

FUNDAMENTAL RESEARCH

OBJECTIVE:

THE STUDY OF TOBACCO PRODUCTS
FOR THE PURPOSE OF ALLEVIATING PERCEIVED HEALTH RISKS

THE COURSE OF ACTION: DESIGN A PROGRAMME THAT TAKES US FROM OUR PRESENT PROGRAMME OF GROSS REDUCTION OF TOXIC TOBACCO SMOKE COMPONENTS TO A PROGRAM OF SELECTIVE REDUCTION OF SPECIFIC TOBACCO SMOKE COMPONENTS TO REDUCE THE SPECIFIC TOXICITY OF TOBACCO SMOKE. THIS PROGRAMME WILL BE BASED ON THE RECOMMENDATIONS OF MEDICAL AND SCIENTIFIC EXPERTS, SOME OF WHOM ARE IDENTIFIED ON PAGE 2.

FUNDAMENTAL RESEARCH IS NOT, IN ITSELF, AN OBJECTIVE; IT IS A STRATEGY.

IT IS A SELECTED COURSE OF ACTION WHICH AFFORDS THE MOST SUPPORT TO THE ACHIEVEMENT OF AN OBJECTIVE.

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FUNDAMENTAL RESEARCH

FUNDAMENTAL

A. OBJECTIVE

"THE ONGOING PROGRAMME OF FUNDAMENTAL RESEARCH IS WORLDWIDE IN SCOPE AND ENTAILS AN IN-DEPTH STUDY OF TOBACCO PRODUCTS FOR THE PURPOSE OF ALLEVIATING PERCEIVED HEALTH RISKS."

PAUL PARE

JUNE 7, 1985

A MODEL WAS DEVELOPED TO FACILITATE EXAMINATION OF THE FACTORS PERCEIVED AS HEALTH RISKS, AND TO FORMULATE AN APPROACH FOR THE REMOVAL OF THE IDENTIFIED UNDESIRABLES.

EMN

THE ACTIVITY WOULD BE IN THREE PHASES

ELIMINATE

MODIFY

NEUTRALIZE

THE NEXT STEP WAS TO GET AN IDEA OF THE MODIFICATIONS THAT OTHER PEOPLE THOUGHT SHOULD BE MADE TO A CIGARETTE, TO REDUCE PERCEIVED HEALTH RISKS.

HERE ARE SOME EXAMPLES

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B. SOME RELEVANT SUGGESTIONS

1 D.M. WARBURTON ET AL

2 SMOKING & ARTERIAL DISEASE
M. JARVIS

3 JOURNAL OF CHRONIC DISEASE
D.B. PETITTI & G.D. FRIEDMAN

4 ROYAL COLLEGE OF PHYSICIANS

5 ROYAL COLLEGE OF PHYSICIANS

6 DIETRICH HOFFMAN & ERNST L. WYNDER

7 FOURTH SCARBOROUGH CONFERENCE ON PREVENTIVE MEDICINE

8 ASSESSMENT OF CARCINOGEN EXPOSURE IN MAN

9 BIOLOGICAL ACTIVITY USING SIX IN VITRO SHORT-TERM
TESTS

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EMN

C. IDENTIFY THE UNDESIRABLES

1. THIS MODEL USES THE LIST OF THE MAJOR TOXIC AGENTS IDENTIFIED IN THE 1981 SURGEON GENERAL'S REPORT.

GAS PHASE

2. IT IS SUGGESTED THAT AN ATTEMPT BE MADE TO IDENTIFY THRESHOLD VALUES SO THAT PRIORITIES CAN BE DETERMINED.
3. THE DOSE MAKES THE POISON
4. RELATIVE RISK
5. MAJOR TOXIC AGENTS - THRESHOLD
6. DOSE RESPONSE CURVE
7. COMPLETE DOSE RESPONSE CURVE
8. EXAMPLES OF THRESHOLD APPLICATION
VINYL CHLORIDE
HEAVY METAL

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EMN

D. ELIMINATE THE UNDESIRABLES

LEAF
BIO-TECH
PROCESS

E. MODIFY

PRODUCT DESIGN
CIGARETTE

F. NEUTRALIZE

NUTRIENTS

G. PAST BIOLOGICAL RESEARCH
IN THE BAT GROUP

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SUSCEPTIBILITY TO THE SMOKING HAZARD

ROYAL COLLEGE OF PHYSICIANS

- 1 EXTERNAL INFLUENCES
- 2 GENETIC FACTORS

CAUSES OF
CANCER

IF WE LOOK AT THE MAJOR FACTORS - DIET - THERE ARE SOME INTERESTING OBSERVATIONS THAT CAN BE MADE

- 1 DIETARY CARCINOGENS AND ANTICARCINOGENS,
BRUCE N. AMES
- 2 ACCOUNTS OF CHEMICAL RESEARCH,
CARCINOGENS ACCEPTABLE IN FOOD
- 3 CHEMICAL CARCINOGENS AND INHIBITORS OF CARCINOGENESIS
IN THE HUMAN DIET
- 4 AMERICAN OCCUPATIONAL HEALTH CONFERENCE
CARCINOGENS, ANTI-CARCINOGENS, AND CANCER CAUSATION,
BRUCE N. AMES
- 5 RECOGNITION OF THE ROLE OF DIET HAS PROMPTED THE
PUBLICATION OF THE FOLLOWING DOCUMENTS
- 6 CANCER PREVENTION RESEARCH SUMMARY
U.S. DEPT. OF NUTRITION HEALTH & HUMAN SERVICES
- 7 CANCER PREVENTION RESEARCH: CHEMOPREVENTION & DIET
NATIONAL CANCER INSTITUTE
- 8 DIET NUTRITION AND CANCER
NATIONAL RESEARCH COUNCIL
- 9 DIET, NUTRITION, AND CANCER: DIRECTIONS FOR RESEARCH
COMMITTEE ON DIET, NUTRITION, AND CANCER.
COMMISSION ON LIFE SCIENCES, NATIONAL RESEARCH COUNCIL

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THE ROYAL COLLEGE OF PHYSICIANS ALSO IDENTIFIED GENETIC FACTORS
AS PART OF

"SUSCEPTIBILITY TO THE SMOKING HAZARD"

SIMILAR VIEWS AS EXPRESSED BY R.L. WHITE IN

"HUMAN GENETICS"

WHILE IN AN ARTICLE

"REDUCING RISK: A CHANGE OF HEART"

COVERS MOLECULAR GENETICS, AND THE ENVIRONMENTAL APPROACH
OF DR. LEONARD SYME.

THIS LEADS US TO A CONSIDERATION OF

LIFE STYLE
ENVIRONMENT

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LIFE STYLE ENVIRONMENT GENETIC

THE DOTTED LINE SIGNIFIES THE CORRELATION BETWEEN SMOKING AND DISEASE; IT IS DOTTED RATHER THAN SOLID TO SUGGEST THAT THE CORRELATION MAY NOT BE BASED ON ANY DIRECT CAUSATION.

THE SOLID LINES IN THE FIGURE SUGGEST

- 1 THAT GENETIC FACTORS PLAY A LARGE PART OF THE CAUSATION OF DISEASE.
- 2 THAT GENETIC FACTORS PLAY A LARGE PART OF THE CAUSATION OF SMOKING; IT IS SUGGESTED THAT THESE FACTORS ARE LIKELY TO OVERLAP
- 3 GENETIC FACTORS ARE VERY INFLUENTIAL IN DETERMINING INDIVIDUAL DIFFERENCES IN PERSONALITY, AND THAT THESE DIFFERENCES IN TURN ARE RELATED TO
- 4 SMOKING
- 5 DISEASE
- 6 STRESS IS RELATED TO SMOKING
- AND
- 7 DISEASE

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REVIEW OF PAST BIOLOGICAL RESEARCH

ASSOCIATION OF SMOKING WITH CHRONIC DISEASES

1. CANCER

MECHANISMS BEGINNING TO BE UNDERSTOOD
BIOASSAYS AVAILABLE

- A) MOUSE SKIN PAINTING
- B) INHALATION TESTS
- C) SHORT-TERM TESTS

2. CARDIOVASCULAR DISEASES

MECHANISMS POORLY UNDERSTOOD
NO SUITABLE ANIMAL MODEL

3. CHRONIC OBSTRUCTIVE LUNG DISEASES

MECHANISMS POORLY UNDERSTOOD
NO SUITABLE LABORATORY MODEL

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CANCER - POSSIBLE MECHANISMS

1. EXISTENCE OF A RELATIONSHIP BETWEEN
CARCINOGENESIS AND MUTAGENESIS

2. THE MUTATION THEORY OF CANCER
CANCER RESULTS FROM MUTATION OF SOMATIC CELL

3. MUTATED SOMATIC CELLS OUTGROW SURROUNDING CELLS

4. LONG PERIOD BETWEEN MUTATIONAL EVENT
AND DEVELOPMENT OF CANCER

5. TWO-STAGE THEORY
 - A) INITIATION
 - B) PROMOTION

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TOBACCO SMOKE CARCINOGENICITY - N.C.I., U.S.A. STUDIES

FACTORS ASSOCIATED WITH		
REDUCED ACTIVITY	NO CHANGE	INCREASED ACTIVITY
1. HIGH POROSITY PAPER (CITRATE)	1. WIDTH OF TOBACCO CUT	1. FILTERS A) CELLULOSE ACETATE B) PERMANGANATE
2. TOBACCO STEM & EXPANDED	2. PAPER POROSITY	
3. RECONSTITUTED SHEET A) RTS PAPER PROCESS B) WATER EXTR PAPER PROCESS	3. RECONSTITUTED SHEET A) RTS SLURRY PROCESS B) PAPER PROCESS WITH & WITHOUT ADDITIVES	2. RECONSTITUTED SHEET A) SLURRY PROCESS B) PAPER PROCESS - EXTRACTED WATER 65%; INORGANIC, 25%; ADDITIVES, 10% C) PAPER PROCESS - NORMAL NICOTINE
4. LOW NICOTINE TOBACCO	4. EXPANDED TOBACCO	
5. EXPANDED TOBACCO A) PHILIP MORRIS PROCESS B) FREEZE DRIED	5. REYNOLDS PUFFED TOBACCO	
6. ARTIFICIAL TOBACCO SUBSTITUTES - ATS-A	6. SUGAR	3. ARTIFICIAL TOBACCO SUBSTITUTE - ATS-B
7. ADDITIVES A) POTASSIUM NITRATE B) MAGNESIUM NITRATE	7. HUMECTANT	
8. FILTER VENTILATION	8. ADDITIVES A) ZINC OXIDE B) COCOA	
	9. SUCKERING AGENTS - FATTY ALCOHOL	

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TOBACCO SMOKE CARCINOGENICITY - B.A.T. - SUPPORTED STUDIES

FACTORS ASSOCIATED WITH		
REDUCED ACTIVITY	NO CHANGE	INCREASED ACTIVITY
1. LOWER CIRCUMFERENCE	1. REDUCING TOBACCO MOISTURE	1. PAPER POROSITY
2. HIGHER PUFF VOLUME	2. GRANULATED TOBACCO	2. SILICA GEL FILTER
3. INCREASED FLOW RATE	3. FILTERS	3. INCREASING TOBACCO MOISTURE FROM 12% TO 20%.
4. INCREASED CUTS PER INCH	A) ACETATE	4. DARK TOBACCO - GERMAN
5. BURLEY TOBACCO AND STEM	B) POLYETHYLENE GLYCOL	5. SUN-CURED - INDIAN
6. VIRGINIA STEM	C) CHARCOAL	6. CIGAR LEAF
7. RECONSTITUTED SHEET	D) CHARCOAL (PELLET TYPE)	7. GRANULATED IN CIGAR
A) GERLACH	E) CELLULOSE ACETATE	8. RECONSTITUTED SHEET
B) PCL	4. ADDITIVES	A) ARENCO
C) SRT	A) MALIC ACID	B) BORGWALDT
D) SCHWEITZER	B) 2% DIETHYLENE GLYCOL	C) AMF
8. ADDITIVES	C) 1% GALLIC ACID-N- PROPYL ESTER	9. ADDITIVES
A) POTASSIUM NITRATE		A) POTASSIUM MALATE
B) COPPER NITRATE		B) POTASSIUM HYDROGEN MALATE
C) POTASSIUM NITRITE		C) COPPER POTASSIUM MALATE
D) SODIUM NITRATE		D) POTASSIUM CARBONATE (NO STEAM)
E) POTASSIUM CARBONATE		E) AMMONIUM SULPHAMATE

201909001 (PLUS STEAM)
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A SUMMARY OF B.A.T. MUTAGENICITY STUDIES

FACTORS ASSOCIATED WITH		
REDUCED ACTIVITY	NO CHANGE	INCREASED ACTIVITY
1. LOWER CIRCUMFERENCE	1. PUFF DURATION	1. FILTER VENTILATION
2. PAPER POROSITY	2. PUFF FREQUENCY	2. HIGHER FILTER PRESSURE DROP
3. HIGHER PUFF VOLUME	3. WIDTH OF TOBACCO CUT	3. HIGHER TOBACCO MOISTURE
4. VIRGINIA TOBACCO	4. BUTT LENGTH	4. BURLEY TOBACCO
5. SHEET MATERIALS	5. FILTERS	5. DARK TOBACCO
A) GERLACH	A) HEMIN	6. TOBACCO PROTEIN
B) PCL	B) IONEX	7. NITRATE
C) SCHWEITZER	6. ANNULAR CIGARETTES	8. NICOTINE
D) CYTREL	7. NICOTINE	9. CASINGS
6. STEM	8. MENTHOL	10. DITHIOCARBAMATE
7. EXPANDED TOBACCO	9. COCOA	(MANEB) APPLICATION
8. REDUCING SUGAR		
9. CASINGS		
10. BUTTERFAT		
11. KRETEK		

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A COMPARISON OF THE JANUS SERIES IN
CARCINOGENICITY AND MUTAGENICITY TESTS

CIGARETTES	EFFECT ON	
	CARCINOGENICITY	MUTAGENICITY
<u>B9 SERIES</u>		
ETHANOL EXTRACTION	-	-
ETHANOL EXTRACT RETURNED	0	0
PCL-PLUS GERLACH ADDITIVE	-	-
GERLACH SHEET	-	-
GERLACH SHEET FROM ETHANOL EXTRACTED TOBACCO	-	-
<u>B11 SERIES</u>		
PCL	-	-
SRT	-	-
<u>B15 SERIES</u>		
INCREASED PAPER POROSITY	+	-
INCREASED PRESSURE DROP	0/+	+
FILTER TIP VENTILATION	0	0
ELECTROSTATIC PERFORATION	+	+
PAPER ADDITIVE	0	0

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A COMPARISON OF BIOLOGICAL ACTIVITIES OF CONDENSATE
IN THE CARCINOGENICITY AND MUTAGENICITY TESTS

CONCLUSIONS DRAWN FROM TESTS FOR WHICH THERE WAS	
AGREEMENT	DISAGREEMENT
LOWER CIRCUMFERENCE (-)	PAPER POROSITY
FILTER VENTILATION (+)	VIRGINIA TOBACCO
HIGHER PUFF VOLUME (-)	BURLEY TOBACCO
	EXPANDED STEM
WIDTH OF TOBACCO CUT (0)	CASINGS
HIGHER TOBACCO MOISTURE (+)	
DARK TOBACCO (+)	
EXPANDED TOBACCO (-)	
GERLACH SHEET (-)	
PCL SHEET (-)	
CYTREL (-)	
SCHWEITZER SHEET (-)	
VIRGINIA STEM (-)	
COCOA ADDITION (0)	

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FUTURE STUDIES

1. EXPLORE THE SHORT TERM TESTS, INCLUDING TESTS FOR "PROMOTION" ACTIVITY OF TOBACCO SMOKE.
2. STUDY PROTECTIVE MECHANISMS IN ANIMAL MODELS.
3. USE OF AMES TEST TO STUDY:
 - A) TOBACCO TYPES, PARTICULARLY DIFFERENT BURLEYS.
 - B) SMOKE FRACTIONATION.
 - C) ANTIMUTAGENS.
 - D) ROLE OF NICOTINE.
 - E) DESIGN AND TEST "LOW ACTIVITY" CIGARETTES.
4. USE OF AMES TEST TO MONITOR:
 - A) RECONSTITUTED TOBACCOS.
 - B) ADDITIVES - FLAVOURINGS, CASINGS, ETC.
 - C) NEW MARKET ENTRIES.

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THE WAY FORWARD - RECOMMENDATIONS FOR FUTURE RESEARCH

ASSOCIATION OF SMOKING WITH CHRONIC DISEASE

1. CANCER

2. CARDIOVASCULAR DISEASE
 - MECHANISMS POORLY UNDERSTOOD

3. CHRONIC OBSTRUCTIVE LUNG DISEASE (BRONCHITIS, EMPHYSEMA)
 - MECHANISMS POORLY UNDERSTOOD

4. HYPERTENSION
 - MECHANISMS POORLY UNDERSTOOD
 - LINK WITH SMOKING BEING SERIOUSLY DEBATED

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TOBACCO AND HEALTH RESEARCH
APPROACHES TO RENDERING CIGARETTES LESS HARMFUL

1. SMOKE CHEMISTRY - REDUCTION OF TOXIC COMPONENTS
2. SHORT TERM AND LONG TERM BIOASSAYS
3. EPIDEMIOLOGICAL STUDIES
4. MECHANISMS OF DISEASE PRODUCTION

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APPROACH 1.

SMOKE CHEMISTRY

REDUCTION OF TOXIC COMPONENTS

1. TAR REDUCTION - FILTRATION
2. TAR MODIFICATION - COMBUSTION
3. IDENTIFIED SMOKE COMPONENTS ASSOCIATED WITH DISEASE,
ELIMINATED BY
 - A) SPECIFIC FILTRATION
 - B) REMOVING PRECURSORS
4. IDENTIFICATION OF SMOKE COMPONENTS WITH MULTIPLE
PATHOLOGIC EFFECTS
 - EG. FREE RADICALS

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APPROACH 2.

SHORT TERM AND LONG TERM BIOASSAYS

1. CORRELATION OF CARCINOGENESIS - MUTAGENESIS
LONG TERM, SHORT TERM TESTS

I.E. MOUSE SKIN PAINTING - AMES TESTS

2. IDENTIFY SMOKE FRACTIONS ASSOCIATED WITH
BIOLOGICAL ACTIVITY; IDENTIFY SPECIFIC COMPONENTS
IN THOSE FRACTIONS.

3. EXPERIMENTAL ANIMAL MODELS

- LOOKING FOR POSSIBLE SYNERGY WITH OTHER FACTORS

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APPROACH 3.

EPIDEMIOLOGICAL STUDIES

1. STUDIES SHOWING STRONG LINKS BETWEEN SMOKING AND DISEASE

2. EVIDENCE OF DOSE RESPONSE
TOTAL INTAKE OF SMOKE REDUCTION CORRELATED WITH REDUCED INCIDENCE

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APPROACH 4.

MECHANISMS OF DISEASE PRODUCTION

1. PRODUCTION MECHANISMS
2. SMOKING AND IMMUNE MECHANISMS
3. IDENTIFICATION OF SUSCEPTIBLE INDIVIDUALS
4. GENETIC APPROACH

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IMPACT ON LONG TERM BUSINESS REQUIREMENTS

MARKET SHARE

1. PRODUCT DIFFERENTIATION ON BASIS OF MUTAGENIC (CARCINOGENS?) ACTIVITY
2. MICROBIOLOGICAL QUALITY
3. PRODUCT MODIFICATION BASED ON TOXICOLOGICAL KNOWLEDGE
4. NEW MARKET ENTRIES BASED ON NEW SCIENTIFIC CRITERIA

INDUSTRY

1. PARTICIPATION INTO REGULATORY LAWS

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