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TOBACCO AND HEALTH-R&D APPROACH

Presentation to R & D Committee
by Dr. H. Wakeham
at meeting held in New York Office
on
November 15, 1961

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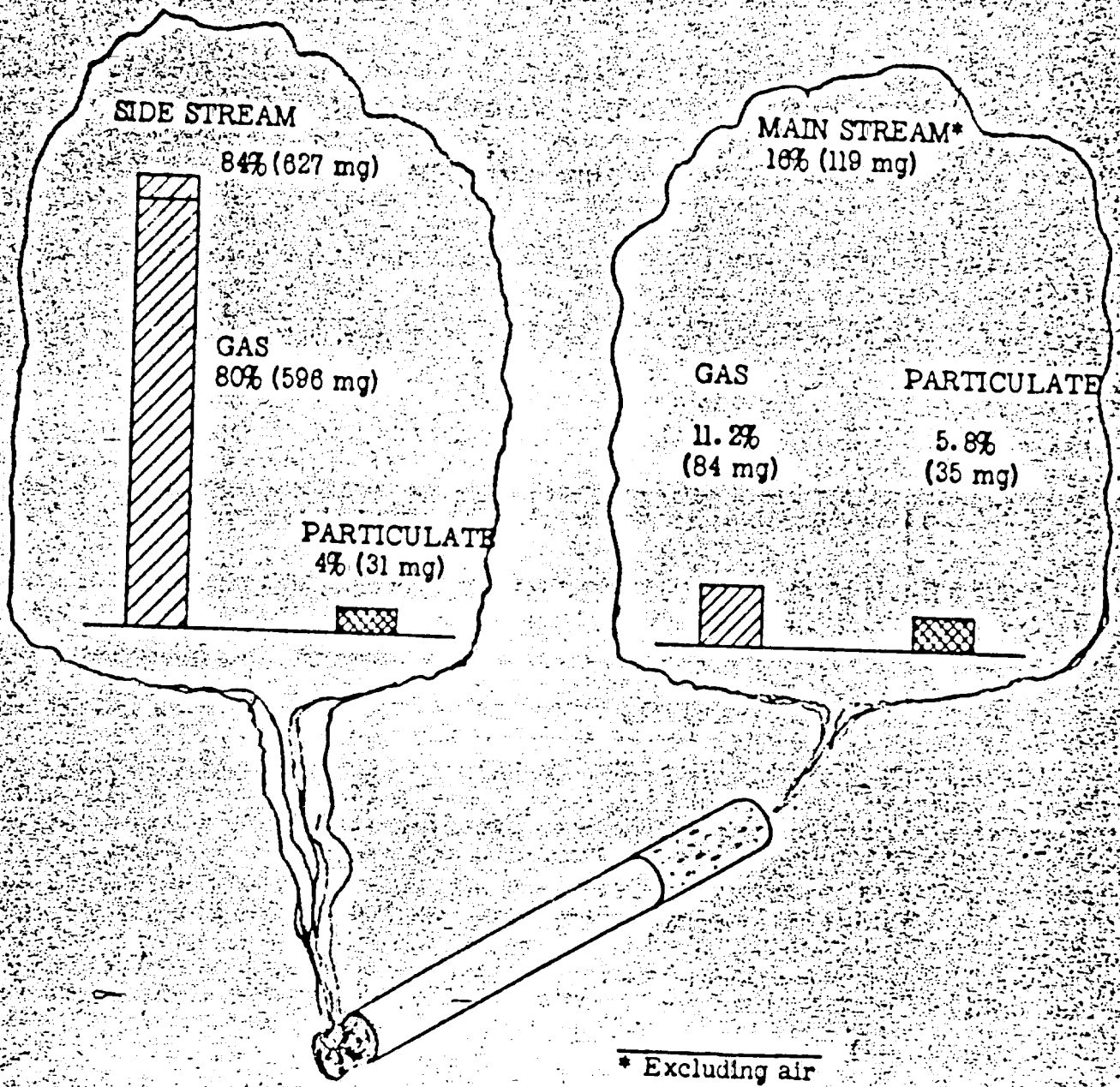
TOBACCO AND HEALTH - R & D APPROACH

CHEMISTRY OF CIGARETTE SMOKE



* Excluding air

Total of more than 400 compounds of which about 50 have been identified for the first time by the Philip Morris Research Center.

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COMPOSITION OF MAINSTREAM SMOKE

GAS PHASE		PARTICULATE PHASE	
Air	444 mg.	Water	5 mg.
Carbon dioxide	55	Bases	4
Carbon monoxide	10	Humectants	3
Water	11	Hydrocarbons	1
Nitrogen oxides	0.03	Carbonyls	1
Ammonia	Trace	Organic Acids	2
Organic vapors	"	Phenols	0.3
		Esters	Trace
Isoprene	1.4		
Methyl chloride	0.7	+ 15 - 20 mg. of substances not quantitatively established	
Hexenes	0.4		
Acetone	0.6		
Methanol	0.7		
Ethane	0.7		
Pentenes	0.6		
Methyl furan	0.2		
Toluene	0.2		
Benzene	0.1		
Acetaldehyde	1.0		

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MAJOR CONSTITUENTS OF MAINSTREAM PARTICULATE PHASE

ACIDS

Acetic	0.8 mg.
Lactic	0.3
Succinic	0.2
Propionic	0.2
Formic	0.1
Butyric	0.1
2-Aminobutyric	0.1
Glutamic	0.1
Malonic	0.1
Malic	0.05
Oxalic	0.05
Valeric	0.05

BASES

Nicotine	1-2 mg.
Anabasine	Trace
Nornicotine	"
Myosmine	"
Nicotyrine	"
Nornicotyrine	"
Anatabine	"

CARBONYL COMPOUNDS

Biacetyl (butanedione)	0.2 mg.
Butyraldehyde	0.3
Diethyl ketone	0.2
Glyoxal	0.2
Furfural	0.1
Hydroxy methyl furfural	-
Methyl furfural	-
Pyridyl ketones	-

HYDROCARBONS

Paraffin Waxes	0.3 mg.
Neophytadrene	0.2
Toluene	0.1
Dipentene (d-limonene)	0.1
Xylenes	Trace
Ethyl toluenes	-
Naphthalene	-
Anthracene	-

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FLAVOR AND IRRITATION STUDIES

Independent Evaluations at Cigarette Smoke Concentrations

	Flavor Intensity 0 - 10	Irritation Intensity 0 - 10
Acrolein	3.7	4.1
Acetone	2.0	0.7
Diacetyl	5.2	2.4
Diethyl Ketone	4.7	1.7
Furan	6.0	0.9
Isoprene	4.7	1.8
Methanol	0.8	0.5
Methyl Acetate	1.1	0.2
Propyne (acetylene)	5.1	3.5

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THE CANCER CONTROVERSY

Some Definitions

CARCINOMA - a malignant growth arising from epithelial tissue (skin, gastric or intestinal mucosa, lungs, etc.)

SARCOMA - a malignant growth arising from connective or muscle tissues (muscles, blood vessels, cartilage, bone, lymph, etc.)

CARCINOGEN - a substance which applied to the tissue of a test animal gives rise to tumor formation. In tests for carcinogens it is assumed that tumors ultimately lead to cancerous growths and that a carcinogen so demonstrated in test animals is dangerous to man.

TUMOR PROMOTER - a substance which by itself does not show carcinogenic activity but which applied before or concurrently with a carcinogen enhances the effect of the latter.

ANTICARCINOGEN - a substance which inhibits the normal activity of a carcinogen in a test animal.

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EVIDENCE LINKING CANCER AND TOBACCO

Based on two main points

1. Statistical evidence that certain diseases are more prevalent among smokers than non-smokers.

   Lung cancer
   Bladder cancer
   Cardiovascular diseases

   These associations suggest that smoking may be a causative factor.

2. Physiological tests in which animals treated with smoke condensates, extracts, or compounds therefrom, suffer from increased tumor frequency. Most tests involve skin painting or injections on special strains of mice. Smoke inhalation experiments have failed to produce lung cancer.

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THE PROBLEM OF CARCINOGEN IDENTIFICATION

1. Many factors need to be considered in studying carcinogenesis.

   J. P. Greenstein, Biochemistry of Cancer - "The carcinogenic potency of an agent does not reside in the nature of the agent alone but is a function of the following factors:

   (a) The dosage, the nature of the vehicle, the mode and length of time of administration of the agent;

   (b) The strain, the species, the sex, and the age of the test animals;

   (c) The site of application, the presence of concomitant factors such as the level of essential dietary constituents and the number of animals kept in a cage."

2. One in five of all randomly performed chronic toxicity tests reveals the presence of a carcinogen.

   Hartwell, Survey of Compounds Which Have Been Tested for Carcinogenic Activity, U. S. Public Health Service - About one-half (83) of the new carcinogens belongs to five chemical classes as follows:

Class	New Compounds	Carcinogens
Aliphatic Carbamates	16	15
Tricyclic Aminofluorenes	14	12
Tetracyclic Cyclopentenophenanthrenes	14	6
Azo compounds	88	36
Heterocyclic Benzacridine	22	14
	154	83

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RELATIVE POTENCY OF CARCINOGENS TO THE SKIN OF MICE; COMPARISON OF DIFFERENT SYSTEMS OF GRADING

COMPOUNDS	PER CENT TUMORS	LATENT PERIOD (days)	IBALL'S INDEX	BLUM'S GRADE	BADGER
9:10 - dimethyl - 1, 2 - benzanthracene	65	43	151	X	++++
20 - methyl - cholanthrene	88.5	109	80	VIII	++++
3, 4-benzpyrene	89.5	119	75	VIII	++++
2-methyl-1, 2 - benzphenanthrene	75	155	48	VII	+++
10-methyl - 1, 2 - benzanthracene	66.5	147	45	VI (?)	+++
5-methyl - 1, 2 - benzanthracene	87.5	317	28	V	++
1, 2, 5, 6 - dibenz-anthracene	63	239	26	VI	++
3, 4 - benz-phenanthrene	67	387	17	V	+

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PARTIAL LIST OF COMPOUNDS IN CIGARETTE SMOKE ALSO IDENTIFIED AS CARCINOGENS

Arsenic
Benzo(a)pyrene +++
Benzo(e)pyrene +
Benzo(c)pyrene +
Benz(o)anthracene +
Benzo(k)fluoranthene +
Benzo(b)fluoranthene ++
Benzene
p-Benzoquinone
n-Butyric acid
Benzo(g, h, i)perylene +
Chrysene +
Chromium
Cobalt
5, 6-Cyclopenteno-1, 2-benzanthracene
6, 7-Cyclopenteno-1, 2-benzanthracene
Dibenz(a, h)anthracene +++
Dibenz(a, j)acridine ++
7H-Dibenzo(c, g)carbazole ++
Dibenz(a, h)acridine +
Dibenzo(a, h)pyrene ++
9, 10-Dimethylbenzo(a)anthracene ++++
Diethylene glycol
a-Dimethylchrysene
Dibenzo(a, l)pyrene
Dibenzo(a, i)pyrene
Ethyl alcohol
Fructose
Glucose
Lactic acid
3-Methyl-1, 2-benzanthracene +
2-Methyl-3, 4-benzphenanthrene
Nickel
2-Naphthol
Oleic acid
l-Proline
Pyrrole
Xylene
Indeno [1, 2, 3-cd]pyrene
3-Methylpyrene

CANCER PROMOTING AGENTS IN CIGARETTE SMOKE

Roe, Salaman, and Cohen, British Journal of Cancer, 1959

"Present evidence suggests that smoking has stronger tumor-promoting than tumor-initiating effect. Strong tumor-promoting effect by a phenolic fraction of cigarette smoke condensate applied after a single tumor-initiating dose of 9,10-dimethyl-1,2-benzanthracene (DMBA) to the dorsal skin of "101" strain mice was observed: 65 benign and two malignant tumors arose on 30 mice during 40 weeks of treatment. The same dose of DMBA alone produced a negligible number of tumors, and the phenolic fraction alone produced none."

SOME PROMOTING AGENTS

*Phenols
*Liquid paraffin hydrocarbons
Organic acid esters
Fats
Oleates
Cholesterol
Benzene
Iodoacetic acid
Chloracetophenone
Proflavine
Ethanolamine
Turpentine

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PHENOLS IN CIGARETTE SMOKE

	UG/CIGT.
Phenol	125
p-Dihydroxybenzene	83
p-Cresol	40
Catechol	30
Guaiacol	25
o-Cresol	22
∝-Tocophenol	20
m-Cresol	18
Resorcinal	8
2-Naphthol	0.5
1-Naphthol	0.3
Dihydroxybenzopyrene	-
3, 7-Dimethylquercetin	-
m-Hydroxyacetophenone	-
p-Hydroxyacetophenone	-
2, 4, 6-Trimethylphenol	-
3-Methylquercetin	-
Scopoletin	-
Tetrahydro-2-naphthol	-
2, 4-Dimethylphenol	-
3, 5-Dimethylphenol	-
Caffeic acid	-
Esculetin	-

ANTI-CARCINOGENS

Phospholipid fractions

Bromobenzene

Maleic acid) Other unsaturated
Citraconic acid) dibasic acids

Heptaldehyde

*Napthalene

*Anthracene

*Phenanthrene

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SMOKING AND CARDIOVASCULAR DISEASES

BELIEF - Cardiovascular ailments which may arise from smoking are due to the physiological effects of nicotine.

(1) Effects on the nervous system giving rise to both stimulating and/or depressant symptoms on various body functions.

(2) Specific effects on the adrenal medulla, causing it to discharge epinephrine, a hormone which accelerates the heartbeat, contracts the peripheral blood vessels, and raises the blood pressure.

It is difficult to separate these effects from those due to normal pressures of modern living.

Other complications:

(a) Low nicotine doses stimulate, but high doses depress functions.

(b) Continued usage develops tolerance.

(c) People vary greatly in their response to nicotine.

In contrast to these effects, it is also recognized that smoking produces pleasurable reactions or tranquility, and that this is due at least in part to nicotine, and not entirely to the physical manipulations involved in smoking.

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R & D PROGRAM LEADING TO A MEDICALLY ACCEPTABLE CIGARETTE

Present knowledge and current research indicate three main approaches:

I. Reduction of Irritating Factors in Smoke.

This involves extension of current work in tobacco chemistry, flavor and irritation studies, and selective gas phase filtration. Cost guestimate: $3,000,000.

II. Controlled Nicotine in Filler and Smoke.

This program is partially complete and could be finished in 18-24 months. Cost guestimate (to small pilot plant stage): $1,000,000.

III. Reduction of the General Level of Carcinogenic Substances in Smoke (but without Complete Elimination of More than a Few Specific Compounds.)

Cost and time guestimate: $10,000,000 and 7 to 10 years.

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I. REDUCTION OF IRRITATING FACTORS IN SMOKE

A. This approach is based on the hypothesis that physiological irritations are a first step in the initiation of more serious ailments.

B. Plan.

1. Development of objective test for irritation.
2. Identification of irritating constituents.
3. Selective elimination of irritants from smoke.

   a. By selective filtration of gas phase.
   b. By modification of cigarette chemistry through

      (1) Additives to control pyrolysis reactions
      (2) Selection of filler blends

C. This program is closely related to flavor improvement and increased consumer acceptability; hence it has a double advantage to product enhancement.

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II. CONTROLLED NICOTINE IN FILLER AND SMOKE

Even though nicotine is believed essential to cigarette acceptability, a reduction in level may be desirable for medical reasons.

Problems:

1. How much nicotine reduction will be acceptable to the smoker?
2. What taste difference will be tolerated?
3. Is it better to extract burley, bright, or both for low nicotine product of maximum consumer acceptability?

Consumer tests are under way to answer these questions.

Two processes available for flavorful, low nicotine tobacco:

1. The Rosenthal process--now being negotiated.
2. The MEK extraction process--it is planned to design a small pilot plant, applicable to either burley or bright:

   (a) To provide engineering process data useful for upscaling if desired.

   (b) To serve as a standby unit suitable for production of a minor brand which could be introduced in response to public demand.

The use of low-nicotine tobaccos will also be considered.

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III. REDUCTION OF CARCINOGENS IN SMOKE

To achieve this objective will require a major research effort, because

1. Carcinogens are found in practically every class of compounds in smoke.

   This fact prohibits complete solution of the problem by eliminating one or two classes of compounds.

   The best we can hope for is to reduce a particularly bad class, i.e., the polynuclear hydrocarbons, or phenols.

2. Present technology does not permit selective filtration of particulate smoke.

3. Flavor substances and carcinogenic substances come from the same classes, in many instances.

4. Many pyrolysis products have multiple precursors in tobacco.

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THE PRODUCTION OF POLYCYCLIC HYDROCARBONS FROM TOBACCO VS. CIGARETTE PAPER

COMPOUND	AMOUNT FROM TOBACCO	AMOUNT FROM PAPER
Acenaphthylene	20.5*	1.41*
Anthracene	48.0	0.74
Pyrene	55.0	2.92
3,4-Benzpyrene	4.0	0.69
1,12-Benzperylene	0.5	0.38
Phenanthrene	--	2.92
Fluoranthene	--	2.92

* Values are in µg/500 cigarettes

CONCLUSION: Tobacco is the main source of polynuclear hydrocarbons in cigarette smoke.

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POLYCYCLIC HYDROCARBONS COME FROM MANY TOBACCO CONSTITUENTS

µg/100 grams burned at 650°C

	Cellulose	Lignin	Pectin	Starch	Glucose	Malic Acid
Per cent in tobacco	9.0	3.5	10.7	4.0	11.0	10.1
Acenaphthylene	160	80	20	56	27	16
Fluorene	584	8000	287	32	7	632
Anthracene	337	544	539	104	36	70
Pyrene	219	33	133	35	66	166
Fluoranthene	164	58	152	94	45	136
3-Methylpyrene	131	-	29	11	1	119
1:2-Benzanthracene	186	44	273	116	43	130
1:2-Benzpyrene	65	22	34	4	11	8
3:4-Benzpyrene	78	47	45	17	29	35

CONCLUSION: Removal of any single precursor will not eliminate polycyclic hydrocarbons from smoke.

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SOME POSSIBLE WAYS TO REDUCE CARCINOGENS IN TOBACCO SMOKE

1. Discover major precursors for carcinogens and/or cancer promoters.
2. Discover mechanism or conditions by which carcinogens are produced and modify those conditions.
3. Select experimental tobaccos which produce a minimum of carcinogens.
4. Add anticarcinogens.
5. Discover differences in particulate fractions which will permit separation of carcinogens in smoke.

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SUMMARY

Low irritation and low nicotine cigarettes for commercial exploitation will be developed in the course of our present R & D program during the next two to five years with an expenditure of not more than 25% of the R & D budgets during this period.

A medically acceptable low-carcinogen cigarette may be possible. Its development would require

TIME

MONEY

UNFALTERING DETERMINATION