

Private and Confidential.

Research & Development Establishment,  
British-American Tobacco Co.Ltd.,  
Southampton.

16th July, 1958.

7th INTERNATIONAL CANCER CONGRESS

LONDON, 6-12th JULY, 1958.

The Congress was attended on two days only, 7th July and 11th July, when papers were presented, concerned particularly with the problems of Smoking and Health.

Monday, 7th July.

Dr. Neukomm (Lausanne) read a paper in which he described his rapid test using the newt. He is now in contact with Bock (Buffalo) and has studied the same hydrocarbons used by the latter in his assessment of the value of the sebaceous gland suppression test as a rapid indicator of potential carcinogenic properties. With three exceptions, the newt test and the sebaceous gland test yield identical results. The exceptions were 7,12-dimethylbenz[a]anthracene and 12-methylbenz[a]anthracene which Bock found to be strongly positive but which Neukomm found to be negative. One hydrocarbon gave a positive newt test but failed to suppress sebaceous gland formation in Bock's test.

In the afternoon there was a group of papers directly related to the biological effect of cigarette smoke and smoke fractions. Lyons (Glasgow) described studies of the unstable components (free radicals) of cigarette smoke. Using electron magnetic resonance, he showed that whole smoke tar contained  $10^{15}$  free electrons per gram and that on fractionation these were distributed as follows:-

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Whole tar	100%
Residue after water extraction	80%
Residue after extraction with dilute acid	43%
Residue after extraction with alkali	50%
Residue after extraction with dilute acid and then with dilute alkali	28%

Separation by Chromatography

Whole tar	100%
Hexane fraction	0%
Benzene fraction	35%
Acetone fraction	50%

He also described the investigation of cigarette smoke using diphenylpicrylhydrazyl as a stable free radical reagent. This showed that the water soluble reactive material constituted 60% of the whole reactive material. The discrepancy between the two methods was not explained, however.

Kosak (N.Y.U.) gave a rather pedestrian account of some of his fractionation of cigarette smoke condensate from American blended cigarettes. He has now isolated squalene and 1:8-p-menthadiene. The latter compound, also known as dipentene or limonene, is a major constituent of oil of lemon, and has a characteristic lemon smell. It may be an important flavour component of smoke. (its isolation from smoke by Clono had earlier been communicated privately by

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I.T. Co. Research Department). Other compounds isolated by Kosak included diethyl ketone, diacetyl, benzene, toluene, ethyl acetate, phenol and ethanol.

Royer et al (Paris) described their work on the inhibition of benzpyrene formation by the use of ammonium sulphamate and of oxidising reagents.

Neukomm and Bonnet (Lausanne) described their procedure for the chemical fractionation of smoke from Maryland cigarettes without producing any really fresh evidence of carcinogenic fractions. They had found that brown polymeric substances in the acidic and alkaline fractions produced tumours when mice were treated with them. The incidence of tumours was said to be greater than that of control animals (10% in 15 months as against 10% in 22 months in the controls), but serious doubt was cast on the statistical significance of this in the discussion.

Kotin (Los Angeles) gave an account of the work which he and Falk had carried out on the effect of artificial smog, produced by ozonolysis of gasoline vapour, on the mammalian lung. He also described the elution hypothesis and experiments on the dissolution of hydrocarbons, adsorbed on carbon particles, in plasma solution. The effect of smog in paralysing cilia in the bronchus and oesophagus was also mentioned and the consequent epithelial denudation was illustrated by photomicrographs.

Leuchtenberger (Cleveland) described her work on the causation of bronchitic conditions in the lungs of mice exposed to cigarette

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smoke. These changes in the lungs became progressively worse with increase in exposure and resembled "carcinoma in situ" as described by Auerbach. When exposure was terminated, however, the tissues in time reverted to normal. Consequently, the state of carcinoma in situ, as described histologically here, is not a true premalignant state, although Leuchtenberger did not stress this.

Cowdray (St.Louis) described histological changes in the bronchus leading to squamous cell metaplasia in human smokers. The reason for the localisation of these lesions in the bronchus was ascribed to smoke settling out in those parts of the bronchial tree where eddies are most likely to occur. The smaller passages of the alveoli are less likely to be sites than are the bronchial branches.

Friday Morning, 11th July

This was occupied by a discussion of the Aetiology of Cancer of the Lung.

Dr. W.C. Hueper (Bethesda) made a strong case for the primary implication of atmospheric pollution by metals and asbestos and discounted the effect of cigarette smoking, especially in the ensuing discussion.

Doll (M.R.C. London) was concerned to answer alternative explanations of the connection between smoking and lung cancer and to claim that the statistical connection was one of primary cause and effect. He still maintained that there was no difference between those who inhaled and those who did not, although pipe and especially cigar smokers show little statistical association.

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Wynder (Sloan-Kettering, New York) who followed, presented evidence that, if anything, pipe and cigar smoke was more carcinogenic to mice. He accepted Lindsay's figures that the polycyclic hydrocarbon content, especially of benzopyrene, was higher in pipe and cigar smoke. No one pointed to the obvious discrepancy between this and the statistical figures for pipe and cigar smokers, which if inhalation is not a factor, become incompatible. Wynder followed his usual theme - there is a threshold for biological activity and a reduction of 40-50% in the tar intake would reduce the dosage below threshold. For this purpose he suggests the use of cigarette filters and less tar. He also mentioned the possible use of catalysts and perhaps the use of metals such as aluminium to reduce the combustion temperature below the critical 800-850°. In the latter connection, he said that it seemed as if the latter possibility was a very frail one. (Perhaps he has checked Mrs. Lawrence's cigarettes). In the discussion following, he was challenged by Doll as to the meaning he attached to threshold dose, Doll pointing out that there was a finite risk even for light smokers. Wynder wriggled a little at this and said he used threshold "in quotes". He called attention to a Russian cigarette he had been given, two thirds of which was filter, and said this was a step in the right direction.

Waller (London) closed the session with a paper on the possible effect of air pollution as an aetiological factor in lung cancer.

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He interpreted tables of mortality statistics for a series of towns in England and Wales in terms of the population coming into equilibrium with a new factor eg. smoking. Contrary to Stocks and to Hueper, Waller feels that air pollution due to urbanisation is a very minor factor and put the cause fairly and squarely onto smoking.

The discussion afforded a number of people the opportunity to call attention to their own work, in particular Neukomm, an Italian professor and a Cuban giving fairly lengthy accounts which tended to reiterate the usual charges.

Persons Contacted.

(a) Neukomm and Bonnet. Mr. Anderson had earlier written to Dr. Neukomm, inviting him and Dr. Bonnet to R. & D.E., Southampton. Neukomm, at first, thought that we wished to consult him on a particular matter, but was told it was merely reciprocal hospitality and an opportunity to show him some of our work. There were difficulties, however, in that Neukomm and Bonnet wished to attend all the Congress and were then leaving at once for Brussels. In the circumstances, and in view of difficulties in visiting I.T.Co. Bristol, where Dr. Bentley was now in hospital, Neukomm and Bonnet asked to be allowed to postpone their visit until the early autumn (latter half September, beginning of October) when they would again be visiting the U.K. Their suggestion was accepted and it was left that they would contact us nearer the time and arrange a date.

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(b) Dr. Hans Falk. Dr. Kotin introduced Dr. Falk, who is the Chemist working with Kotin on the smog production and on the inhibition of ciliary action by smog and cigarette smoke. Kotin had already explained something of this work without going into detail.

In the course of two fairly extensive discussions with Falk, the procedure for the evaluation of the activity of particular constituents of cigarette smoke was explained. Clearly it is not feasible to fractionate cigarette smoke chemically and still apply it to isolated frog oesophagus preparations as an aerosol. The technique adopted has been to survey the known constituents of smoke and to divide the spectrum into arbitrary classifications depending on the amounts found. The major component or components of each class are then applied to the preparation as an aerosol of the pure compound and the inhibitory or stimulatory effect noted. As yet, no effort has been made to elucidate any synergism which may occur through two or more compounds acting together and, clearly, in some cases, chemical interaction may take place between two components. These effects, which will take some disentangling, will be studied in the future.

Falk provided the following list of results to date. In view of Kotin's reluctance to say anything to the I.M.S.C. Sub-Committee about stimulation of ciliary activity, some results are of considerable interest. The results are classified into stimulatory effects (+) inhibitory effects (-) and no effect (0) and are reported for

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- a) 1 minute exposure
- b) 60 minutes exposure
- c) chronic effect, showing a trend of activity.

They are as follows:-

	<u>1 minute</u> <u>exposure</u>	<u>60 minutes</u> <u>exposure</u>	<u>Chronic trend</u>
	+ = stimulation of ciliary action		
	- = inhibition of ciliary action		
	0 = no effect		
Acetyl peroxide	-	(+)	(+)
Paracetic acid	-	(-)	(-)
Pyridine	-	0	+
Formaldehyde	-	-	-
Acetaldehyde	+	-	±
Acetone	+	0	-
<u>iso</u> Butyraldehyde	0	+	(+)
<u>n</u> -Butyraldehyde	+	+	+
Propionaldehyde	0	0	(+)
Methyl bromide	-	+	+
Methyl chloride	-	(+)	0
Butadiene	-	+	+
Carbon monoxide	-	+	(+)
Propylene oxide	-	+	-
Bromoform	-	0	(+)
Methylamine	-	0	0
Trimethylamine	-	0	0
Propylene	0	(+)	0
Thiocyanic acid	0	+	0
Acetic acid	-	0	0
Formic acid	-	0	(-)

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	<u>1 minute exposure</u>	<u>60 minutes exposure</u>	<u>Chronic Trend</u>
2-methylbut-2-ene	0	+	(+)
2-methylpentane	0	0	0
2-methylpent-2-ene	0	(+)	0
Carbon tetrachloride	-	(+)	(+)
Methylene dichloride	(-)	(+)	0
Cyclohexene oxide	-	0	(-)
Ammonium hydroxide	-	+	0
Methane thiol (methyl mercaptan)	-	-	0
Methanol	(-)	(+)	+
Ethanol	-	+	+
Acetonitrile (methyl cyanide)	-	+	0
Phenol	-	+	0

As a number of these compounds are gaseous, they are not removed by a cigarette filter, even of the Cambridge absolute filter type. Falk stated that the activity of whole cigarette smoke was diminished by filtration to some extent, but was unable to give any quantitative measure of this, nor of its relation to filtration efficiency of the filter.

Dr. Falk was invited to Southampton, but was unable to find a suitable day during the Congress. It was learned later that he visited I.T.Co. (Bristol) on Wednesday, 9th July.

#### Scientific Exhibition

Drs. Kotin and Falk had an exhibit along the lines of the paper read by Kotin and of the discussion at the T.S.C. meeting. Blacklock showed photographs illustrating his technique of thoracotomy and

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inoculation of benzpyrene, methylcholanthrene or cigarette smoke condensate. One carcinoma and one sarcoma from eight rats treated with cigarette smoke condensate have resulted. KreybEing (Oslo) had illustrations of histological preparations implicating cigarette smoking as a factor in lung cancer.

An exhibit unrelated to lung cancer but which was of some interest was that by the Oppenheimers and their collaborators (Columbia U. N.Y.) on carcinogenesis by Polymer films. Implantation of plastic films of many kinds into rodents, have produced carcinomata. That this is due solely to the physical nature of the film follows from the lower tumour incidence when perforated or woven membranes or sponges of the polymers are used, and from the virtual absence of tumours when the same materials in powder form are embedded. The possibility that carcinogenesis is due to residual free radicals in the polymer structure seems to be thereby disproved.

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