highly undesirable competitive scramble for a cigarette with the smallest amount of smoke consistent with good flavour ("maximum filtration for the smoothest smoke") and advertising with implied health claims is in full cry.

If any form of "causation", direct or indirect is accepted then the Wynder argument makes sense. There is a good case for the U.K. industry collectively, through T.M.S.C., starting a programme of research to discover to what extent the overall production of smoke per unit weight of tobacco is influenced by such factors as chemical composition and physical properties of leaf, and to discover the most acceptable means by which the amount of smoke from a cigarette can be reduced (consistent with good flavour) by chemical or physical treatment of the leaf during manufacture or by means of a filter plug.

#### CONCLUSIONS

1. Although there remains some doubt as to the proportion of the total lung cancer mortality which can fairly be attributed to smoking, scientific opinion in U.S.A. does not now seriously doubt that the statistical correlation is real and reflects a cause and effect relationship.
2. There remains an area for debate as to what is meant by "causation". Opinion differs as to

BAT CO LTD - MINNESOTA TOBACCO LITIGATION

105408498

TIOK 0034798

whether or not cigarette smoke is likely to exert its effect by direct action on the lung. An indirect mechanism of causation is thought by some to be more likely.

3. The direct carcinogenicity of smoke condensate to animal tissue, which is consistent with direct causation, is now fully confirmed but the evidence so far obtained makes it unlikely that this activity is due to any single "super carcinogen" in smoke.
4. We were advised unanimously that on scientific grounds T.M.S.C. would be fully justified in carrying out biological research. Advice on the form which such research should take, however, was fairly evenly divided between
  - (a) research with tobacco smoke, related directly to smoking and lung cancer, and
  - (b) long range research on carcinogenesis in an industry-endowed institution, with no strings attached.
5. The U.S. tobacco industry has accepted, *de facto* if not *de jure*, the opinion of Wynder and others that a reduction of overall production of smoke per unit weight of cigarette is a useful step. We do not think that the way this situation is now being exploited commercially in U.S.A. is a useful model for the U.K. manufacturers represented on T.M.S.C.

We recommend :-

1. that early consideration be given to research by T.M.S.C. on the factors influencing and means of controlling the overall production of smoke per unit weight of a cigarette.
2. that consideration be given to direct research by T.M.S.C. in the biological field. This should at first have the limited aim of trying to show whether or not it is possible to alter the carcinogenicity of cigarette smoke condensate for animals.

It is impossible to predict whether or not research on these lines is likely to produce results of commercial value to the industry. We think, however, that, if T.M.S.C. is to contribute directly to work on smoking and lung cancer, there is no real alternative.

We do not recommend consideration of the alternative favoured by some of our contacts in U.S.A. on the grounds that there is hardly room in the U.K. for yet another institution to join B.I.C.C., M.R.O., Chester Beatty and others in fundamental cancer research.

11th June, 195E

BAT Co LTD - MINNESOTA TOBACCO LITIGATION

105408499  
TIOK 0034799