WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

TOBACCO: A MAJOR INTERNATIONAL HEALTH HAZARD

Proceedings of an International Meeting organized by the IARC and co-sponsored by the All-Union Cancer Research Centre of the Academy of Medical Sciences of the USSR, Moscow, USSR, held in Moscow, 4–6 June 1985

EDITORS

D. G. ZARIDZE R. PETO

IARC Scientific Publications No. 74

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
LYON
1986

The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as an independently financed organization within the framework of the World Health Organization. The headquarters of the Agency are at Lyon, France.

The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

The publications of the Agency are intended to contribute to the dissemination of authoritative information on different aspects of cancer research.

Distributed for the International Agency for Research on Cancer
by Oxford University Press, Walton Street, Oxford OX2 6DP, UK

London New York Toronto
Delhi Bombay Calcutta Madras Karachi
Kuala Lumpur Singapore Hong Kong Tokyo
Nairobi Dar es Salaam Cape Town
Melbourne Auckland

Oxford is a trade mark of Oxford University Press

Distributed in the USA
by Oxford University Press, New York

ISBN 92 832 1174 X
ISSN 0300-5085

PRINTED IN SWITZERLAND

CONTENTS

IV. TOBACCO – SPREAD OF THE HABIT AND TRENDS

V. SMOKING – CURRENT RESEARCH ISSUES

VI. HEALTH EFFECTS OF LOW-TAR, LOW-NICOTINE CIGARETTES

VII. SMOKING CONTROL IMPLEMENTATION

FOREWORD

Tobacco smoking is one of the major causes of disease and death today: it causes cancer, pulmonary obstructive disease and cardiovascular disease. The list of target sites for tobacco-related cancers is impressive: lung, urinary bladder, renal pelvis, oral cavity, pharynx, larynx, oesophagus, pancreas and possibly kidney and liver.

The evidence, therefore, of the severe consequence for health of smoking is so compelling and so overwhelming that it is difficult to understand why it has been, and still is, so difficult to initiate successful preventive measures. The answer is probably two-sided.

The first is the difficulty that individuals have in renouncing a habit that has become solidly rooted in their culture and in their daily life. Most people believe that making the choice to smoke is their privilege and is made freely. They derive satisfaction from it and, at the same time, they are unable to perceive or to accept the evidence of chronic accumulation of risk. The second part of the answer is the interest of governments around the world in tobacco-derived income. Many governments, although genuinely concerned about the good health of their citizens, still continue to allow the sale of tobacco and to make money out of it; and, of course, in many countries powerful private interests are involved. When these private interests coincide with those of the governments, the resulting alliance is probably the strongest possible. Governments should perhaps be convinced that not only is the sale of tobacco inconsistent with public health, but also that there are other ways of supporting the national economy.

Recently, evidence has become available that smokers of cigarettes yielding high levels of tar and nicotine have a greater risk of developing lung cancer than smokers of cigarettes that yield less tar. Tobacco is a mixture containing a large number of chemicals, many of which are recognized carcinogens and/or mutagens. Tar, which results from the pyrolysis of tobacco, certainly contains carcinogenic chemicals, and one can therefore assume that, by decreasing the delivery of at least one of the carcinogenic fractions of smoke, a less intense carcinogenic activity of the total mixture may result. Tobacco smoke will, however, clearly continue to be a carcinogen even if it contains less tar.

The abolition of cigarettes with high levels of tar will potentially reduce the risk of lung cancer, but there is absolutely no doubt that any measure that still involves the production and use of cigarettes is only provisional and represents only a preliminary step towards the truly adequate measure of preventing damage to health from smoking, i.e., avoidance of smoking, and replacement of tobacco as a widespread crop. It must also be clearly stressed that there is no evidence whatsoever that the consumption of so-called 'low-tar' cigarettes has any effect on decreasing the incidence of and mortality from cardiovascular diseases.

The achievement of complete avoidance of smoking and replacement of tobacco by another crop will necessitate, inevitably, a phase of intense and widespread education of

the public, which should begin early in life. It is important that everybody becomes aware that the introduction of tobacco into our culture is a very recent event and that the consumption of cigarettes is a habit that became widely disseminated only within the last century. There is therefore no reason that humanity cannot continue its course without tobacco.

It is also important to stress that tobacco is carcinogenic not only when it is burned and smoked, but also when it is chewed. Recent advertising in which it is claimed that tobacco chewing is harmless contradicts very clear, definite evidence that tobacco is carcinogenic when it is chewed.

The diffusion of the habit of smoking all over the world makes the problem a truly international one of public health, and the All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR is to be commended on its initiative in calling this meeting jointly with the IARC. Professor Blokhin and Professor Trapeznikov, in particular, are to be congratulated on their foresight and for the excellent organization of this international forum.

L. Tomatis, MD
Director,
IARC

LIST OF PARTICIPANTS

F. Adelkofer	Forschungsgesellschaft Rauchen und Gesundheit, Mittelweg 17, 2000 Hamburg 13, Federal Republic of Germany
K. Aoki	Department of Preventive Medicine, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466, Japan
F. Berrino	Istituto Nazionale per lo Studio e la Cura dei Tumori, via Venezian 1, 20133 Milan, Italy
K. Bjartveit	Norwegian Council on Smoking and Health, PO Box 8155, DEP 0033, Oslo 1, Norway
N.N. Blokhin	Director, All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR, ul. Solianka 14, Moscow 109801, USSR
P.A. Bogovski	Director, Institute of Experimental and Clinical Medicine, Ministry of Public Health of the Estonian SSR, Ilmarise 25-6, Tallinn 200015, Estonia, USSR
J. Cullen	Deputy Director, Division of Cancer Prevention and Control, National Cancer Institute, Building 31, Room 4A-32, Bethesda, MD 20205, USA
I.I. Djachkin	Tobacco Production and Research Institute, Krasnodar, USSR
R. Doll	Cancer Epidemiology and Clinical Trials Unit, Radcliffe Infirmary, Oxford OX2 6HG, United Kingdom
V.V. Dvoirin	Head of Department, All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR, Kashirskoye shosse 24, Moscow 115478, USSR
S. Eckhardt	Director, National Oncological Institute, Rath Gyorgy Str. 7, 1525 Budapest, 114 Pf21, Hungary

Y.T. Gao	Departement of Epidemiology, Shanghai Cancer Institute, 270 Dong An Road, Shanghai, China
V.N. Gerasimenko	Director, Institute of Clinical Oncology, All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR, Kashirskoye shosse 24, Moscow 115478, USSR
I.S. Glasunov	Head, Division of Cooperative Preventive Programmes, Institute of Preventive Cardiology, All-Union Cardiology Research Center, 10 Petroverigsky Lane, Moscow, USSR
L.A. Griciute	Director, Lithuanian Cancer Research Institute, 341 Dzerzhinskio str., 232021 Vilnius, USSR
P.C. Gupta	WHO Collaborating Center for Oral Cancer Prevention, Tata Institute of Fundamental Research, Homi Bhabha Road, Bombay 40005, India
E. Heseltine	International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France
D. Hoffmann	Naylor Dana Institute for Disease Prevention, American Health Foundation, Dana Road, Valhalla, NY 10595, USA
V.V. Khudoley	N.N. Petrov Research Institute of Oncology, USSR Ministry of Public Health, Leningradskaya st. 66, Pesochny-2, 188646 Leningrad, USSR
H. Klus	Department of Research and Development, Austria Tabakwerke AG, Hasnerstrasse 124, 1160 Vienna, Austria
V.A. Kobljakov	All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR, Kashirskoye shosse 24, Moscow 115478, USSR
I.P. Komjakov	N.N. Petrov Research Institute of Oncology, USSR Ministry of Public Health, Leningradskaya st. 66, Pesochny-2, 188646 Leningrad, USSR
M. Kunze	Institute of Social Medicine, University of Vienna, Kinderspitalgasse 15, 1095 Vienna, Austria
E. Leparski	World Health Organization, Regional Office for Europe, 8 Scherfigsvej, 2100 Copenhagen Ø, Denmark

C.S. Muir	International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France
R.S. Paffenbarger, Jr	Department of Family, Community and Preventive Medicine, Medical Center, School of Medicine, Stanford University, Stanford, CA 94308, USA
H. Peach	Department of Community Medicine, United Medical and Dental Schools, St Thomas' Campus, London SE1 7EH, United Kingdom
R. Peto	Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford OX2 6HE, United Kingdom
V.P. Pisklov	Head of Department, All-Union Research Institute of Tobacco, 350072 Krasnodar, USSR
L.M. Ramström	Director, NTS, National Smoking and Health Association, Sveavägen 166, 113 45 Stockholm, Sweden
R. Saracci	International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France
M. Sorsa	Department of Industrial Hygiene and Toxicology, Institute of Occupational Health, Haartmaninkatu 1, 00290 Helsinki 29, Finland
S.D. Stellman	American Cancer Society Inc., 4 West 35th Street, New York, NY 10001, USA
S. Tanneberger	Director, Zentralinstitut für Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, 1115 Berlin-Buch, German Democratic Republic
L. Tomatis	Director, International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France
S. Tominaga	Chief, Division of Epidemiology, Aichi Cancer Center Research Institute, Tashiro-cho, Chikusa-ku, Nagoya, Japan
N.N. Trapeznikov	Deputy Director, All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR, Kashirskoye shosse 24, Moscow 115478, USSR
V.G. Veitsler	Head of Department, Scientific Research Institute of Food Industry, USSR Food Industry Ministry, Krasnodar, USSR

U. Veronesi — Director, Istituto Nazionale dei Tumori, via Venezian 1, 20133 Milan, Italy

D.G. Zaridze — International Agency for Research on Cancer, 150 cours Albert-Thomas, 69372 Lyon Cedex 08, France

I. IMPLICATIONS AND RECOMMENDATIONS

IMPLICATIONS

These pages highlight the scientific deliberations, but do not represent a full summary of the proceedings.

Despite the fact that the main adverse health effects of smoking have been well known for many years, smoking remains one of the most important public health problems both in developed and in developing countries. Between one-quarter and three-quarters of the men smoke in virtually all countries from which survey data are available. Women generally smoke less than men, but the proportion of adult women smokers in many parts of Europe and North America is about 30%, and increasing numbers of women are taking up the habit. Smoking continues to increase in many (though not all) developed and almost all developing countries.

Tobacco smoking, particularly of cigarettes, is an important cause of chronic disability and death from a wide range of neoplastic, vascular and respiratory diseases. The neoplastic diseases caused by smoking include cancers of the lung, oral cavity, pharynx, larynx, oesophagus, urinary bladder, renal pelvis and pancreas. The most important of these neoplastic diseases is lung cancer. In most developed countries for which data are available, the proportion of lung cancer attributable to smoking is 80–90% in men and the attributable proportion in women is approaching this level in many of these countries. Even if a smaller fraction of lung cancers in other countries is induced by tobacco, a substantial proportion of the global total must be attributable to this single cause.

Tobacco is probably the most important known carcinogen for human society today. It accounts for more cancer deaths than all other reliably known effects put together, and the annual number of lung cancer deaths due to tobacco is still rising rapidly. By the end of the century, this number is expected to exceed one million, to which must be added an even greater number of tobacco-induced deaths from diseases other than lung cancer.

In countries where the oral consumption of smokeless tobacco in various forms is popular, it is also a cause of cancer, chiefly of the oral cavity. Oral use of smokeless tobacco is spreading to other countries and this can only be considered deleterious.

In addition, smoking causes even more deaths from non-neoplastic diseases than from cancer. Coronary heart disease (CHD) is the leading cause of death in most developed countries and in those where prolonged smoking is widespread about one-third of all CHD deaths in middle-aged people may be attributed to cigarette smoking. Smoking also contributes to the development of various other arterial diseases, and is the predominant cause of chronic obstructive lung disease (a term that includes chronic bronchitis and emphysema).

On the basis of knowledge of the chemical composition of sidestream smoke, experimental data and human exposure measurements, 'passive' exposure to other people's tobacco smoke must be presumed to cause some risk of developing lung cancer. However,

the exact extent to which it does so requires additional research. Although less firm, evidence has emerged that involuntary smoking may also increase the incidence of CHD.

Those who stop smoking before they have cancer or serious heart or lung disease can avoid much of the excess risk of death from smoking that they would have suffered if they had continued. The longer the period of cessation, the greater the diminution of risk.

Cessation of smoking results in a rapid and substantial reduction in death rates from CHD. Approximately 10 years after cessation, the primary onset rate of coronary heart disease for exsmokers approaches that of lifelong nonsmokers. An important part of the treatment of atherosclerotic diseases – coronary, cerebral, aortic and peripheral vascular and obstructive lung disease – is persuading patients who are smokers to give up the habit.

The rise in cigarette consumption observed in many countries in the past few decades suggests that, in future decades, important increases will be observed in the rates of lung cancer and other smoking-related diseases in those countries, unless some measures are taken to prevent at least part of these long-term adverse effects.

The excess risks of death produced by smoking in middle and old age depend strongly not only on what is currently smoked but also, perhaps surprisingly, on what was smoked in early adult life, even if this was several decades earlier. Hence, there is a potentially misleading delay of several decades between the widespread adoption of cigarette smoking by the young adults in a particular country and the eventual emergence of its full effects. Indeed, during the period while large increases in cigarette smoking are taking place among young adults, there may (temporarily) be little increase in mortality for decades after the main increases in cigarette usage cease. Thus, large increases in conditions such as lung cancer may be observed as a delayed result of long-past increases in cigarette usage by young adults.

Because of the long delay that may occur between the adoption of a particular smoking habit and the emergence of its full effects on cancer risks, there has been uncertainty about the effects on health of changes in design of cigarettes. Evidence on this subject has, however, emerged (IARC, 1986) and the present meeting endorsed the conclusion of the IARC Working Group that: '. . . the risk of lung cancer associated with the types of cigarettes commonly smoked before the middle 1950s is greater than that for modified cigarettes with low tar levels now generally available in some countries.

'The health benefits from the cessation of smoking, however, greatly exceed those to be expected from changes in cigarette composition.' But, it was considered by no means certain that current changes in cigarette composition would have any comparable effect on the risk of other tobacco-related diseases. Particularly, it was uncertain whether such changes would have any effect on the risk of developing CHD.

Worldwide, the number of tobacco-induced deaths is still increasing rapidly, so the elimination of smoking would ultimately result in the avoidance of several million tobacco-induced deaths each year, and even moderate decreases in smoking would prevent substantial numbers of such deaths.

RECOMMENDATIONS

The ultimate response to the disastrous facts outlined above must be the eradication of virtually all tobacco use. All responsible bodies should declare their commitment to such a programme in all countries, which would probably be the most effective means of protecting present and future public health.

A series of measures is therefore urgently needed, as intermediate steps towards this final goal. As a first step, reduction in the consumption of tobacco would be the most important means. Each country should therefore formulate a specific strategy for reduction of smoking rates within a defined period.

Measures to discourage the use of cigarettes are of substantial public health importance in areas such as the USSR, Europe, North America and Australia, where cigarettes have been used widely for many decades, and where they may already account for 20–35% of all cancer deaths. They are also important in areas such as China, other parts of Asia, and Africa, where widespread use of cigarettes is so recent that even though at present the habit may account for only a small percentage of all cancer deaths, causation of a much higher proportion in future decades can already be foreseen.

The meeting consequently RECOMMENDS that in all countries specific measures should be taken to discourage continuation of the habit among smokers and adoption of the habit among nonsmokers.

The measures that are most appropriate to achieve this will, of course, differ widely from country to country. Expert committees of the World Health Organization (1979) and International Union Against Cancer (1977) have already formulated extensive lists of recommendations that deserve detailed consideration, as they contain much carefully thought out advice. These recommendations emphasize the need to give national smoking control programmes a multicomponent nature.

Most of the measures recommended, however, are concerned not with restriction but with education. Partly as a result of these, the majority of smokers in most industrialized countries may by now be aware that smoking is hazardous, but probably most remain unaware of the relative magnitude of the hazards involved.

The meeting consequently RECOMMENDS that responsibility be taken for ensuring that the majority of cigarette smokers be led to understand the approximate size of the excess risk of disability and death associated with the habit, and of the benefits of cessation of the smoking habit.

One method that might be particularly appropriate in all countries, since it gains access to all cigarette smokers at negligible cost, is to have on each pack of cigarettes a quantita-

tively informative health warning (or a set of health warnings that are cyclically altered, some of which are quantitatively informative). The warning should be large enough to be prominent, and its wording should be reviewed (and perhaps revised) at regular intervals to help it communicate the *size* of the hazard to ordinary smokers.

Appropriate health education programmes could be given a prominent position in the school curriculum. Health education could be made a routine part of many clinic visits, for some patients in ill health are influenced by doctors and nurses to cease smoking. In order to achieve implementation on a really broad basis, special efforts must be made to give specific training to key professionals such as teachers and health workers. Health education programmes could be offered through various mass media. Finally, a systematic effort could be made to discourage smoking by various particularly influential individuals such as teachers, health professionals and media personalities – indeed, schools, clinics and television studios might exert a useful influence by becoming completely nonsmoking areas.

One programme component that is consistently recommended, and for which there is particularly clear evidence that it is helpful, is substantial increases in the real price of cigarettes, maintaining those increases against inflation. Increases in price should make any very hazardous cigarettes (e.g., nonfilter, high-tar) at least as expensive as hazardous cigarettes.

Other widely recommended components include a ban on all forms of tobacco sales promotion, and various measures to give nonsmokers freedom from the annoyance and hazards of breathing other people's smoke. Such measures may also help to change smokers' perception of their habit.

A complementary approach to the elimination of tobacco consumption could be changes in cigarette design. It would be necessary to analyse cigarette composition, especially for nicotine and tar delivery. If tar deliveries are relatively high, they should be lowered, since there is evidence that the risk of lung cancer associated with high-tar cigarettes is greater than that for low-tar cigarettes.

The meeting therefore RECOMMENDS that, although elimination of tobacco consumption should be the final goal, an upper limit, such as, perhaps, 15 mg, on cigarette tar deliveries be introduced as quickly as possible.

It should be noted, however, that there is no evidence that this step will reduce the incidence of other smoking-related diseases, such as heart disease. An initiative to reduce tar levels should not provide an excuse to avoid introducing other, much more important aspects of a smoking and health programme, and great care should be taken to ensure that efforts to reduce tar levels do not give the impression that smoking of low-tar cigarettes is without substantial hazard.

In view of the global extent of the smoking problem, international collaboration should be sought in controlling smoking. Several of the agencies of the United Nations family are ready to act, and it is recommended that member states stimulate these organizations to give priority to such activities and to seek their active assistance in national work, e.g., the World Health Organization could be asked to assist in planning and implementing various actions. Further, the Food and Agriculture Organization and the World Bank could be asked for assistance in finding alternative crops to replace tobacco in national agriculture.

Substantial assistance could be supplied by various nongovernmental organizations, e.g., the UICC.

To be fully effective, measures may have to be maintained for many years. The achievement and maintenance of a strong, consistent and effective strategy over such a long period poses obvious difficulties.

The meeting consequently RECOMMENDS that some permanent mechanism be established in each country where there are appreciable numbers of tobacco smokers to ensure that the control of tobacco-related diseases continues, over a long period, to receive an appropriate degree of attention.

REFERENCES

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon

International Union Against Cancer (1977) *Lung Cancer Prevention: Guidelines for Smoking Control (UICC Tech. Rep. Ser., Vol. 28)*, Geneva

World Health Organization (1979) *Controlling the Smoking Epidemic. Report of the WHO Expert Committee (WHO Tech. Rep. Ser., No. 636)*, Geneva

II. TOBACCO – A MAJOR HEALTH HAZARD

TOBACCO: AN OVERVIEW OF HEALTH EFFECTS

R. DOLL

Emeritus Professor of Medicine, University of Oxford,
Honorary Member Imperial Cancer Research Fund,
Cancer Epidemiology and Clinical Trials Unit,
Radcliffe Infirmary, Oxford, UK

INTRODUCTION

When tobacco was first introduced into Europe at the end of the sixteenth century, smoking was recommended for medicinal purposes; but its use soon became controversial and it was condemned as a noxious vice as often as it was praised for its prophylactic value. Little scientific evidence was, however, obtained about its effects until the late 1940s, at which period medical textbooks either ignored the subject altogether or referred briefly to tobacco amblyopia, a form of blindness associated with heavy pipe smoking and poor nutritional status, to tobacco angina, a rare form of angina in which chest pain was precipitated by smoking, and to cancers of the lip and tongue, which experienced surgeons had for long suspected were associated with the smoking of pipes. Then, in 1950, five papers appeared in the UK and the USA describing studies in which the smoking habits of large numbers of patients with cancer of the lung or, in some studies, with cancers of the mouth, pharynx, or larynx, were compared with the smoking habits of control patients (Doll & Hill, 1950; Levin *et al.*, 1950; Mills & Porter, 1950; Schrek *et al.*, 1950; Wynder & Graham, 1950). In one of these it was concluded that 'smoking is a factor, and an important factor, in the production of carcinoma of the lung' (Doll & Hill, 1950), and the modern era of the study of the health effects of smoking had begun.

The results of these studies are summarized in Table 1, together with those of three smaller and less detailed studies that had been published in Germany and the Netherlands in the preceding 11 years. In six, comparisons could be made between heavy smokers and nonsmokers, the results of which suggested that the risk of lung cancer among the former might be some 3–30 times greater than that among the latter, the differences being due partly to the different methods of smoking in different countries, but more importantly to the different definitions employed in the categorization of nonsmokers, who in at least one study included exsmokers.

The obvious way to check the conclusions drawn from these studies was to record the smoking habits of large numbers of men and women who smoked different amounts, to

Table 1. Smoking and lung cancer: results of early case-control studies

Reference	No. of men		Percentage of 'nonsmokers'		Percentage of 'heavy smokers'	
	With lung cancer	Without lung cancer	With lung cancer	Without lung cancer	With lung cancer	Without lung cancer
Müller, 1939[a]	86	86	3.5	16.3	65	36
Schairer & Schöniger, 1943[a]	93	270	3.2	15.9	52	27
Wassink, 1948[b]	134	100	4.5	19.0	55	19
Doll & Hill, 1950[c]	649	649	0.3	4.2	26	13
Levin *et al.*, 1950[d]	236	481	15.3	21.7	–	–
Mills & Porter, 1950[d]	444	430	7	31	–	–
Schrek *et al.*, 1950[d]	82	522	14.6	23.9	18	9
Wynder & Graham, 1950[d]	605	780	1.3	14.6	51	19

[a] Germany
[b] The Netherlands
[c] UK
[d] USA

follow them up over a period of years, and to see whether the recorded habits would serve to predict the risk of developing disease. By this method, it was, moreover, possible to study not only the relationship between smoking and lung cancer, but also that between smoking and all other diseases that were common enough for a substantial number of cases to be observed within the period of observation.

Many such studies have now been carried out, eight of which cover a large enough number of individuals for a long enough period for useful information to be obtained about a wide range of diseases (Hammond & Horn, 1958; Dunn *et al.*, 1960; Best *et al.*, 1961; Hammond, 1966; Kahn, 1966; Cederlöf *et al.*, 1975; Doll & Peto, 1976; Hirayama, 1977; Doll *et al.*, 1980). All have been limited to the study of mortality and all give qualitatively similar results, despite the fact that four were carried out in the USA, and one each in Canada, the UK, Japan and Sweden. All agree in showing that cigarette smoking is, in general, associated with a higher mortality than the smoking of pipes and cigars and most agree that pipe and cigar smoking are only weakly associated with any disease other than cancers of the upper respiratory and digestive tracts (lip, tongue, mouth, pharynx other than nasopharynx, larynx and oesophagus).[1] The rest of this paper will, therefore, be largely confined to the effects of cigarette smoking, which is, outstandingly, the principal way in which tobacco is now smoked throughout the world, apart from some parts of Asia and Africa where tobacco continues to be smoked in local forms that resemble small cigars more closely than cigarettes. When smoked, some of these local preparations deliver very large amounts of nicotine and tobacco tar, and the health effects of each need to be studied separately.

All these cohort studies show large differences in risk of the order of ten- to 40-fold between men smoking 20 or more cigarettes a day and lifelong nonsmokers for death due to cancer of the lung, some other cancers of the upper respiratory and digestive tracts, chronic bronchitis and emphysema (now preferably called chronic obstructive lung dis-

[1] Exceptionally, in Sweden the relative risk of lung cancers is equally high in pipe and cigarette smokers.

ease), respiratory heart disease, and aortic aneurysm, and smaller differences for the risk of death from several other cancers and a wide variety of other diseases ranging from ischaemic heart disease through pulmonary tuberculosis and peptic ulcer to cirrhosis of the liver and suicide. For many of these diseases, however, it has not been easy to decide how far these differences in mortality rates reflect the role of cigarette smoking in the production of disease and how far they are due to confounding, that is, to an association between smoking and other aspects of the individual's way of life, or aspects of his character, which are the direct cause of the condition.

PROOF OF CAUSATION

Intervention studies to produce disease are unacceptable in a civilized society, while intervention studies with random allocation of a measure to prevent disease are possible in theory but are seldom practicable for they cannot be carried out until people are already convinced that the proposed measure is likely to be beneficial, and if they are, it may be unethical to conduct the study. In these circumstances, we have to make up our minds on the basis of epidemiological observations combined with the results of animal experiments. The latter are, however, less helpful in relation to cigarette smoking than they are in relation to many other putative agents of human disease, partly because it is difficult to make animals smoke in the way that humans do, partly because of different anatomical features which modify the distribution of inhaled smoke droplets, and partly because cigarette smoke interacts with other aspects of human disease, such as diet-induced atheroma, that are not easily reproducible in laboratory experiments. The epidemiological evidence alone is, however, sometimes so clear that there is no difficulty in concluding that the factor being studied is a cause of the disease, just as Snow was able to conclude that water polluted with human faeces was a cause of cholera, before the cholera vibrio was discovered. Proof of causation, in the strict logical sense, is not, in these circumstances, obtainable, although the range of evidence that has accumulated about the relationship between smoking and some of the diseases with which it is associated – lung cancer, for example – is now sufficient to provide proof of causation, in the legal sense (i.e., proof beyond reasonable doubt).

Before reaching a conclusion that cigarette smoking actually causes many of the diseases with which the habit is associated, however, we have to consider not merely the fact of the association, but many other features as well. These include the strength of the association (a ten-fold increase in risk being, for example, much less easily explained on other grounds than an increase of, say, only 50%), the existence of a graduated risk proportional to the amount smoked, a reduction in risk following the cessation of smoking, the correspondence between the incidence of the disease in the two sexes, in different populations, and at different times with group figures for the consumption of cigarettes, and the results of laboratory investigations. In some cases, too, it has been possible to obtain biological evidence that is almost impossible to explain on any grounds other than that cigarette smoking causes the disease.

We have noted, for example, two such observations relating to lung cancer in the cohort study of British doctors whose smoking habits were recorded in 1951 and subsequently again at intervals of five to seven years. One showed that the mortality from lung cancer in

the British doctors fell relative to that in the country as a whole, corresponding to the relative reduction in the amount smoked, while the relative mortality from other cancers remained the same (Doll & Peto, 1976). The other showed that, among those who stopped smoking, the incidence of the disease hardly changed with the passage of time, something that has never been observed to occur under any other circumstances (Doll, 1978). Another example was recorded by Fletcher *et al.* (1976) and Fletcher and Peto (1977) when they followed 800 men for eight years, taking detailed smoking histories and making measurements of their respiratory function every six or 12 months. Their results showed that the deterioration in respiratory function progressed with time more rapidly in cigarette smokers than in non-smokers, but that when cigarette smokers stopped smoking, the rate of deterioration slowed down and approximated to that in men who had never smoked and whose deterioration was dependent on age alone.

These three observations, together with all the other human evidence, leave no room for doubt that cigarette smoking is one of the principal causes of both cancer of the lung and chronic obstructive lung disease and, in view of its relation to the latter, it must also be regarded as a cause of respiratory heart disease. Nor can there be any doubt that cigarette smoking contributes to the causation of several other diseases, including myocardial infarction, which because of its importance as a cause of death has been subject to intensive investigation in many countries, peripheral vascular disease (the clinical progress of which is clearly dependent on the continuation of smoking), aneurysm of the descending aorta, and half a dozen types of cancer, the relations of which to tobacco have recently been reviewed by the IARC (1986). These include cancers of the upper respiratory and digestive tracts and cancers of the bladder and pancreas.

For many of the other diseases that are associated with smoking, the conclusion that it contributes to their causation or lethality is more fairly described as presumptive than proved. This is unimportant for public health policy, as several of those diseases for which smoking is sufficiently well established as a cause to justify its avoidance are so common, and the death rate attributed to them so high, that it is immaterial whether another one or two dozen less common diseases are added to them. A proper understanding of the role of tobacco is, however, important medically, as, for some diseases, we need to know whether the cessation of smoking improves the results of treatment (as in the case of gastric ulcer) and, for all diseases, it helps our attempts to unravel the mechanism by which they are produced – or hinders them if we have judged incorrectly.

QUANTITATIVE ASSESSMENT OF EFFECTS OF SMOKING

For some of the diseases which, it is agreed, smoking helps to cause, it is not possible to say that the whole of the difference in incidence between smokers and nonsmokers is due to the effect of tobacco, as smoking is confounded with other factors that contribute independently to the aetiology of disease. This is certainly so for those cancers of the upper respiratory and digestive tracts that are also due to the consumption of alcohol, and this makes it very difficult to assess what proportion of the total incidence of these diseases can properly be ascribed to the effects of either.

Associations reflecting causation

For the other diseases that we can now confidently assert are caused by smoking, most or all of the difference in mortality between smokers and nonsmokers can be attributed directly to the habit. These are listed in Table 2. Three are among the most common causes of death in developed countries, as is shown in Table 2 by the proportion of deaths attributed to them in three of the countries for which detailed enumeration of deaths by cause are regularly published (that is, Denmark, England and Wales, and the USA). Reasonable proportions to attribute to smoking, taking into account that smaller proportions are attributable to smoking in women than in men, would be about 85% for the combined group of deaths due to cancer of the lung, chronic obstructive lung disease and aortic aneurysm, and 25% for the combined group of deaths due to cancers of the pancreas and bladder and ischaemic heart disease. This leads to the conclusion that 14–17% of all deaths in the three countries referred to in Table 2 would be caused prematurely by smoking, as a result of the contribution of smoking to these nine causes of death alone.

Positive associations of mixed or uncertain character

Table 3 lists 18 other diseases (or groups of diseases) that have nearly always been associated with smoking, whenever they have been examined separately. Five are specific types of cancer, one is a group of cancers of the upper respiratory and digestive tracts, and one consists of cancers of unspecified types, composed of a variety of cancers that are associated with smoking in different ways. Smoking and alcohol are both causes of cancers of the tongue, mouth, pharynx and larynx and of cancer of the oesophagus, and both act independently and synergistically. The attribution of risk is, moreover, complicated by the fact that smoking and the consumption of alcohol tend to be associated in the same individual so that very large numbers of people would have to be studied before it was possible to make any accurate estimate of the proportion of these cancers that would be avoided in the absence of smoking. In many countries it would certainly be large. In others,

Table 2. Proportion of deaths due to diseases the excess of which in smokers is attributable to smoking (three countries)

Cause of death	No. of deaths as % of total		
	Denmark 1982	England & Wales 1983	USA 1979
Cancer of lip	<0.1	<0.1	<0.1
Cancer of lung	5.2	6.1	5.1
Cancer of pancreas	1.4	1.0	1.1
Cancer of bladder	0.9	0.8	0.5
Ischaemic heart disease	29.9	27.0	28.8
Respiratory heart disease	<0.1	<0.1	<0.1
Aortic aneurysm	0.5	1.2	0.7
Peripheral vascular disease	0.1	0.2	0.1
Chronic obstructive lung disease	3.1	4.0	2.4
Total	41.1	40.3	38.9

Table 3. Proportion of deaths due to diseases the excess of which in smokers may be attributable to smoking in whole or in part (three countries)

Cause of death	No. of deaths as % of total		
	Denmark 1982	England & Wales 1983	USA 1979
Cancer of oesophagus	0.4	0.7	0.4
Cancer of tongue, mouth, pharynx and larynx	0.5	0.4	0.6
Cancer of stomach	1.4	1.8	0.7
Cancer of liver	0.3	0.2	0.3
Cancer of kidney	0.6	0.4	0.4
Cancer of cervix uteri	0.5	0.3	0.3
Cancer of unspecified site	0 9	1.4	1.3
Respiratory tuberculosis	<0.1	<0.1	<0.1
Hypertension	0.7	1.0	1.7
Myocardial degeneration	0.2	1.0	3.7
Arteriosclerosis	1.7	1.1	1.5
Cerebral thrombosis	1.5	1.7	2.0
Other cerebrovascular disease	8.1	10.0	6.8
Pneumonia	2.9	9.6	2.3
Other respiratory disease	1.0	1.3	1.1
Gastric ulcer	0.4	0.3	0.2
Duodenal ulcer	0.2	0.4	0.2
Hernia	0.1	0.1	<0.1
Total	21.4	31.5	23.6

where other and as yet unknown factors cause extremely high risks of cancer of the oesophagus (as in parts of the USSR, China and South and East Africa) and where chewing various mixtures of tobacco, betel and lime are responsible for high risks of cancers of the buccal cavity, the proportion of deaths from these causes that are attributable to smoking may be relatively low.

Whether any cancers of the stomach, liver, kidney and cervix uteri are attributable to smoking is still uncertain. Cohort studies have regularly shown higher rates in smokers than in nonsmokers, but the possibility of confounding with other factors exists – specially for cancers of the liver and cervix uteri – and the IARC (1986) was unable to come to a conclusion about them. It seems likely, however, that some cancers of the renal pelvis can be attributed to smoking, along with cancer of the bladder, even if adenocarcinomas of the body of the kidney cannot.

The relationship between smoking and the other 11 causes of death has not yet been studied in great detail. The excess mortality in smokers is generally relatively small (though sometimes absolutely large) and may, perhaps, be attributed to smoking on the grounds of analogy with, or misdiagnosis of, a disease that smoking is known to cause. On these grounds, for instance, some deaths from cerebral thrombosis may be attributed to smoking because of the known effect of smoking on the development of atheroma, and some deaths attributed to myocardial degeneration or nonspecifically to arteriosclerosis may also be due to smoking because they were really due to undiagnosed ischaemic heart disease.

For others the evidence is confused. Gastric ulcer, for example, has become less common as smoking has increased, yet controlled trials have shown that gastric ulcers heal more quickly when smoking is stopped and it seems very unlikely that the grossly increased mortality in smokers that has been found consistently in cohort studies does not reflect, at least in part, the inhibitory effect of smoking on an ulcer's healing. In part, too, it may reflect the greater liability of smokers to die of postoperative complications following haemorrhage or perforation.

Other diseases, such as pulmonary tuberculosis and inguinal hernia, can hardly be said to be caused by tobacco in the ordinary sense; but they may be aggravated by the cough that accompanies chronic productive bronchitis (which is certainly due to smoking) and they may, consequently, have a higher fatality in those who smoke than in those who do not. Some of the excess mortality from respiratory tuberculosis in smokers could, however, be due to confounding with alcoholism.

Associations reflecting confounding

For a few other causes of death that are more common in smokers than in nonsmokers, the difference in mortality can be attributed wholly to confounding. These are listed in Table 4. In people who die from these causes, smoking is presumably confounded with the consumption of alcohol, personality features, psychological stress, or even with all three.

For these causes of death, cultural differences that affect the nature and prevalence of the factors that are truly responsible for them may well also affect their confounding with tobacco, and it need not be assumed that similar relationships would be observed in studies in other countries. In any case, none of the deaths due to these causes need be attributed to tobacco – unless perhaps it proves that toxic chemicals in cigarette smoke make a small contribution to the grossly increased mortality from cirrhosis of the liver that is regularly observed in heavy cigarette smokers.

Associations possibly reflecting protection

Against the large number of diseases caused, or aggravated, by smoking there are some that smoking may help to prevent or ameliorate. That this should be so is hardly surprising, since tobacco smoke contains some 3000 chemicals with many different pharmacological

Table 4. Proportion of deaths due to diseases the excess of which in smokers is attributable to confounding (three countries)

Cause of death	No. of deaths as % of total		
	Denmark 1982	England & Wales 1983	USA 1979
Alcoholism	0.1	<0.1	0.3
Cirrhosis of liver	1.0	0.4	1.6
Poisoning	0.3	0.2	0.2
Suicide	2.7	0.7	1.4
Total	4.1	1.3	3.4

Table 5. Proportion of deaths due to diseases that smoking may help to prevent or ameliorate (three countries)

Cause of death	No. of deaths as % of total		
	Denmark 1982	England & Wales 1983	USA 1979
Cancer of endometrium	0.4	0.2	0.1
Parkinsonism	0.3	0.4	0.2
Ulcerative colitis	<0.1	<0.1	<0.1
Pre-eclampsia	<0.1	<0.1	<0.1
Total	0.7	0.6	0.4

effects. Four diseases that may fall into this category are listed in Table 5. Only parkinsonism has been studied intensively (Godwin-Austen *et al.*, 1982). The evidence that has been obtained from both case-control and cohort studies is strong, and suggests that the mortality attributable to it may be reduced by at least a half. Less data are available for ulcerative colitis, but those that have been obtained certainly suggest that smoking may help to prevent relapse (Jick & Walker, 1983). It is probable, too, that it reduces the risk of some hormone-dependent diseases, particularly cancer of the endometrium, as it reduces the level of oestrogens in the blood and lowers slightly the age of menopause (Baron, 1984), and it may (perhaps because of the hypotensive effect of thiocyanate) reduce the risk of pre-eclampsia (Palmgren *et al.*, 1973; US Surgeon General 1979a). It may also protect against post-operative venous thrombosis (Emerson & Marks, 1977), but this has not been included in Table 5, as the evidence is too incomplete.

Diseases generally unrelated to smoking

There remain, of course, many diseases that are unrelated to smoking. Few, however, are common in the three countries represented in Tables 2–5 and, in these countries, they account, in total, only for between a quarter and a third of all deaths.

Involuntary (or passive) smoking

In addition to the many effects on the smoker, smoking may also affect others, either by releasing smoke into the ambient atmosphere, where it is inspired involuntarily by non-smokers or by causing the absorption of toxic products into the circulation which, in pregnant women, may cross the placenta and affect the fetus.

The sidestream smoke that is not directly inspired by smokers differs in composition from the mainstream smoke that is directly inspired and from the remains of the mainstream smoke that is eventually exhaled. The differences are, however, differences in quantity rather than quality, so that involuntary smoking may have similar effects on non-smokers as voluntary smoking has on smokers, although the chance of the effects occurring will be very much less. Whether it represents a hazard or not will depend on whether the effect is one that occurs in proportion to the dose received down to the lowest levels, as is believed to be the case with the production of cancer, or whether there is a threshold dose for the effect, below which none is produced. How great the risk is for individual non-

smokers will be discussed later in this Symposium, but it is generally too small to have any measurable effect nationally in comparison with that produced by smoking voluntarily. An exception is the effect on young children, who have been found to have more respiratory symptoms and twice as many attacks of bronchitis and pneumonia when their parents smoke as when they refrain (Colley *et al.*, 1974; Leeder *et al.*, 1976).

The fetus, as would be expected, responds differently from the child and adult, the principal effect of the mother's smoking being a reduction in weight at each stage of gestation with, in consequence, a small increase in perinatal mortality (US Surgeon General, 1979b). Whether any of the chemicals in smoke are absorbed in sufficient amounts to be teratogenic is still in dispute; but if any malformations are produced, the increase in incidence over the background rate in children born to nonsmoking mothers is certainly small (see Landesman-Dwyer & Emmanuel, 1979 and Johnston, 1981, for reviews). The fetus might also be affected if smoking had damaged the germ cells in either parent. No such effect has, however, yet been observed.

CONCLUSION

The smoking of tobacco, it is now clear, has many gross effects on health which, in some countries, lead to premature death in a substantial proportion of the whole population. For the three countries for which data are given in Tables 3–5, the proportion must be at least one in seven and may be materially greater, depending on the proportion of the excess mortality from the diseases listed in Table 3 which occurs in smokers that is attributed to smoking, and the proportion that is attributed to the confounding of smoking with other etiological agents.

In many other countries the proportion must be much the same, while in others it is likely to be less, depending on the amount of illness due to other causes, the prevalence of etiological agents that interact with smoking in the production of disease, and the smoking habits of the population, both now and in the past.

In countries where infectious diseases are common, particularly tropical countries where a great deal of illness is due to parasitic infections, the proportion of illness attributable to smoking is small; and, as the consumption of tobacco in these countries tends also to have been small in the past, the proportion of all illness that is now attributable to smoking is, in some of these countries, very small indeed at present, although in those where large increases in the habit have emerged recently, large increases in smoking-related disease are likely to follow eventually.

In other countries smoking may be common and may have been so for many years, yet the effects may be different, because of variation in the prevalence of other agents with which it interacts. It interacts, for example, with alcohol in the production of cancer of the oesophagus and with asbestos in the production of cancer of the lung. The former interaction results in a grossly increased risk of cancer of the oesophagus in north-west France, where the consumption of alcohol is both common and heavy, and the latter grossly increases the amount of lung cancer attributable to smoking in some occupational groups. It is, however, relatively unimportant everywhere at the national level, as the proportion of the population exposed to material amounts of asbestos is generally small.

Smoking interacts, too, with the level of blood cholesterol, approximately multiplying the effect of high levels (Mann *et al.*, 1976) and, in countries where these levels are low, the amount of myocardial infarction it produces, though still absolutely large, can be relatively small. This is so, for example, in Japan and some other parts of Eastern Asia, where low levels of blood cholesterol are due to a diet that includes relatively little fat, much of which is polyunsaturated. How far smoking interacts with other factors to increase the risk of many other smoking-related diseases is still unclear. It is, for example, uncertain how far the effect of smoke in producing chronic obstructive lung disease is modified by background levels of atmospheric pollution and by social conditions that lead to respiratory infection in childhood.

The third factor – the variation in smoking habits – is obviously important as the amount of disease produced by smoking cannot be large when smoking is uncommon. The effect is, however, much more complex than may appear at first sight, not only because of the importance of the method of smoking and the type of cigarettes (particularly the amount of tar that they deliver) but also because heavy consumption is associated with little disease until smoking has been common for many years. The relationship between the risk of disease and the duration of smoking has been worked out most clearly for cancer of the lung and chronic obstructive lung disease, but a similar relationship probably holds for the other smoking-induced cancers and may hold for many other smoking-induced diseases as well. The importance of the relationship between risk and duration of smoking has been shown most clearly in the trends in mortality from lung cancer in the UK, Finland and the USA, which will be discussed later in this Symposium. Because duration of smoking is so important, it not infrequently happens that the amount of tobacco consumed may be much greater in one country than in another while the lung cancer mortality rate may be temporarily much lower, as is the case in Japan in comparison with the UK.

All these factors combined make it very difficult to estimate the contribution of smoking to morbidity and mortality in different countries. It certainly cannot be estimated solely from knowledge of current smoking habits, and the figures for each country can be determined only after detailed study of the local conditions.

REFERENCES

Baron, J.A. (1984) Smoking and estrogen-related disease. *Am. J. Epidemiol.*, ***119,*** 9–22

Best, E.W.R., Josie, G.H. & Walker, C.B. (1961) A Canadian study of mortality in relation to smoking habits: A preliminary report. *Can. J. public Health,* ***52,*** 99–106

Cederlöf, R., Friberg, L., Hrubec, Z. & Lorich, U. (1975) *The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity,* Stockholm, Department of Environmental Hygiene, Karolinska Institute

Colley, J.R.T., Holland, W.W. & Corkhill, R.T. (1974) Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. *Lancet,* ***ii,*** 1031–1034

Doll, R. (1978) An epidemiological perspective of the biology of cancer. *Cancer Res.*, ***38,*** 3573–3583

Doll, R. & Hill, A.B. (1950) Smoking and carcinoma of the lung. *Br. med. J.*, ***ii,*** 739

Doll, R. & Peto, R. (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. *Br.med. J.*, ***ii,*** 1525–1536

Doll, R., Gray, R., Hafner, B. & Peto, R. (1980) Mortality in relation to smoking: 22 years' observations on female British doctors. *Br. med. J.*, ***i***, 967–971

Dunn, J.E., Linden, G. & Brelow, L. (1960) Lung cancer mortality experience of men in certain occupations in California. *Am. J. public Health*, ***50***, 1475–1487

Emerson, P.A. & Marks, P. (1977) Preventing thromboembolism after myocardial infarction: Effect of low dose heparin on smoking. *Br. med. J.*, ***i***, 18–20

Fletcher, C. & Peto, R. (1977) The natural history of chronic airflow obstruction. *Br. med. J.*, ***i***, 1645–1648

Fletcher, C., Peto, R., Tinker, C. & Speizer, F.E. (1976) *The Natural History of Chronic Bronchitis and Emphysema*, Oxford, Oxford University Press

Godwin-Austen, R.B., Lee, P.N., Marmot, M.G. & Stern, G.M. (1982) Smoking and Parkinson's disease. *J. neurol. neurosurg. Psychiatry*, ***45***, 577–581

Hammond, E.C. (1966) *Smoking in relation to the death rates of one million men and women.* In: Haenszel, W., ed., *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases (National Cancer Institute Monograph No. 19)*, Bethesda, MD, National Cancer Institute, pp. 127–204

Hammond, E.C. & Horn, D. (1958) Smoking and death rates: Report on forty-four months of follow-up of 187,783 men. *J. Am. med. Assoc.*, ***166***, 1159–1172 and 1294–1308

Hirayama, T. (1977) *Smoking and cancer: A prospective study on cancer epidemiology based on census population in Japan.* In: *Health Consequences, Education, Cessation Activities, and Governental Action. Smoking and Health II (Proceedings of the Third World Conference on Smoking and Health, DHEW Publication No. (NIH) 77-1413)*, Washington DC, US Government Printing Office, pp. 65–72

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon

Jick, H. & Walker, A.M. (1983) Cigarette smoking in ulcerative colitis. *New Engl. J. Med.*, ***308***, 261–263

Johnston, O. (1981) Cigarette smoking and the outcome of human pregnancies: A status report on the consequences. *Clin. Toxicol.*, ***18***, 189–209

Kahn, H.A. (1966) *The Dorn study of smoking and mortality among US veterans: Report on eight and one half years of observation.* In: Haenszel, W., ed., *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases (National Cancer Institute Monograph No. 19)*, Bethesda, MD, National Cancer Institute, pp. 1–125

Landesman-Dwyer, S. & Emmanuel, I. (1979) Smoking during pregnancy, *Teratology*, ***19***, 119–126

Leeder, S.R., Corkhill, R.T., Irwig, L.M., Holland, W.W. & Colley, J.T.R. (1976) Influence of family factors on the incidence of lower respiratory illness during the first year. *Br. J. prev. soc. Med.*, ***30***, 203–213

Levin, M.L., Goldstein, H. & Gerhardt, P.R. (1950) Cancer and tobacco smoking. *J. Am. med. Assoc.*, ***143***, 336–338

Mann, J.I., Doll, R., Thorogood, M., Vessey, M.P. & Waters, W.E. (1976) Risk factors for myocardial infarction in young women. *Br. J. prev. soc. Med.*, ***30***, 94–100

Mills, C.A. & Porter, M.M. (1950) Tobacco-smoking habits and cancer of the mouth and respiratory system. *Cancer Res.*, ***10***, 539–542

Müller, F.H. (1939) Tobacco abuse and carcinoma of the lung (Ger.). *Z. Krebsforsch.*, **49**, 57–85

Palmgren, B., Wahlen, T. & Wallander, B. (1973) Toxaemia and cigarette smoking during pregnancy: Prospective consecutive investigation of 3,927 pregnancies. *Acta obstet. gynecol. scand.*, **52**, 183–185

Schairer, E. & Schöniger, E. (1943) Lung cancer and tobacco use (Ger.). *Z. Krebsforsch.*, **54**, 261–269

Schrek, R., Baker, L.A., Ballard, G.P. & Dolgoff, S. (1950) Tobacco smoking as an etiologic factor in disease: Cancer. *Cancer Res.*, **10**, 49–58

US Surgeon General (1979a) *Smoking and Health*, Washington DC, US Government Printing Office, pp. 8/41–8/42

US Surgeon General (1979b) *Smoking and Health*, Washington DC, US Government Printing Office, pp. 8/11–8/30

Wassink, W.F. (1948) Etiology of lung cancer (Dutch). *Med. Tijdschr. Geneesk*, **92**, 3732–3747

Wynder, E.L. & Graham, E.A. (1950) Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *J. Am. med. Assoc.*, **143**, 329–336

INFLUENCE OF DOSE AND DURATION OF SMOKING ON LUNG CANCER RATES

R. PETO

Imperial Cancer Research Fund,
Reader in Cancer Studies,
Nuffield Department of Clinical Medicine,
Radcliffe Infirmary, Oxford, UK

SUMMARY

Lung cancer risks depend far more strongly on the duration than on the daily dose-rate of cigarette smoking. For example, a three-fold increase in the daily dose-rate may produce only about a three-fold increase in effect, while a three-fold increase in duration might produce about a 100-fold increase in effect. Hence, a few decades after cigarette smoking becomes widespread, national lung cancer rates may remain very misleadingly low, even though they will eventually become extremely high.

INTRODUCTION

Worldwide, lung cancer already kills more people than any other neoplastic disease does, and the annual number of deaths it causes is still rising rapidly in many countries. For example, in the USSR, the number of men diagnosed each year as having lung cancer was about 40000 in 1970, but it will be about 80 000 in the mid-1980s and well over 100 000 by the early 1990s, and still rising rapidly (Zaridze & Gurevicius, this volume, p. 87). These increases are due partly to increases in the numbers of older men and partly to increases in the thoroughness of detection of the disease, but chiefly they are due to the *delayed* effects of past increases in cigarette usage. This delay between cause and full effect may mean that the main increase in cigarette usage in a country takes place over a decade or two during which no large absolute increase in lung cancer incidence occurs, and that later on a vast increase in lung cancer incidence then takes place over the course of a few decades during which no large further increase in smoking is occurring. Obviously, without a quantitative understanding of the relevance of *dose* and of *time* in tobacco carcinogenesis, there would be plenty of scope for misunderstandings to become established during the decades while tobacco smoke exposure is approximately constant but lung cancer rates are increasing

rapidly. Hence, the present chapter is on dose and time relationships for tobacco-induced lung cancer, although some other aspects of the epidemiology of lung cancer will also be drawn in. The first section discusses the time relationships, and then other aspects of the effects of smoking are reviewed.

THE NEED FOR PROLONGED EXPOSURE

There are a few key features of the effects of tobacco on lung cancer incidence that are slightly counter-intuitive. Chief among them, and the key to any proper understanding of tobacco carcinogenesis, is the extraordinary relevance of the *duration* of smoking to lung cancer onset rates. For example, after 45, 30 and 15 years of cigarette smoking, the excess annual incidence rates of lung cancer might be about 0.5%, 0.1% and under 0.01% (Table 1). The annual lung cancer incidence rates to be expected among smokers may be estimated by adding up a *background* (i.e., nonsmoker) rate, which, like the onset rates of many other types of cancer, depends strongly on age (but not, by definition, on tobacco exposure), plus an *excess* rate, which depends strongly on duration of regular tobacco exposure (but not otherwise, at least to a first approximation, on age). Typical background and excess rates for males are depicted in Figure 1 (from Doll, 1971), and those for females might be about two-thirds as great.

Thus, a three-fold increase in the duration of regular tobacco use can increase the annual incidence of lung cancer about 100-fold. This particular relationship, which has been derived from detailed epidemiological studies on defined populations, may apply quite widely, even though in other populations the absolute risks may differ slightly. For example, in the entire adult male population of England and Wales in the 1970s, the

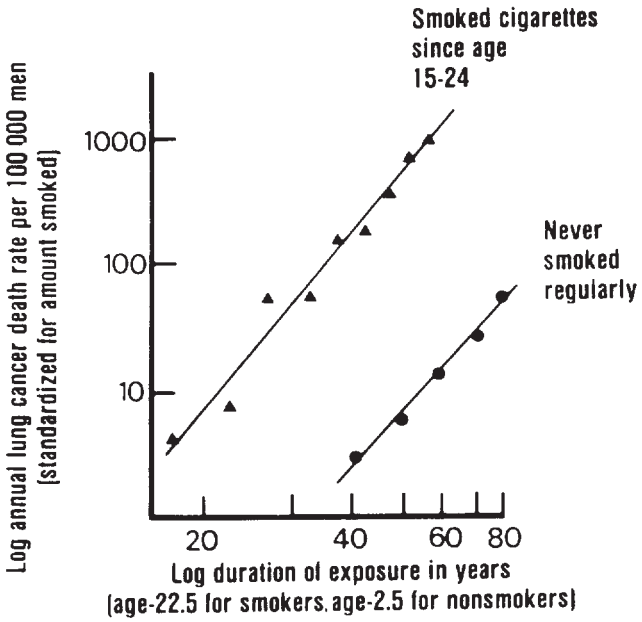
Table 1. Approximate[a] effects of various durations of cigarette smoking on annual incidence of lung cancer

Years of cigarette smoking	Annual[b] excess incidence	
	Moderate smokers	Heavy smokers
15	0.005%	0.01%
30	0.1%	0.2%
45	0.5%	1%
(60)	(1.5%?)	(3%?)

[a] Estimated from data reported by Doll and Peto (1978) for male British doctors. The cumulative risks would be far greater than these annual risks, of course, so an eventual total of over 10% of regular cigarette smokers may die of tobacco-induced cancer, depending on the number and type of cigarettes smoked.

[b] The *cumulative* incidence will, of course, be far greater than the annual incidence. For example, at the above lung cancer rates (and in the absence of other causes of death), men who smoked cigarettes regularly from early adult life onwards would have about a 10% (if moderate) or 20% (if heavy) probability of developing lung cancer at or before their mid-seventies. Since, in addition, smoking kills more people by diseases other than lung cancer than it kills by lung cancer, a minimal statement of the total risks associated with the habit would be that *about a quarter of all young adults who smoke cigarettes regularly will be killed before their time by the habit.* (Some of those killed would have died soon anyway, but others would have lived on for another 5, 10, 20, 30 or more years, the average amount of life lost being 10–15 years.)

Fig. 1. Background and excess risks. Lung cancer death rates among nonsmokers (lower line) in relation to age, and among regular cigarette smokers (upper line) in relation to approximate years of smoking (from Doll, 1971).



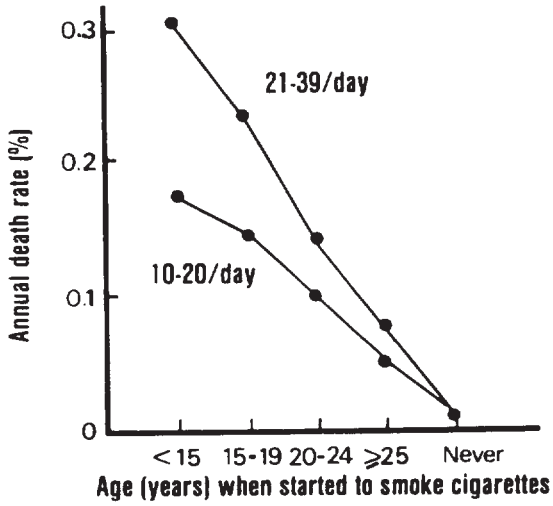
These two lines can be used directly to indicate the approximate background and excess risks, for in middle and old age the lung cancer incidence rates among people who have smoked cigarettes throughout adult life greatly exceed the rates among nonsmokers of similar age. (This might not, however, be true for people who did not begin to smoke substantial numbers of cigarettes until middle age, for the background and the excess risks indicated by these lines are, respectively, approximately 10^{-3} of the fourth power in years of age and 10^{-4} of the fourth power of years of regular cigarette smoking.)

proportions of smokers at various different ages were not very different, but the male lung cancer death rate at 80 years of age was about 100 times that at 40 years of age. This is probably because the 80-year-old smokers had been smoking cigarettes for about three times as long as the 40-year-old smokers (and not chiefly because of the frailty of the old; Peto, 1985).

The most surprising consequence of the overwhelming effects of the *duration* of smoking is illustrated, using real data[1], in Figure 2, which shows how strongly the annual excess risk of death from lung cancer at 60 years of age depends on whether men started smoking at 15 or at 25 years of age (i.e., on whether by the age of 60 they had smoked for 45, or for only 35, years). Failure to appreciate the relationship illustrated in Figure 2 has led to a variety of unjustifiable conclusions, e.g., that cigarettes do not cause lung cancer or, less perversely, that low-tar cigarettes have at least as great an effect as high-tar ones (National Academy of Sciences/National Research Council, 1982), that air pollution is of com-

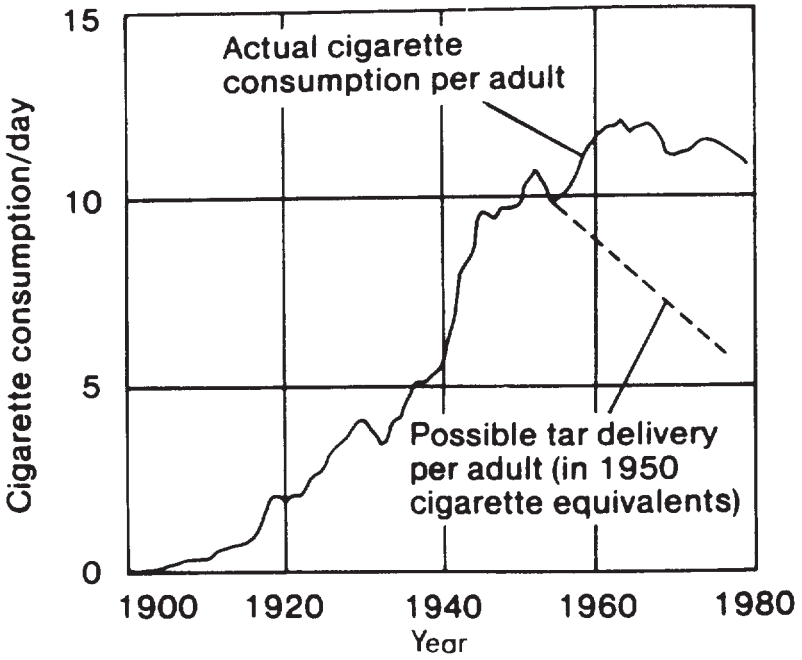
[1] The data utilized are from the third largest prospective survey yet reported, and are similar to the findings of the larger two surveys; the corresponding results from all three of these surveys are presented in the US Surgeon-General's 1982 report (US Department of Health and Human Services, 1982).

Fig. 2. The relevance of smoking in early adult life



Relationship, in prospective survey data of regular smokers, between the age when regular cigarette smoking began in early adult life and lung cancer death rates at age 55–64 (mean, age 60) for US males (from Doll & Peto, 1981, Appendix E). Data are presented separately for heavy and for moderate smokers.

Fig. 3. Trends in US cigarette consumption

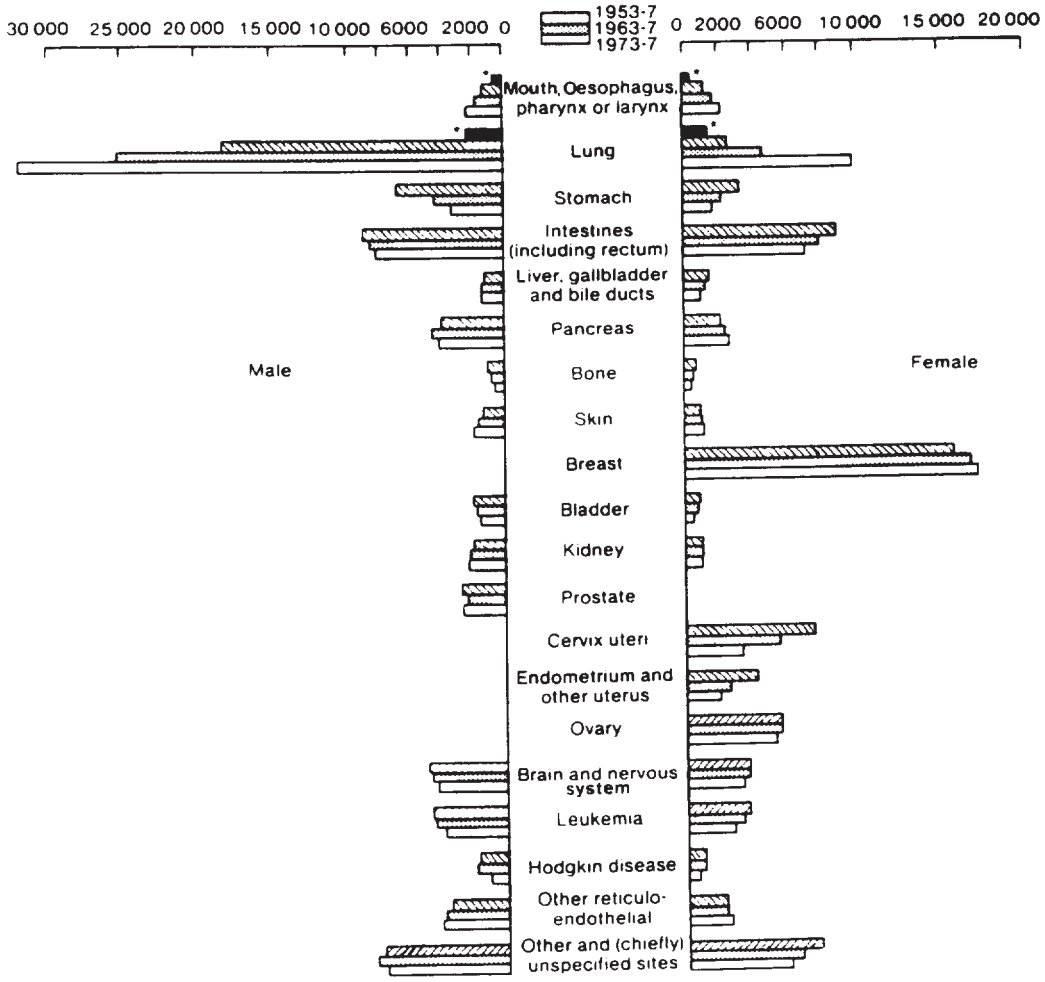


Mean daily sales of manufactured cigarettes per US adult aged over 18 years, with a crude estimate of tar yield per adult (from Doll & Peto, 1981). The estimate of tar yield allows approximately for decreases since the 1950s in tar yield per cigarette smoked in a standard manner, but not for any systematic changes in the manner in which cigarettes are smoked.

parable importance to tobacco (but see, however, Cederlöf *et al.*, 1978), or that new causes of lung cancer (rather than the delayed effects of past changes in tobacco usage) are chiefly responsible for the rapid increase in lung cancer in recent years. In each case, the point that is often overlooked is that current patterns of lung cancer mortality in late middle age or in old age depend strongly not only on current patterns of tobacco usage, but also on the patterns of cigarette usage among young adults as much as half a century ago.

Thus, current trends, current urban/rural differences and current international differences in lung cancer reflect, among other things, past trends, past urban/rural differences

Fig. 4. Recent trends in US cancer mortality

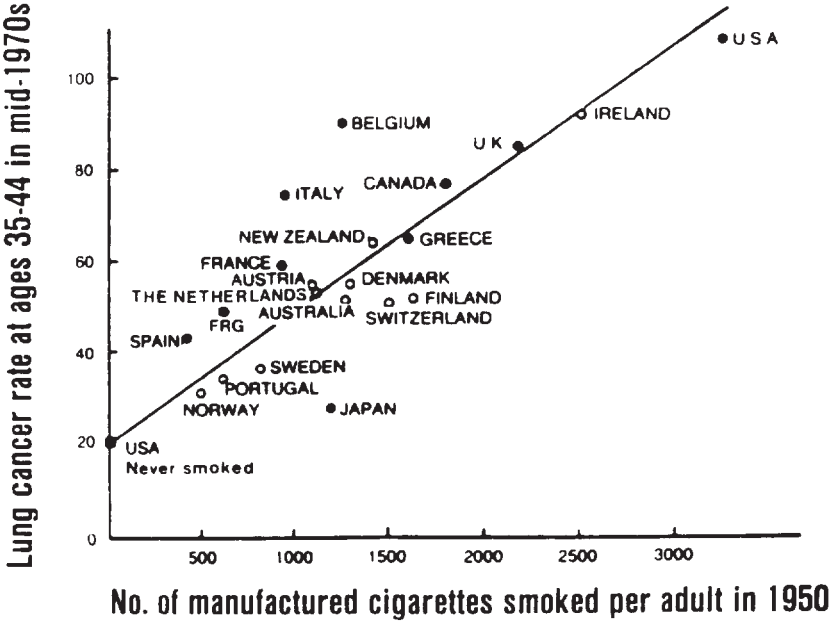


Age-standardized death certification rates (per 100 million people aged under 65) in the 1950s (top bar), the 1960s (middle bar) and the 1970s (bottom bar) for various types of cancer in the USA (from Doll & Peto, 1981). For cancers of the lung and upper respiratory and digestive tracts, estimated rates for lifelong nonsmokers are also given (bar*, above the rates for the 1950s).

and past international differences in cigarette usage by young adults. Consider, for example, the extent to which current trends in US lung cancer mortality rates among men now aged 70 might be affected by the large trends in cigarette consumption 50 years ago among people then aged 20. (For details, see Appendix E of Doll & Peto, 1981.) In 1930, US cigarette consumption was increasing rapidly among young men, and national sales rose from 1 cigarette/adult per day in 1915 to about 10/adult per day in 1945. The effects of those increases are only now becoming fully apparent, and largely or wholly as a delayed result of them US lung cancer rates in men in late middle and old age are still rising steeply, despite the fact that cigarette sales per adult have remained at a fairly steady 10–12/day ever since 1945, and that tar levels per cigarette have fallen substantially (Fig. 3). Contrary to various suggestions, the 'discrepancy' that has been seen for the past 25 years in the USA between rising lung cancer rates (see Fig. 4) and falling tar levels does *not* imply, or even suggest, that Americans are exposed to increasing levels of carcinogenic pollutants other than tobacco, nor, as a recent report (National Academy of Sciences/National Research Council, 1982) suggested, that tar-level reductions in cigarettes have been ineffective. (Indeed, but for tar-level reductions, the current increases in US lung cancer mortality rates would probably be appreciably more rapid.)

Likewise, in many countries, the smoking of manufactured cigarettes by young adults may have tended to become widely established in towns before it became so in the

Fig. 5. Lung cancer and smoking in the same generation



Relationship between lung cancer mortality rates (mean of male and female rates) for one generation in early middle age with manufactured (excluding hand-rolled cigarettes in Belgium and smuggled cigarettes in Italy) cigarette consumption when that generation of people were in early adult life: data for various countries, and for US nonsmokers estimated by fitting a power-law relationship to the prospective survey data reported by Garfinkel (1981). From Doll & Peto (1981)

surrounding countryside. If so, then half a century ago cigarette smoking was probably more prevalent among young men in towns than among young men in the country. Disparities in recent years between urban and rural lung cancer rates among today's old smokers may therefore be chiefly due not to air pollution, but rather to a delayed effect of past urban/rural differences in cigarette usage among the people who were then young but who are now old.

Finally, it is wholly wrong to suggest that the poor international correlation between *current* smoking habits and *current* lung cancer rates indicates that smoking is not the chief determinant of worldwide lung cancer mortality. For, such a correlation effectively relates the lung cancer rates of the grandparents to the smoking habits of their grandchildren. If instead the national lung cancer rates *for one generation* are related to national cigarette consumption rates when *that* generation consisted of young adults, a moderately close relationship does emerge (Fig. 5).

OTHER FEATURES OF THE EPIDEMIOLOGY OF SMOKING AND LUNG CANCER

Dose-response relationships

In Table 1, it may be seen that doubling the dose may *approximately* double the excess risk at each age. Partly because of difficulties of dosimetry[2], it is not really known whether, as Doll and Peto (1978) tentatively suggested, a doubling of the true dose-rate produces an approximately four-fold increase in the age-specific effect, or whether, as is suggested by much other data, it produces merely a two-fold increase. (Whatever the exact truth, however, it is clear that smoking two packs/day for 20 years is far less hazardous than smoking one pack/day for 40 years, so any analyses based on inappropriate concepts such as 'pack-years' should be treated warily.)

Time course of the effects of stopping smoking

If smoking ceases, the annual excess risk remains roughly (perhaps to within a factor of two?) constant thereafter. Referring to Table 1, it may be seen that the annual excess risk after 30 years of smoking is about 0.1%, so if a smoker stops after 30 years then approximately this annual excess risk may persist indefinitely. Thus, for example, 15 years later the annual excess risk might still be about 0.1% instead of the 0.5% that it would have been had smoking continued, so about 80% of the excess risk is being avoided. (It is not, however, true that the annual *absolute* excess risk decreases substantially, and still less is it true that it decreases to zero after 10 years; only one prospective study has suggested that,

[2] The effective dose may not be simply proportional to the number of cigarettes smoked per day, for the carbon monoxide uptake per cigarette appears to be less for heavy than for moderate smokers. Also, since the chief target area is the main airways, rapid inhalation may deposit less on them than slow inhalation does (a suggestion reinforced by reports, e.g., Doll & Peto, 1976, that in some, although not all, studies heavy smokers who describe themselves as 'not inhaling' get *more* lung cancer than do comparably heavy smokers who 'do inhale'!).

and the others clearly refute it.) Because the large increases in annual risk that would otherwise develop are avoided by stopping smoking, from a practical public health viewpoint this means that cessation works, since *people who stop smoking before they have cancer thereby avoid most of the risk of getting cancer from the habit.* The time course of the effects of changes in smoking that fall short of complete cessation will be discussed in the chapter on the effects on national mortality rates of changes in cigarette manufacture that reduce the amount of 'tar' delivered per cigarette (see p. 211).

The importance of cigarettes as opposed to pipes

In the UK and the USA, cigarettes appear to have a far greater effect than pipe or cigar tobacco did, and so the switch earlier this century from pipes to cigarettes has produced vast increases in lung cancer rates. The reasons for this difference are not adequately known, especially as the smoke from pipes and cigars is about as carcinogenic for laboratory animals as that from cigarettes. One suggestion is that the difference depends chiefly on the greater alkalinity of the smoke from pipes and cigars, which might make inhalation less pleasant and facilitate the transport of nicotine across the oral mucosa, thereby obviating the need to inhale (see Wald *et al.*, 1981). This suggestion might not be difficult to test, and, if confirmed, might point to an important way of diminishing the hazards of cigarettes, although at present this remains speculative.[3] A related suggestion is that the 'air-cured' tobacco of, for example, certain French cigarettes somewhat resembles pipe tobacco and is therefore substantially less carcinogenic than the 'flue-cured' tobacco typical of British and American cigarettes; but the international differences in lung cancer rates on which this suggestion rested were not reliable, because they owed so much to differences in *duration* of cigarette smoking. (During the 1930s and 1940s, for example, British cigarette consumption was four times that in France.) Recently, evidence has emerged from a large case-control study (Benhamou *et al.*, 1985) that, if anything, the converse is likely to be true – that is, that regular use of cigarettes made of dark French tobacco may be early twice as hazardous as similar use of cigarettes made of 'light' tobacco.

'Interaction' with other causative factors

A variety of other causative factors for lung cancer are known, of which the best studied are asbestos, ionizing radiations and urban air pollution. All these have a far greater absolute extra effect on smokers than on nonsmokers (illustrated, for asbestos, in Table 2), as may various other causative factors. Some of the benefits of control of certain other causes of lung cancer may therefore be attainable indirectly by reducing exposure to tobacco. Since, however, effective exposures to tobacco are currently increasing in many countries (and, even where they are decreasing, the immediate decreases are unlikely to be

[3] In the study of Cederlöf *et al.* (1975), in Sweden, pipe smokers had the same ten-fold excess risk of lung cancer that cigarette smokers had, which rather suggests that the smallness of the effects in the UK or the USA might be due more to traditions of pipe smoking than to the pharmacology of the smoke – and, it is unlikely that such traditions are themselves *wholly* determined by pharmacological factors.

Table 2. Multiplicative effects of heavy exposure to asbestos and of smoking on lung cancer risks[a]

	Relative risk of lung cancer for	
	Nonsmokers	Smokers
No known asbestos exposure	1 (reference category)	11
Heavy asbestos exposure (prolonged employment as a lagger before 1968 US dust controls were introduced)	5	53

[a] Data from Selikoff (1981). Note that although such heavy exposure to asbestos is no longer permitted in many countries, places where heavy occupational exposures do still occur may offer excellent opportunities for limited disease prevention, since even if the workers do not smoke (so the excess risk of bronchial carcinoma is low) the risk of mesothelioma, which does not depend on synergy with tobacco, will still be high.

enormous), the theoretical possibility of avoiding exposure to tobacco clearly does not justify inaction when other substantial causes of lung cancer can be materially reduced.[4]

Miscertification of lung cancer deaths

People, and especially old people, dying of lung cancer may never have their disease recognized, and may be miscertified as dying of some other condition. Progressive rectification of such errors produces large, purely artefactual, increases in lung cancer death certification rates. In middle-aged people, such effects were substantial during the first half of the century, even in developed countries – for example, when diagnostic radiology was introduced during the 1920s it produced about a three-fold increase in British lung cancer death *certification* rates. Now, for middle-aged people, such effects are chiefly limited to the developing countries. In people in old age, however, large (e.g., two-fold) artefactual increases have continued to emerge since 1950, even in various developed countries, while among old people in many developing countries lung cancer death certification rates are still grossly unreliable [as are 'age-standardized' lung cancer death certification rates, unless standardization is to the truncated age-range 35–64 recommended by the IARC (Waterhouse *et al.*, 1976) to circumvent such difficulties].

Effects of age

The effects of the duration of smoking are so strong, and so closely correlated with age, that it is virtually impossible to determine exactly whether ageing *per se* has any independent effect on excess lung cancer rates among people of different ages who have all smoked similarly for a similar number of years, or whether it has no material effect. If age has any

[4] Apart from smoking, asbestos, ionizing radiations and combustion products, the other reliably established causes of lung cancer are bis(chloromethyl) ether, mustard gas, and certain compounds or oxidation states of arsenic, chromium and nickel (Doll & Peto, 1981).

independent effect, however, this is small compared with the effect of duration of smoking (e.g., Peto, 1985). For practical purposes, of course, the reason smoking in the teenage years produces high risks (see Fig. 2) is immaterial: it does not matter whether it acts merely through increasing the total duration of smoking by a few extra years, or whether in addition the teenage lung is slightly more, or slightly less, vulnerable than the adult lung. What chiefly matters from a public health viewpoint is that damage to the body accumulates so *those who start to smoke in their teens will be at much greater risk of being killed by tobacco in middle or old age than those who start later in life.*

CONCLUSION

Among regular cigarette smokers, the excess lung cancer risk depends strongly not only on smoking habits during the past few years, but also on smoking habits during early adult life. Hence, current lung cancer rates in countries where smoking among young adults became widespread less than half a century ago may be serious underestimates of the eventual magnitude of the tobacco-induced lung cancer hazard.

REFERENCES

Benhamou, S., Benhamou, E., Tirmarche, M. & Flamant, R. (1985) Lung cancer and use of cigarettes: a French case-control study. *J. natl Cancer Inst.*, ***74***, 1169–1175

Cederlöf, R., Friberg, L., Hrubec, Z. & Lorich, U. (1975) *The Relationship of Smoking and Some Covariables to Mortality and Cancer Morbidity*, Stockholm, Department of Environmental Hygiene, Karolinska Institute

Cederlöf, R., Doll, R., Fowler, B., Friberg, L., Nelson, N. & Vouk, V. (1978) Air pollution and cancer: risk assessment methodology and epidemiological evidence. *Environ. Health Perspect.*, ***22***, 1–12

Doll, R. (1971) The age distribution of cancer: implications for models of carcinogenesis (with discussion). *J. R. Statist. Soc. A*, ***134***, 133–136

Doll, R. & Peto, R. (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. *Br. med. J.*, ***ii***, 1525–1536

Doll, R. & Peto, R. (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. *J. Epidemiol. Commun. Health*, ***32***, 303–313

Doll, R. & Peto, R. (1981) Quantitative estimates of avoidable risks of cancer in the United States today. *J. natl Cancer Inst.*, ***66***, 1191–1308

Garfinkel, L. (1981) Time trends in lung cancer mortality among non-smokers and a note on passive smoking. *J. natl Cancer Inst.*, ***66***, 1061–1066

National Academy of Sciences/National Research Council (1982) *Reduced Tar and Nicotine Cigarettes: Smoking Behavior and Health*, Washington DC, National Academy Press

Peto, R. (1985) *There is no such thing as ageing, and cancer is not related to it.* In: Likhachev, A., Anisimov, V. & Montesano, R., eds, *Age-related Factors in Car-*

cinogenesis (IARC Scientific Publications No. 58), Lyon, International Agency for Research on Cancer, pp. 43–53

Selikoff, I.J. (1981) *Constraints in estimating occupational cancer mortality*. In: Peto, R. & Schneiderman, M.A., eds, *Quantification of Occupational Cancer*, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 3–17

US Department of Health and Human Services (1982) *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General*, Washington DC, US Public Health Service

Wald, N., Idle, M., Boreham, J., Bailey, V. & Van Vunakis, H. (1981) Serum cotinine levels in pipe smokers: evidence against nicotine as a cause of coronary heart disease. *Lancet*, ***ii***, 775–777

Waterhouse, J., Muir, C., Correa, P. & Powell, J., eds (1976) *Cancer Incidence in Five Continents Vol. III (IARC Scientific Publications No. 15)*, Lyon, International Agency for Research on Cancer

SMOKELESS TOBACCO AND CANCER: AN OVERVIEW

C.S. MUIR & D.G. ZARIDZE[1]

International Agency for Research on Cancer, Lyon, France

Tobacco is used in many ways other than smoking. This communication describes briefly those habits associated with the use of smokeless tobacco and reviews the key evidence linking most of them to an increased risk of cancer of the mouth and pharynx.

SNUFF: INHALED

In 1761, Hill described two patients with nasal cancer which was ascribed to heavy snuff inhalation (Redmond, 1970). However Harrison (1967), describing antral lesions in a series of confirmed snuff users, remarked that the use of commercial snuffs available in the UK did not appear to be associated with an increased risk of sinus cancer. Brinton *et al.* (1984) in a case-control study in North Carolina and Virginia (1970–1980) found an increased relative risk of 3.1 for adenocarcinoma of the nasal cavity and sinuses and of 1.9 for squamous-cell carcinoma in snuff users in the USA, but the snuff was 'dipped' (see below) rather than inhaled.

The snuffs currently used for inhalation in Europe and North America, denoted as dry (Scotch) snuff, comprise powdered tobacco and a variety of additives which blenders guard secret. In South Africa, the snuffs used by the Bantu peoples comprise tobacco leaves admixed with the ash of aloes (*Liliaceae* family), oil, lemon juice and a variety of herbs. Keen *et al.* (1955) obtained a history of prolonged and heavy use of these snuffs in 80% of patients with cancer of the maxillary sinus compared to 34% in persons with cancer at other sites. It has been suggested that the relatively high nickel and chromium content of these snuffs, as well as their benzo[*a*]pyrene content may explain part of their carcinogenic action (Baumslag *et al.*, 1971).

SNUFF: 'DIPPED'

Snuff 'dipping' is the name given in the southern USA to the habit of placing snuff between cheek and gum. The highly alkaline snuff used for this purpose is termed wet. The

[1] Present address: All-Union Cancer Research Center of the Academy of Medical Sciences of the USSR, Kashirskoye shosse 24, Moscow 115478, USSR.

Table 1. Relative risk (RR) for cancers of oral cavity and pharynx associated with snuff use and smoking by 196 white women in North Carolina[a]

Habit	RR	Numbers	
		Cases	Controls
Snuff only	4.2	79	80
Smoking only	2.9	70	101
Snuff and smoking	3.3	11	14
None	1.0	36	153

[a] Adapted from Winn *et al.* (1981)

snuff so deposited, usually many times a day, is chewed or sucked, a proportion being eventually expectorated. As early as 1915, Abbe had reported on a case of tongue cancer in a woman who habitually rubbed powdered tobacco along the lingual edge. In 1957, Wilkins and Vogler reported on persons with gingival cancer in Georgia in the USA: 23 of 44 women patients dipped snuff and 12 of 37 men either snuffed or chewed tobacco, frequencies considered much higher than expected.

The *US Cancer Mortality Atlas* (Mason *et al.*, 1975) revealed an unexpectedly high level of oral cancer in females in several southern and eastern states (Blot & Fraumeni, 1977). Investigations showed that many women employed in the textile industry, unable to smoke at work for safety reasons, had recourse to snuff.

A case-control study (Winn *et al.*, 1981) of females in North Carolina with cancers of the tongue, gum, floor of mouth, other mouth, oropharynx, hypopharynx and pharynx unspecified (*International Classification of Diseases*, 8th revision, codes 141, 143–146 and 148–149; WHO, 1967) showed considerable excess of risk for snuff dippers (Table 1). For snuff dippers only, use for 1–24 years, 25–42 years and 50 years and more carried relative risks of 14, 13 and 48 respectively for the gum and buccal mucosa. One third of snuff dippers had developed the habit by the age of 10 years; the average duration of use was 45 years.

The results for a large prospective study of about 250 000 US veterans holding Government insurance policies followed up from 1954 to 1982, whose use of chewing tobacco and snuff is known, are expected in 1986 (Winn, personal communication).

CHEWING TOBACCO

Tobacco, whether cut from a roll or plug, twist, or in the commoner loose-leaf form, is still chewed in parts of the USA and elsewhere. Few of the published studies have taken smoking into account and many of the chewers probably had both habits. Williams and Horm (1977) conducted a population-based case-control study based on the interview of a random sample of patients from the Third National Cancer Survey of the USA. Controls were persons with other cancers – lung, larynx and bladder excluded. Among men, use of chewing tobacco and snuff was strongly associated with cancer of the gum and mouth, but not with cancer of the lip or tongue. Controlling for age, race and smoking, a highly significant relative risk of 3.9 was observed for moderate use; for heavy use, the relative

risk was 6.7 (not significant). Brinton *et al.* (1984) found, however, a relative risk of 0.7 for tobacco chewing in a case-control study using hospital and death certificate controls.

In recent years, tobacco chewing and snuff-dipping habits have increased among US college students, especially athletes. For example, in a survey of 1119 high-school students, Greer and Poulsen (1983) found that 117 (11%) used 'smokeless tobacco'; among these, 43% had oral mucosal lesions in the labial groove in the form of hyperkeratotic or erythroplakic areas. The tobacco was kept in the mouth for from one to three hours daily.

NASS

The word *nass* means a state of oblivion. The use of *nass* is widespread in Soviet Central Asia, northern Iran, and parts of Pakistan and Afghanistan *(nasswar)*. *Nass* is a mixture of variable composition and usually contains tobacco (50%), wood ash (20–30%), lime (9–10%) and oil (10–15%) (Table 2). In some areas, lime is not added to *nass* (Paches & Milievskaya, 1980). In Afghanistan, cardamom oil and menthol are added to the mixture.

Akin in many ways to Bantu snuff, *nass* is placed in the oral cavity. In Chimkent (Kazakh SSR), 60% of users place the *nass* under the tongue and 40% between the lower lip and the gums (Nugmanov & Baimakanov, 1970). In Djambul in the same republic, 96% are said to place the *nass* between the lower lip and the gums (Alexandrova, 1970), whereas in Samarkand (Uzbek SSR), most place the mixture under the tongue (Zaridze *et al.*, 1985). Depending on the republic, sex and age, some 5–50% of the population are *nass* users.

The habitual use of *nass* is associated with oral leukoplakia (Table 2).

Table 2 Frequency of oral leukoplakia in *nass* users and smokers, Djambul, Kazakh SSR

Habit	No	% with leukoplakia
Nass[a]	289	7.3
Smoking[a]	243	2.1
Neither habit[a]	1480	0.5
Nass[b]	1510	6.5
Neither habit[b]	4674	0.3

[a] Data from Alexandrova (1970)
[b] Data from Chasanov & Fasiev (1970)

Zaridze *et al.* (1985) presented data in which the relative risk for oral leukoplakia in smokers, *nass* users, and *nass* users who also smoked was examined (Table 3). Relative risks were significantly elevated in *nass* users and in smokers; the combined habits were accompanied by an additive increase in risk.

Leukoplakia usually occurs more frequently at the sites within the oral cavity that are in direct contact with *nass* (Zaridze *et al.*, 1985). There seems little doubt that this habit not only increases the risk of leukoplakia, as does betel-quid chewing (see below), but is also associated with oral cancer. In a study of 93 oral cancer cases and 247 controls, Nugmanov and Baimakanov (1970) found that 30% of cancer patients were *nass* users, compared to only 8% of controls. Chasanov (1965), in a series of 248 oral cancers in Bukhara (Uzbek

Table 3. Relative risks (95% confidence intervals) for oral leukoplakia associated with use of *nass* with and without smoking in 1569 men aged 55–69 years in Samarkand, Uzbek SRR [a]

Habit	Relative risk	
	Nonsmoker	Smoker
Non-user of *nass*	1.0	7.8 (4.4–14.2)
Nass user	5.6 (3.4–9.5)	11.5 (5.4–24.3)

[a] Data from Zaridze *et al.* (1985)

SSR), noted that their distribution followed that of the use of *nass*, namely: floor of mouth, 25%; tongue, 49%; palate, 17%; cheek, 17%; and alveolar ridge, 1%.

BETEL QUID

The chewing of the betel quid, with or without tobacco, is a very widespread habit in the Indian sub-continent, South-East Asia and parts of Oceania. The habit is of great antiquity, tobacco being added from the sixteenth century onwards. The basic quid comprises the leaf of the betel vine (*Piper betle*), sliced or shaved areca nut from the so-called betel palm (*Areca catechu*), and powdered slaked lime, to which are added one or more of a wide variety of additives (gambier, catechu, cardamom, cloves, aniseed, etc.) which frequently depend on locality (for an exhaustive review see Peeters, 1970). The method of preparation of ingredients varies and this may entail differences in chemical composition. For example, the uncured areca nuts used in Assam have a much higher content of tannin and arecoline than those used elsewhere.

The leaf contains the essential oil eugenol (a weak animal carcinogen), terpenes and potassium nitrate, but the main pharmacological effect comes from the alkaloids in the areca nut, mainly the arecoline present at a level of 0.1%. It is this alkaloid which induces a sensation of well-being as well as sweating and a considerable increase in saliva output.

There is still debate as to whether the habit as outlined above is carcinogenic. However when tobacco (usually of the sun-dried variety) is added to the chew, the risk of oral and,

Table 4. Relative risks of oral cancer in chewers and nonchewers in the case-control studies of Orr (1933) and Hirayama (1966)

Frequency of chewing	Relative risk	
	Orr study	Hirayama study
Never	1 [a]	1
Occasional	5	8
3–5 times per day	18	15
>5 times per day	34	18
Sleeps with quid in mouth	200 [a]	63

[a] Risk estimate based on two cases

probably, oropharyngeal, hypopharyngeal and oesophageal cancer is substantially increased.

One of the first case-control studies ever conducted, that by Orr (1933) in Travancore, South India, showed not only very large increases in the relative risk for oral cancer but also a strong dose-response. It is of interest to compare the results of Orr, who contrasted the habits of 100 cases of oral cancer with those of 100 controls (how these were chosen is not stated) without cancer, with those obtained by Hirayama (1966), who interviewed 545 cases and 440 controls, over 30 years later – the similarity is quite remarkable (Table 4), suggesting that Orr's controls were properly chosen.

Unfortunately Orr (1933) did not distinguish between chewers who included tobacco in the quid and those who did not, nor did he mention whether smoking was prevalent at the time, let alone by those in his study. Hirayama (1966) addressed this question and the salient findings are presented in Table 5.

Table 5. Relative risk and attributable risk % due to betel-quid chewing, with or without tobacco, in smokers and nonsmokers [a]

Habit	Relative risk	Attributable risk %
No habit	1	–
Smoking only (S)	4	67
Betel-quid chewing only (B)	3	22
B + S	4	50
Betel quid chewed with tobacco (T)	15	89
B + T + S	22	92

[a] Data from Hirayama (1966)

From Table 5 it is clear that smoking and chewing of the tobacco-less betel quid are associated with modest increases in risk of about the same order. Addition of tobacco to the quid increases risk very substantially and if this category of chewers also smoke there is a small incremental risk.

The data of Sanghvi *et al.* (1955) can be interpreted as showing that the combined habit of chewing and smoking is somewhat more carcinogenic for the oropharynx and hypopharynx than for the mouth. In this pioneering paper, however, betel-quid chewers who included tobacco in the quid were not separated from those who did not.

The findings are thus consistent: oral use of smokeless tobacco, whether prepared industrially or by artisanal means, increases the risk of oral cancer (IARC, 1985).

OTHER HABITS

There are numerous other ways in which tobacco is used – several are mentioned below. In general, their carcinogenicity has not been formally studied.

Mishri

Mishri is prepared by heating sun-dried Indian tobacco on a heated metal plate until it turns black. The powder prepared thereafter is used for cleaning the teeth. The habit is

usually practised by women and may give rise to habituation, users applying and retaining *mishri* in the mouth several times a day.

Khaini

Powdered sun-dried Indian tobacco and lime are the main ingredients of ***khaini***. The powder, like snuff, is placed between cheek and gum and allowed to dissolve away rather than being chewed. This habit has been linked with oral cancer (Khanolkar & Suryabai, 1945).

Zarda, kiwan

During *zarda* manufacture tobacco leaf is first broken into small pieces and boiled in water with lime and spices. The residue is dried and coloured with vegetable dyes. To prepare *kiwan*, the leaves are soaked and boiled in rose-water and spices. The mixture is allowed to macerate and pills or granules prepared.

Gudakhu

This is a paste consisting of sun-dried tobacco, molasses and other ingredients used mainly for cleaning teeth in Orissa and southern Bihar, India.

Shammah

This mixture of powdered tobacco leaf, carbonate of lime and ash is used in parts of southern Saudi Arabia. Some 68% of *shammah* users have leukoplakic lesions at the point of contact and in a series of 29 biopsies of such lesions squamous-cell carcinoma was diagnosed in seven (Salem *et al.*, 1984).

DISCUSSION

The foregoing brief review[2] outlines the evidence linking most of the habits involving the use of smokeless tobacco to cancer, cancer which usually arises at the point of contact. Unfortunately, many of the epidemiological studies do not separate such tobacco habits from smoking and a proportion do not define the sites of cancer studied precisely. Thus it is not always easy to decide what is meant by 'oral cancer'.

These habits are far from being esoteric curiosities in that they are very widely practised by large numbers of people, possibly as many as 400 million, and give rise to an estimated 100 000 and 50 000 cancers each year in males and females respectively (Parkin *et al.*, 1985).

[2] For further details, including manufacture, consumption statistics, particulars of other epidemiological studies, the chemistry of the substances mentioned, the results of animal testing for carcinogenicity and of mutagenicity assays, etc., see Volume 37 of the *IARC Monographs* (IARC, 1985).

The preparation of snuff and chewing tobacco in the USA is on an industrial scale, some 40 million lb of snuff being produced in 1980. Estimates of the number of current users of smokeless tobacco range from 7–22 million (Squier, 1984). In the Orient, however, much of the preparation of the betel quid and its components is at the artisan level and production figures are difficult to obtain. Nonetheless, the sums spent on the habit must be relatively very large.

Perusal of a series of records of the Bombay Cancer Registry, which collects information on selected habits from all cancer patients, indicates that the average daily expenditure on the betel quid is stated to be 50 paise or 15 rupees a month. This represents a very high proportion of income as the monthly family cash income is frequently given as 150 rupees. The poor man's luxury is expensive. (Permission to examine these records was kindly given by Dr D. Jussawalla, Director of the Bombay Cancer Registry.)

For control measures to have a chance of success the motives underlying adoption of a habit should be understood. Much work has been done in this area for smoking but very little for the oral use of tobacco.

Schonland and Bradshaw (1969) examined these questions in Indian betel-quid chewers in Natal Province, South Africa. The effects as perceived by habitués (tobacco is not a common ingredient in the chew) are listed in Table 6. The results are of the greatest interest in that over one-third were chewing by force of habit. More females considered the habit good for health than considered it pleasurable. Paradoxically, health reasons were often advanced to explain diminution or cessation of habit.

Burton-Bradley (1979) writing from Papua New Guinea, where tobacco is rarely added to the chew, although concomitant smoking is common, refers to arecadainism or addiction to the areca nut alkaloids, and is of the opinion that to give this habit up may lead to others which are more harmful.

However, arecoline may not be without its dangers, as in-vitro nitrosation yields 3-methylnitrosaminopropionitrile which is highly carcinogenic for the experimental animal (Wenke & Hoffmann, 1983).

Mehta *et al.* (1982) have shown that, in the setting of the Indian village, it is possible to influence behaviour and reduce the frequency of betel-quid chewing, and Warnakulasuriya *et al.* (1984) have shown in Sri Lanka that paramedical personnel can be trained to reliably identify leukoplakia and other oral lesions with a view to referral for

Table 6. Effects of betel-quid chewing as perceived by chewers, by sex, in Natal Province, South Africa[a]

Effect	% observing effect	
	Men	Women
Soothing	40	30
Stimulating	9	12
Both above effects	12	15
No effect	39	32

[a] Data from Schonland & Bradshaw (1969). Numbers in sample: 77 men, 479 women

treatment. It remains to be seen whether these pioneering efforts are applicable on a wider scale and at what cost.

Improvement of diet is likely to reduce risk as Notani and Sanghvi (1976) and Jafarey *et al.* (1977) suggest. However, in many parts of the world it is the poorest who are most likely to have an oral tobacco habit and least likely to have an adequate diet. Winn *et al.* (1984) noted that fruit and vegetable consumption reduced risk in cigarette smokers and those without tobacco habits, but not, apparently, in snuff dippers.

The tobacco companies, faced with lower sales of cigarettes in the developed countries are now, despite clear evidence of the carcinogenicity of the habit, promoting the use of chewing snuff, the product being sold in the form of sachets for oral use (Cameron, 1985). If the sale of these products, which do not carry any health warning, is allowed to continue, the toll of periodontal disease and oral cancer will be high.

REFERENCES

Abbe, R. (1915) Cancer of the mouth: The case against tobacco. *N.Y. med. J.*, ***102,*** 1–2

Alexandrova, H.M. (1970) *Role of nass in the development of pathological changes in the mouth.* In: *Epidemiology of Malignant Tumours*, Alma-Ata, Nauka, pp. 243–246

Baumslag, N., Keen, P. & Petering, H.G. (1971) Carcinoma of the maxillary antrum and its relationship to trace metal content of snuff. *Arch. environ. Health,* ***23,*** 1–5

Blot, W.J. & Fraumeni, J.F. (1977) Geographic patterns of oral cancer in the United States: etiologic implications. *J. chron. Dis.*, ***30,*** 745–757

Brinton, L.A., Blot, W.J., Becker, J.A., Winn, D.M., Browder J.P., Farmer, J.C. & Fraumeni, J.F. (1984) A case-control study of cancers of the nasal sinuses and paranasal sinuses. *Am. J. Epidemiol.*, ***119,*** 896–906

Burton-Bradley, B.G. (1979) Arecaidinism. Betel chewing in transcultural perspective. *Can. J. Psychiatry,* ***24,*** 481–488

Cameron, D. (1985) Warning against US tobacco sachets. *The Scotsman*, July 26 1985, Edinburgh

Chasanov, T.K. (1965) *Cancer of the oral mucosa in relation to use of nass.* In: *Problems of Geographic Pathology of Oropharyngeal Tumours*, Alma-Ata, Nauka, pp. 84–87

Chasanov, T.K. & Fasiev, K.T. (1970) *Epidemiological study of oral precancer in the Bukhara region of Uzbekistan.* In: *Epidemiology of Malignant Tumours*, Alma-Ata, Nauka, pp. 236–238

Greer, R.O. & Poulsen, T.C. (1983) Oral tissue alteration associated with the use of smokeless tobacco by teen-agers. Part 2, Clinical findings. *Oral Surg.*, ***56,*** 275–284

Harrison, D.F.N. (1967) *Snuff – its use and abuse: An essay on nasal physiology.* In: Muir, C.S. & Shanmugaratnam, K., eds, *Cancer of the Nasopharynx*, Copenhagen, Munksgaard, pp. 119–123

Hirayama, T. (1966) An epidemiological study of oral and pharyngeal cancer in central and South-East Asia. *Bull. World Health Organ.*, ***34,*** 41–69

IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 37, *Tobacco Habits Other than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines*, Lyon

Jafarey, N.A., Mahmoud, Z. & Zaidi, S.H.M. (1977) Habits and dietary pattern of cases of carcinoma of the oral cavity and pharynx. *J. Pak. Med. Assoc.*, **27**, 340–343

Keen, P., de Moor, N.G., Shapiro, M.P. & Cohen, L. (1955) The aetiology of respiratory tract cancer in the South African Bantu. *Br. J. Cancer*, **9**, 528–538

Khanolkar, V.R. & Suryabai, B. (1945) Cancer in relation to usages. Three new types in India. *Arch. Pathol.*, **40**, 351–361

Mason, T.J., McKay, F.W., Hoover, R., Blot, W.J. & Fraumeni, J. (1975) *Atlas of Cancer Mortality for US Counties: 1950–1969 (DHEW Publication No. [NIH] 75–780)*, Washington DC, Department of Health, Education, and Welfare

Mehta, F.J., Gupta, P.C., Pindborg, J.J., Bhonsk, R.B., Jalnawalla, P.N. & Sinar, P.N. (1982) An intervention study of oral cancer and precancer in rural Indian populations: A preliminary report. *Bull. World Health Organ.*, **60**, 441–446

Nugmanov, S.W. & Baimakanov, S.Sh. (1970) *The results of an epidemiological study of oropharyngeal tumours in Kazakhstan following the WHO projects.* In: *Epidemiology of Malignant Tumours.* Alma-Ata, Nauka, pp. 227–231

Notani, P.N. & Sanghvi, L.D. (1976) Role of diet in cancers of the oral cavity. *Ind. J. Cancer*, **13**, 156–160

Orr, I.M. (1933) Oral cancer in betel nut chewers in Travancore. Its aetiology, pathology and treatment. *Lancet*, **ii**, 575–580

Paches, A.I. & Milievskaya, I.L. (1980) *Epidemiological study of cancer of the mucous membrane of the oral cavity in the USSR.* In: Levin, D.L., ed., *Cancer Epidemiology in the USSR and USA (NIH Publication No. 80-2044)*, Bethesda, MD, US Department of Health and Human Services, pp. 177–184

Parkin, D.M., Stjernswärd, J. & Muir, C. (1984) Estimates of the worldwide frequency of twelve major cancers. *Bull. World Health Organ.*, **62**, 163–182

Peeters, A. (1970) *La Chique de Betel. Etude Ethnologique [Betel quid. Ethnological study]*, Volume I, Thesis, University of Paris

Redmond, D.E. (1970) Tobacco and cancer: The first clinical report, 1761. *New Engl. J. Med.*, **282**, 18–23

Salem, G., Juhl, R. & Schiodl, T. (1984) Oral malignant and premalignant changes in 'Shammah' – users from the Gizam Region, Saudi Arabia. *Acta odont. Scand.*, **42**, 41–45

Sanghvi, L.D., Rao, K.C.M. & Khanolkar, V.R. (1955) Smoking and chewing of tobacco and relation to cancer of the upper alimentary tract. *Br. med. J.*, **i**, 1111–1114

Schonland, M. & Bradshaw, E. (1969) Upper alimentary tract cancer in Natal Indians with special reference to the betel-chewing habit. *Br. J. Cancer*, **23**, 670–682

Squier, C.A. (1984) Smokeless tobacco and oral cancer: A cause for concern? *Ca Cancer J. Clin.*, **34**, 242–247 (and following Editor's Note)

Warnakulasuriya, K.A.A.S., Ekanayeke, A.W.I., Sivayoham, S., Stjernsward, J.J., Pindborg, J., Sobin, L.H. & Perera, K.S.G.P. (1984) Utilisation of primary health care workers for early detection of oral cancer and pre-cancer cases in Sri Lanka. *Bull. World Health Organ.*, **62**, 243–250

Wenke, G. & Hoffmann, D. (1983) A study of betel quid carcinogenesis. I. On the in-vitro *N*-nitrosation of arecoline. *Carcinogenesis*, **4**, 169–172

Wilkins, S.A. & Vogler, W.R. (1957) Cancer of the gingiva. *Surg. Gynecol. Obstet.*, **105**, 145–152

Williams R.R. & Horm, H.W. (1977) Association of cancer sites with tobacco and alcohol consumption and socio-economic status of patients: Interview study from the Third National Cancer Survey. *J. natl Cancer Inst.*, **58**, 525–547

Winn, D.M., Blot, W.J., Shy, C.N., Pickle, L.W., Tolodo, A. & Fraumeni, J.F. (1981) Snuff dipping and oral cancer among women in the Southern United States. *New Engl. J. Med.*, **304**, 745–749

Winn D.M., Ziegler, R.G., Pickle, L.W., Gridley, J., Blot, W.J. & Hoover, R.W. (1984) Diet in the aetiology of oral and pharyngeal cancer among women from the Southern United States. *Cancer Res.*, **44**, 1216–1222

WHO (1967) *International Classification of Diseases. 1965 Revision. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*, Vol. I, Geneva

Zaridze, D.G., Kuvshinov, J.P., Matiakin, E., Polakov, B.I., Boyle, P. & Blettner, M. (1985) Chemoprevention of precancerous lesions of the mouth and oesophagus in Uzbekistan, USSR. Proceedings of the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin, Hawaii, January 16–20. *Natl Cancer Inst. Monograph* (in press)

CIGARETTE SMOKING AND CARDIOVASCULAR DISEASES[1]

R.S. PAFFENBARGER, Jr[2] & R.T. HYDE

Stanford University School of Medicine, Stanford, CA 94305, USA

A.L. WING & C. HSIEH

Havard University School of Public Health, Boston, MA 02115, USA

SUMMARY

That cigarette smoking is causally associated with development of cardiovascular disease is recognized unequivocally. Epidemiological studies worldwide have documented the many pathways of influence and synergism by which this ubiquitous but artificial habit exerts its ill effects on cardiorespiratory and other body systems, leading not only to cardiovascular disease but to cancer and other ailments. Current investigations among college alumni, women, elderly, and other subgroups provide data on how various independent influences combine with smoking to establish risk and promote pathogenesis of cardiovascular disease. Their findings also confirm that cigarette smoking is one of the strongest instigators. All of this knowledge has implications for the design and implementation of effective intervention programmes.

INTRODUCTION

Cigarette smoking is a major cause of cardiovascular disease among both men and women. Numerous investigations since the mid-1950s have documented higher rates of disease and earlier mortality in cigarette smokers than in nonsmokers. Reports of the US

[1] This is Report No. XXXII in a series on chronic diseases in former college students.
[2] To whom requests for reprints should be sent.

Surgeon General (US Department of Health, Education and Welfare, 1964; US Department of Health and Human Services, 1983) have strongly urged that concerted actions be taken to reduce the causes and incidence of cardiovascular disease throughout all levels of society. Cigarette smoking contributes to development of atherosclerotic lesions, the predominant underlying cause of cardiovascular disease, and to the clinical manifestations of atherosclerotic vascular disease – coronary, cerebral, aortic and peripheral vascular disease, and sudden unexpected death. Although understanding of the precise pathophysiological basis of these clinical manifestions is incomplete, it may relate to several deleterious effects of cigarette smoking on cardiovascular health, accelerating the atherosclerotic process, promoting myocardial oxygen insufficiency, inducing an abnormal plasma lipoprotein-cholesterol profile, disrupting the haemostatic system, and lowering the threshold for ventricular fibrillation. While nicotine and carbon monoxide are the constituents of tobacco smoke most prominent as agents, hydrogen cyanide, oxides of nitrogen, and carbon disulphide also are highly suspect in the pathogenesis of coronary heart disease.

Recognition of the seriousness of the cigarette smoking problem leads to questions as to what to do about it. Strategies of intervention are becoming prominent topics of research and debate. Epidemiological studies may be of value to the establishment of realistic directions and goals for action. The present report seeks to explore some of these contributions.

So much has been published on smoking and cardiovascular disease in the past two decades that a brief initial review of several representative reports from various nations seems appropriate. Consideration will be directed to the effects of cigarette smoking, in combination with other influences, on the risks of cardiovascular disease, as revealed in current studies. These and other recent investigations have implications for intervention strategies. A few comments on trends and perceptions will complete the discussion.

REPRESENTATIVE WORLD STUDIES

Cigarette smoking and incidence of specific clinical manifestations of coronary heart disease were studied among men in the Framingham Heart Study in 1950–1968 (Kannel & Gordon, 1974). Age-adjusted rates for total coronary heart disease increased in a gradient from nonsmokers, to exsmokers, to light smokers, to more than double for smokers of a pack or more of cigarettes per day. About one-fifth of the events recorded were sudden deaths, which displayed a similar gradient. Heavy smokers had higher rates of coronary insufficiency, angina pectoris and myocardial infarction than nonsmokers. The parallel trends corroborate a real association between the level of cigarette smoking and development of coronary heart disease. Similar parallels noted in other populations lend further credence to that causal hypothesis (Friedman *et al.*, 1979; Keys, 1980; US Department of Health and Human Services, 1983; Kuller *et al.*, 1985).

Table 1 shows that studies throughout the world have implicated cigarette smoking in exacerbating the risk of coronary heart disease everywhere. The study of 290 000 US military veterans (Dorn, 1959; Kahn, 1966; Rogot & Murray, 1980) spans a time, 1917–1940, when cigarette smoking and coronary heart disease were rising. Coronary

Table 1. Relative risks[a] of death from coronary heart disease among selected populations, by cigarette smoking habit

Population studied	Composition of study (age in years)	Years of follow-up	No. of deaths	Relative risk of death	
				Nonsmoker	Smoker
USA veterans (Rogot & Murray, 1980)	290 000 men (35–84)	16	34 874	1.00	1.58
American Cancer Society (9 states) (Hammond & Horn, 1958)	188 000 men (50–70)	4	5 297	1.00	1.70
Japanese (29 health districts) (Hirayama & Hamano, 1981)	122 000 men (40+)	13	3 351	1.00	1.71
	143 000 women (40+)	13	2 653	1.00	1.78
American Cancer Society (25 states) (Hammond, 1966; Hammond & Garfinkel, 1969)	358 000 men (35–84)	4	10 771	1.00	1.24–2.81
	483 000 women (35–84)	4	4 048	1.00	1.19–2.00
Canadian veterans (Best, 1966)	78 000 men (30–90)	6	3 405	1.00	1.60
British physicians (Doll & Peto, 1976; Doll *et al.*, 1980)	34 000 men	20	3 191	1.00	1.62
	6 194 women	22	179	1.00	2.00
Swedish random sample (Cederlof *et al.*, 1975)	27 000 men (18–69)	10	916	1.00	1.70
	28 000 women (18–69)	10	457	1.00	1.30
California (9 occupations) (Weir & Dunn, 1970)	68 000 men (35–64)	8	1 718	1.00	1.60
Swiss physicians (Gsell *et al.*, 1979)	3 749 men	18	280	1.00	1.33–2.18

[a] Age-adjusted

heart disease mortality data on these men for the 16-year follow-up, 1953–1969, showed that the risk was 58% higher for smokers than for nonsmokers.

The American Cancer Society studies of huge populations of volunteer study subjects followed for four years yielded detailed information on types of tobacco used, number of cigarettes smoked daily, age at which smoking began, inhalation practices, and other variables that might influence mortality (Hammond & Horn, 1958; Hammond, 1966). Compared with death rates among nonsmokers, more than 11 500 excess deaths were attributable to smoking, amounting to 46% in men and 41% in women.

Canadian veterans (Best, 1966) and Californians in a wide selection of occupations (Weir & Dunn, 1970) experienced similar hazards of smoking.

Among 122 000 men and 143 000 women followed in Japan for 13 years (over 3 million person-years of risk), coronary heart disease mortality ratios for smokers were 1.7 for men and 1.8 for women (Hirayama & Hamano, 1981). After adjustment for predisposing

influences of social class and consumption of meat, milk and alcohol, the risk of death from coronary heart disease remained higher for smokers than for nonsmokers. The proportion of smokers was 76% in men and 10.5% in women, and their proportions of coronary heart disease mortality attributed to cigarette smoking were 34.3% and 9.5%, respectively.

When 34 400 male British physicians were followed for 20 years, 1951–1971, coronary heart disease accounted for 3191 of 10 072 deaths (Doll & Peto, 1976; Doll *et al.*, 1980). Risk of coronary heart disease mortality was 62% higher for the cigarette smokers. Risk was doubled over nonsmokers for British women physicians who smoked 15 or more cigarettes daily.

Among 55 000 Swedish men and women followed for ten years through 1972 (Cederlöf *et al.*, 1975), overall coronary heart disease mortality was 70% higher for male cigarette smokers, and 30% higher for women smokers, than for nonsmokers. A sub-sample queried in 1969 revealed that smoking habits were unchanged since 1963.

Data on 1212 deaths among 3749 Swiss physicians during an 18-year follow-up, 1955–1973, showed that coronary heart disease mortality rates increased with dosage in cigarettes smoked per day, being up 33% for use of ten or fewer, and up 118% for 35 or more smoked per day, over the rate for nonsmokers (Gsell *et al.*, 1979). This pattern is corroborated in each of the studies listed in Table 1.

MECHANISMS OF RISK

Dosage effects are consistent as indicated not only by cigarettes smoked per day but by data on inhalation, use of filters, age at beginning to smoke, years of smoking, cessation of smoking, and risks to nonsmokers in the vicinity of cigarette smokers (passive or secondary exposure). The dose-dependent influence of cigarette smoking on coronary heart disease risk is considered strong evidence that the relationship between the cigarette habit and coronary heart disease is causal.

Cigarette smoking and atherosclerosis

The epidemiological evidence linking cigarette smoking and cardiovascular diseases is reinforced by pathological findings that smoking aggravates and accelerates development of the underlying lesions and occlusive events in coronary, cerebral, aortic and peripheral arteries (Auerbach *et al.*, 1965, 1976; Strong & Richards, 1976; McMillan, 1978; McGill, 1979). A variety of studies have shown more severe atherosclerotic change in smokers than in nonsmokers, and a concomitant increase in the degree of both macroscopic and microscopic pathological change with the amount of cigarette smoking. In addition, some evidence exists to incriminate smoking in altering the serum lipoprotein profile in ways that increase the development of atherosclerosis, e.g., reduction of the high-density lipoprotein cholesterol. Smoking affects the haemostatic system by decreasing platelet survival time and increasing platelet stickiness and tendency to aggregate. The manifold gaseous constituents in cigarette smoke have complex pharmacological and toxic effects that alter metabolism, reduce oxygen transport, lower the threshold of ventricular fibrillation, and promote the atherosclerotic process (Astrup & Kjeldsen, 1979).

COMBINED INFLUENCES ON RISK

College alumni health study

A study of cigarette smoking habits, other ways of living, and health status among male college alumni (former college students) in the USA has shown how past and present characteristics relate to risk of cardiovascular disease in middle and later life (Paffenbarger *et al.*, 1978, 1984). Data on 16 936 former students aged 35–74 years and initially free of coronary heart disease, who had entered Harvard University in the period 1916–1950, were reviewed for personal characteristics, including the cigarette habit. These had been recorded in college student health archives and in post-college, mailed questionnaires returned by alumni in 1962 or 1966. Follow-up data were obtained from repeat questionnaires in 1972 for nonfatal coronary heart disease and from official death certificates through 1978 for fatal cardiovascular disease. The overall experience represented by this study population spans the twentieth century from 1900 to the present, as in 1978 the ages of surviving study subjects ranged from 45-85 years.

During the follow-up interval of six or ten years (1966 or 1962 to 1972), there were 572 first attacks of coronary heart disease, 357 nonfatal and 215 fatal. Incidence rates for coronary heart disease were computed per 10 000 man-years. Overall, the risk for smokers was 68% higher than that for nonsmokers. Mortality rates for fatal cardiovascular diseases were computed similarly for the 12–16-year follow-up from 1966 or 1962 to 1978, in which there were 640 deaths from some form of cardiovascular disease. Excess mortality risks for smokers over nonsmokers were 77% for total cardiovascular disease, 78% for coronary heart disease, 52% for stroke, and 100% (double) for other cardiovascular diseases.

Table 2 shows age-adjusted rates and relative risks of total coronary heart disease and fatal cardiovascular disease, for their respective follow-up intervals, by level of cigarette smoking habit. Prevalence for smoking categories, given as the percentage of man-years, shows a distribution of about one-quarter heavy smokers, one-third nonsmokers, and one-quarter exsmokers. For coronary heart disease, as the number of cigarettes smoked per

Table 2. Age-adjusted rates and relative risks of coronary heart disease and cardiovascular death among Harvard College alumni, by cigarette smoking habit

No. of cigarettes smoked per day	Prevalence in man-years (%)	No. of cases	Cases per 10 000 man-years	Relative risk of disease	*p* for trend
Coronary heart disease (nonfatal and fatal), 1962–1972					
20+	28	179	70.9	1.82	
10–19	6	40	67.2	1.72	
1–9	5	26	48.4	1.24	<0.0001
0	37	178	39.0	1.00	
Former	25	90	42.9	1.10	
All cardiovascular disease (fatal), 1962–1978					
20+	27	214	49.2	1.91	
10–19	6	38	35.9	1.39	
1–9	5	29	30.7	1.19	<0.0001
0	38	208	25.8	1.00	
Former	24	84	22.1	0.86	

day increases from none to a pack or more, a gradient increase in risk to smokers over nonsmokers is seen ranging steadily upward to nearly double (82%) in an evidently dose-dependent trend. Exsmokers have a slightly higher risk (10%) than nonsmokers. The pattern is similar for fatal cardiovascular disease. If the difference for exsmokers is meaningful, it may imply that some may have improved their lifestyle in other respects also.

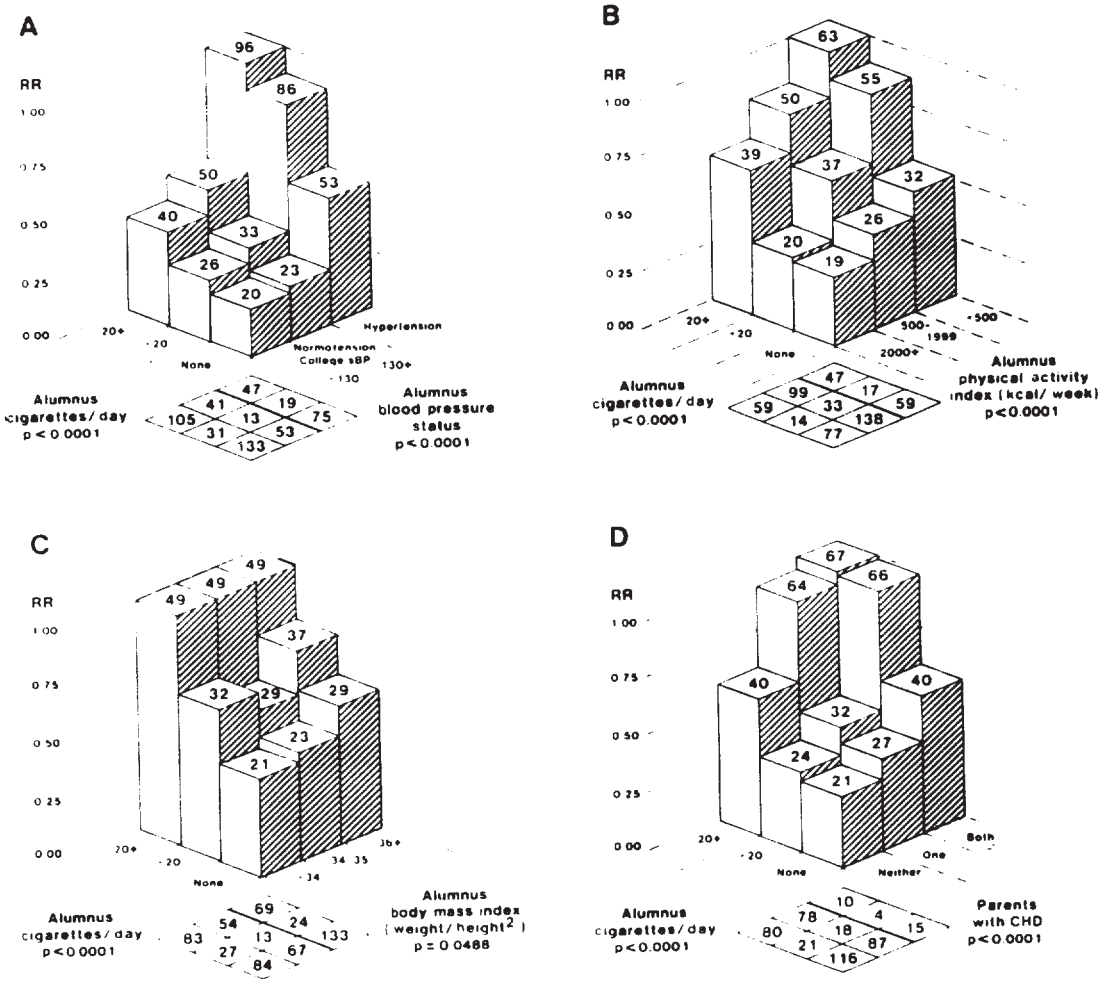
Figure 1 presents a series of graphic cross-tabulations of cigarette smoking habit with other alumnus characteristics (blood pressure status, physical activity, body weight-for-height, and history of parental coronary heart disease) for which cardiovascular mortality rates were computed (shown as numbers on tops of bars). Numbers of deaths are given in a corresponding key beneath each cross-tabulation. Breakpoints were chosen to provide three levels of each characteristic for comparison. Relative risks were established by assigning 1.00 to the death rate for the presumed highest-risk combination, represented by the back corner bar in each cross-tabulation. Mortality trends are sought as the influence of each characteristic is assessed, holding constant the influences of age and the paired characteristic. This permits identification of any confounding of influences, or any gradient effect of contemporary cigarette habit with these other alumnus characteristics.

Three categories of cigarette smoking level were set: nonsmoker (61% of man-years of observation), smoking less than one pack a day (11%), and smoking one or more packs a day (28%). Blood pressure categories consisted of normotensive alumni with student systolic blood pressure below 130 mm Hg (70%), normotensive alumni with student systolic blood pressure of 130 mm Hg or higher (21%), and alumni with physician-diagnosed hypertension (9%). Physical activity was expressed in kilocalories per week, calculated as an estimate of leisure-time energy expended in walking, stair climbing, and sports play; then groups were established as alumni expending 2000 or more kilocalories per week (40% of man-years), 500–1999 kilocalories per week (45%), and less than 500 kilocalories per week (15%). Weight-for-height groups were determined by body mass index (Quetelet's index; 1000 × weight in pounds divided by height in inches squared) and classified as men with an index below 34 units (38% of man-years), 34–35 units (25%), and 36 units or more (37%). The three categories for parental history of coronary heart disease identified alumni having neither parent with such a history (64% of man-years), those having one parent with coronary heart disease (33%), and those having both parents afflicted (3%).

Figure 1 A gives rates and relative risks of fatal cardiovascular disease by alumnus cigarette habit cross-tabulated with student and alumnus blood pressure status. For normotensive alumni, risk was 10–20% lower with decreasing amounts smoked, irrespective of whether student systolic blood pressure was below 130 mm Hg or higher. Among alumni with physician-diagnosed hypertension, however, the relative risk of fatal cardiovascular disease was reduced by nearly one half (relative risk, 0.55) when smoking level was decreased from heavy (a pack or more per day) to none. The effect of the cigarette habit on risk of fatal cardiovascular disease is strong and independent of the influence of hypertension, which is even stronger.

At each level of cigarette smoking in Figure 1 B there was a decline in cardiovascular disease mortality as leisure-time exercise increased and when the data were adjusted for the influence of smoking, exercise continued to be inversely related to death. Cigarette habit is directly related to cardiovascular disease mortality when exercise is held constant.

Fig. 1. Death rates and relative risks of cardiovascular disease per 10 000 man-years of observation among Harvard University alumni, by cross-tabulations of cigarette smoking habit and (A) blood pressure status, (B) physical activity index (kilocalories per week), (C) body mass index (1000 × weight in pounds divided by height in inches squared), and (D) history of parental coronary heart disease. Death rates are given on top of bars, and corresponding numbers of deaths in the diamond keys. A relative risk of 1.00 is assigned to the paired combination with presumed highest risk (each back-corner bar)



The most physically active nonsmokers had only 30% as much fatal cardiovascular disease as the sedentary heavy smokers, and the least physically active nonsmokers 52%.

Figure 1 C shows that cardiovascular disease mortality is related directly to the cigarette habit when body mass index is held constant. If smoking is held constant, risk of fatal cardiovascular disease is related directly also to weight-for-height, but less strongly than to smoking. The most lean nonsmokers (men no more than 10% over 'ideal' weight, having a body mass index below 34) had only 43% the risk of their heavy-smoking, more obese

classmates, 20% or more overweight (smoking a pack or more of cigarettes per day and having a body mass index of 36 or higher). The figure shows substantial benefit from reduced smoking patterns in each weight-for-height group, but among heavy smokers there was no benefit for reduced weight-for-height.

Cross-tabulation of cardiovascular disease mortality risks by cigarette smoking and history of parental coronary heart disease is shown in Figure 1 D. To the extent that such parental history reflects a familial or hereditary tendency toward fatal cardiovascular disease in alumni, the risk implied by that tendency is cut nearly in half (0.60) even among nonsmoking alumni with a double parental history of coronary heart disease. The trend of lower cardiovascular disease mortality with reduced cigarette smoking is substantial, and the influence of parental coronary heart disease status is similarly strong. Throughout this cross-tabulation, as in each of the others, there is a consistent lowering of cardiovascular disease mortality rates as alumnus cigarette smoking declines from heavy to light to none.

Table 3 gives relative and attributable risks of total coronary heart disease in ten years of follow-up and of fatal cardiovascular disease in 16 years of follow-up, by selected characteristics known to predispose to these outcomes. The risks are derived from a multivariate analysis (Cox, 1972) and computed for the presence *versus* the absence of each adverse characteristic, with adjustments for age and each of the other characteristics listed. After allowance for each other variable, it is evident that cigarette smokers were at a 67% greater risk of coronary heart disease, nonfatal or fatal, than nonsmokers; hypertensive men had twice the risk of normotensives; sedentary alumni were at a 38% higher risk than men more physically active; heavier men were at a 23% greater risk than men more lean; and alumni with an adverse parental history of coronary heart disease had a 20% greater risk of

Table 3 Relative and attributable risks [a] of coronray heart disease and cardiovascular death among Harvard College alumni, by selected adverse characteristics

Alumnus characteristic	Prevelance in man-years (%)	Relative risk of disease (95% CL) [b]		*p*	Attributable risk (%)
Coronary heart disease (nonfatal and fatal), 1962–1972					
Cigarette smoking [c]	40	1.67	(1.43–1.91)	<0.0001	21
Hypertension [d]	9	1.99	(1.71–2.27)	<0.0001	8
Sedentary lifestyle [e]	61	1.38	(1.12–1.64)	0.0015	19
Overweight for height [f]	37	1.23	(0.99–1.47)	0.0755	8
History of parental CHD [g]	37	1.20	(0.96–1.44)	0.1185	7
All cardiovascular disease (fatal), 1962–1978					
Cigarette smoking [c]	39	1.84	(1.64–2.04)	<0.0001	25
Hypertension [d]	9	2.18	(1.94–2.42)	<0.0001	9
Sedentary lifestyle [e]	62	1.31	(1.09–1.53)	0.0172	16
Overweight for height [f]	37	1.18	(0.98–1.38)	0.1081	6
History of parental CHD [g]	37	1.33	(1.13–1.53)	0.0062	11

[a] Adjusted for differences in age and each of the other characteristics listed
[b] CL, confidence limits
[c] Any amount
[d] Physician-diagnosed
[e] Energy expenditure of < 2000 kilocalories/week in walking, stair-climbing, and sports play
[f] 20% or more over ideal weight for height (1959 Metropolitan Life Insurance Company standards), i.e., body mass index 36+
[g] CHD, coronary heart disease, in either or both parents

developing coronary heart disease themselves than classmates whose parents were free from such affliction. Attributable risk estimates for the corresponding characteristics suggest that cigarette smoking might account for 21% of the coronary heart disease among alumni; hypertension, 8%; sedentary living, 19%; overweight, 8%; and the genetic or familial tendencies implied by parental coronary heart disease, a further 7%. If all of these adversities for alumni could have been avoided there might have been half as many attacks of coronary heart disease.

Relative and attributable risks of cardiovascular disease mortality for these same alumnus characteristics are of the same general order of magnitude as for coronary heart disease (Table 3). They indicate that there might have been 65% fewer cardiovascular disease deaths during the study interval 1962–1978 in the absence of all five characteristics, or a loss of only 224 alumni instead of the observed 640 decedents from underlying cardiovascular disease causes.

Women smokers

Current study of the relation of cigarette smoking and nonfatal myocardial infarction in women aged 25–49 years living in the north-eastern USA provides new evidence on dose-response and interaction with other personal characteristics known or suspected to predispose to infarction (Rosenberg *et al.*, 1985). This case-control study contrasted 555 women who survived first attacks with 1864 women of similar age hospitalized for a variety of conditions judged to be unrelated to cigarette smoking. The proportion of current smokers among myocardial infarction patients was 80%, as contrasted with 50% among control patients. Relative risk estimates of myocardial infarction increased steadily from 1.4 for smokers of 1–14 cigarettes per day to 2.4 for those using 15–24 cigarettes, to 5.0 for use of 25–34, to 7.0 for smokers of 35 or more cigarettes daily. Among former smokers who had abstained for at least one year, relative risks were the same as for women who had never smoked.

As shown in Table 4, risk of myocardial infarction among current oral contraceptive users was increased 23-fold for heavy smokers over nonsmokers. Women heavy smokers with a serum cholesterol level below 200 mg/dl had a five-fold increased risk of myocardial infarction over comparable nonsmokers; with higher levels the risk for smokers over nonsmokers was ten-fold greater. Furthermore, the risk of myocardial infarction was higher for smokers than nonsmokers among these women with and without such predisposing characteristics as hypertension, angina pectoris, diabetes, obesity, a tendency to time-urgency and competitiveness (so-called type A behaviour), and an adverse history of cardiovascular disease in a parent or sibling.

Elderly smokers

Among elderly (65-74 years) white males from an impoverished urban setting, current cigarette smokers were at 52% higher risk of fatal coronary heart attack in five years of follow-up over nonsmokers, exsmokers, and pipe or cigar smokers (Jajich *et al.*, 1984). The excess risk of mortality in this population of 2674 persons declined within one to five years of cessation of smoking. Smokers of all ages should be encouraged to quit (see Table 5).

Table 4. Relative risks estimates[a] of nonfatal myocardial infarction among women aged <50 years in north-eastern USA, by cigarette habit and selected characteristics[b]

Characteristic	Level	Relative risk of nonfatal myocardial infarction		
		Nonsmokers	Smokers (95% CL)[c]	
Oral contraceptive use	Current	1.00	23	(6.6–82)
	Past	1.00	6.8	(4.5–10)
	Never	1.00	4.8	(3.5–6.6)
Serum cholesterol (mg/dl)	<200	1.00	4.6	(2.5–8.7)
	200–249	1.00	12	(6.4–21)
	250+	1.00	10	(4.0–25)
HDL-cholesterol (mg/dl)[d]	<40	1.00	4.7	(2.7–8.2)
	40+	1.00	14	(8.3–25)
Type A personality	Present	1.00	6.8	(3.3–14)
	Absent	1.00	11	(6.7–17)
Family history CVD[e]	Present	1.00	7.1	(3.9–13)
	Absent	1.00	11	(6.5–18)
Hypertension	Yes	1.00	4.0	(2.4–6.7)
	No	1.00	8.0	(6.0–11)
Angina pectoris	Yes	1.00	5.1	(1.5–17)
	No	1.00	6.2	(4.8–8.0)
Diabetes mellitus	Yes	1.00	3.2	(1.2–8.7)
	No	1.00	6.7	(5.2–8.7)
Pre-menopausal		1.00	8.3	(6.1–11)
Post-menopausal		1.00	3.9	(2.5–6.0)
Body mass index	40+	1.00	5.5	(3.6–8.6)
	<40	1.00	7.1	(5.3–9.7)

[a] Age-adjusted
[b] From Rosenberg *et al.* (1985)
[c] Smokers of 25+ cigarettes per day; CL, confidence limits
[d] HDL-cholesterol, high-density lipoprotein-cholesterol
[e] CVD, cardiovascular disease

Filter cigarette risks

In the Framingham study (Castelli *et al.*, 1981) men were classified as to whether they smoked filter or nonfilter cigarettes. The 58% of men who used filtered brands had been smoking for a shorter period than the comparison group, but despite this more favourable cigarette-smoking history, their incidence rates of coronary heart disease (myocardial infarction, coronary heart disease death, or total coronary heart disease) in 14 years of follow-up showed no differences from those of nonfilter cigarette users. Findings were unchanged when rates were adjusted for differences in levels of blood pressure and serum cholesterol. Thus there was no evidence that filter cigarettes of the 1960s and 1970s conferred any protection against coronary heart disease for Framingham men. Perhaps this is not unexpected, since smokers may alter their smoking behaviour when they switch

to low-yield brands to compensate for nicotine. This altered behaviour may induce accelerated atherogenesis through increased uptake of carbon monoxide, hydrogen cyanide and nitrous oxides (Astrup & Kjeldsen, 1979).

Passive smoking

The effects of passive (involuntary) smoking on nonsmokers are receiving increased attention. Aronow (1978) demonstrated that nonsmoking patients with angina pectoris exposed in a confined space to the cigarette smoke of others experienced an increase in serum carboxyhaemoglobin levels, coronary symptomatology, and electrographic changes indicative of myocardial ischaemia at lower levels of exercise testing than when not so exposed. Garland *et al.* (1985) studied 695 nonsmoking women from a retirement community in California who were classified according to their husbands' cigarette-smoking status as wives of those who had never smoked, and former and current smokers. In ten years of follow-up, nonsmoking wives of current or former smokers experienced an elevated death rate of coronary heart disease compared with nonsmoking wives of those who had never smoked. A dose-response relationship was shown for the quantity of cigarettes smoked by the husband. These findings held when adjustments were made for multiple characteristics predisposing to coronary heart disease. Although the added risk of disease among exposed wives was 14.9, the experience was small and not statistically significant ($p < 0.10$).

The issues relative to coronary heart disease are unsettled, but when passive smokers protest, their complaints against heavy smoking at close quarters often are based on more immediate irritations than remote fears of heart attack. Difficulties of determining atmospheric concentrations of toxic substances are likely to complicate the epidemiological problem of studying the patterns and intensities of involuntary exposure to cigarette smoke and of assessing any influences of subtle exposures of long duration.

TRENDS

Cessation of smoking

Table 5 summarizes several studies in which influence of cessation of cigarette smoking on risk of total coronary heart disease among men is examined in terms of interval since quitting the habit, age at time of cessation, intensity of cigarette use, and duration of use (Hammond, 1966; Hammond & Garfinkel, 1969; Cederlöf *et al.*, 1975; Doll & Peto, 1976). There is a consistent gradient of reduction in risk as the interval since cessation increases, so that men who have abandoned cigarettes for a decade or more have little if any excess risk over men who have never smoked. The risk-reduction benefit is seen in all age groups and for both light and heavy smokers who have dropped the habit. Among men aged 65 years or older, percentage reduction appears less impressive than for younger men aged 30–54 but, in view of age-related rates of coronary heart disease mortality, the numbers spared would be substantial. In general, the greater the relative risk attached to cigarette smoking, the greater the benefit or reduction in risk achieved by quitting the habit.

Table 5. Relative risks of death from coronary heart disease among selected populations, by years since cigarette smoking cessation

Population studied	Years since cessation	Relative risk of death		
		Attained age (years)		
		30–54	55–64	65+
British physicians	None	3.5	1.7	1.3
(Men who smoked cigarettes	1–4	1.9	1.9	1.0
only for 5+ years;	5–9	1.3	1.4	1.3
20-year follow-up)	10–14	1.4	1.7	1.2
(Doll & Peto, 1976)	15+	1.3	1.3	1.1
	Nonsmoker	1.0	1.0	1.0
		No. of cigarettes smoked per day		
		1–19	20+	
American Cancer Society (25 states)	None	1.90	2.55	
(Men who smoked cigarettes only;	<1	1.62	1.61	
6-year follow-up)	1–4	1.22	1.51	
(Hammond, 1966; Hammond &	5–9	1.26	1.16	
Garfinkel, 1969)	10–19	0.96	1.25	
	20+	1.08	1.05	
	Nonsmoker	1.00	1.00	
		Years of smoking cigarettes		
		<20	20+	Total
Swedish random sample	None	–	–	1.7
(Men; 10-year follow-up)	1–9	0.9	1.6	1.5
(Cederlöf *et al.*, 1975)	10+	0.9	1.1	1.0
	Nonsmoker	1.0	1.0	1.0

In five worldwide intervention trials (Puska *et al.*, 1979; Hjermann *et al.*, 1981; Multiple Risk Factor Intervention Trial, 1982; Rose *et al.*, 1982; World Health Organization European Collaborative Group, 1982), cigarette smoking was reduced 10–15% more in the intervention group than in the control group. The intervention group had some 10% fewer coronary heart disease deaths than the comparable control group, but the differences within the individual trials were not significant. When the results of four of these trials were combined, however, coronary heart disease deaths were significantly less common in the intervention group than in the control group.

Chapman (1985) reports that small stop-smoking encounter groups and clinics are inept, expensive and hopeless approaches to the problem of effective intervention. He recommends massive education programmes and dedicated medical collaboration to reach the millions of smokers who must be persuaded to kick the cigarette habit. In the meantime recidivism and prevarication by subjects tend to limit the credibility of data on cessation and weaken results of many studies based on them. Nevertheless, the findings on benefits

of smoking-behaviour modification are meaningful because they do echo strong evidence from other nonexperimental studies of cardiovascular disease and may forecast eventual success for broad, long-range intervention programmes.

Mortality and other patterns

Cardiovascular disease mortality has declined in the USA by 38% since 1950, while deaths from all other causes were declining by about 21% (Epstein, 1984; Feinleib, 1984). Since 1968, coronary heart disease mortality has fallen 27%, as mirrored by 280 000 fewer deaths in the following decade than would have been expected on the basis of 1968 mortality rates. The decline in cigarette smoking since the first Surgeon General's Report (US Department of Health, Education, and Welfare, 1964), 25% among men and 14% among women aged 20 years and over, together with improvement in other lifestyle habits and better blood pressure control, may explain a large segment of the decline in cardiovascular disease mortality. Feinleib (1984) has translated trends in cigarette smoking, blood cholesterol patterns and blood pressure levels into equations and related them to risk of cardiovascular death. From these he made the following predictions: (1) a 20% reduction in numbers of smokers would have induced a 10% decline in mortality; (2) a 5 mg/dl average reduction in serum cholesterol would have induced a 4% drop in mortality; and (3) a 2 mm Hg decrease in diastolic blood pressure would have induced a 9% decline in cardiovascular mortality. Together, such trends might account for a 22% reduction in cardiovascular disease death rates, very similar to the observed decline over the period concerned.

DISCUSSION

The existence of a strong adverse relationship between cigarette smoking and cardiovascular disease is no longer a topic for debate. This report has presented new data and summarized findings that may offer important contributions to the planning of effective large-scale programmes of intervention designed to minimize the cigarette habit as an element of lifestyle. Knowledge of how cigarette smoking promotes disease can be used to educate against it, and no other intervention strategy is likely to be as successful. These aspects have been considered directly or by implication throughout the report. In summary, they reveal that the potential benefits from solving the problem are as manifold as the array of hazards associated with it. Whenever cigarette smoking is abandoned to reduce risk of cardiovascular disease, cancer will be reduced, and other chronic diseases as well. After all, cigarette smoking is an artificial enemy that was created by man himself, and he has the power to destroy it.

ACKNOWLEDGEMENTS

This work was supported by Grant HL37174 from the National Heart, Lung and Blood Institute of the US Public Health Service; and by the G. Unger Vetlesen Foundation; the E.I. du Pont de Nemours Company; the Marathon Oil Foundation, Inc.; and the Mobil Foundation.

REFERENCES

Aronow, W.S. (1978) Effect of passive smoking on angina pectoris. *New Engl. J. Med.*, ***299***, 21–24

Astrup, P. & Kjeldsen, K. (1979) Model studies linking carbon monoxide and/or nicotine to arteriosclerosis and cardiovascular disease. *Prev. Med.*, ***8***, 295–302

Auerbach, O., Hammond, E.C. & Garfinkel, L. (1965) Smoking in relation to atherosclerosis of the coronary arteries. *New Engl. J. Med.*, ***273***, 775–779

Auerbach, O., Carter, H.W., Garfinkel, L. & Hammond, E.C. (1976) Cigarette smoking and coronary artery disease: A macroscopic and microscopic study. *Chest*, ***70***, 697–705

Best, E.W.R. (1966) *A Canadian Study of Smoking and Health*, Ottawa, Epidemiology Division, Health Services Branch, Biostatistics Division, Research and Statistics Directorate

Castelli, W.P., Garrison, R.J., Dawber, T.R., McNamara, P.M., Feinleib, M. & Kannel, W.B. (1981). The filter cigarette and coronary heart disease: the Framingham study. *Lancet*, ***ii***, 109–113

Cederlöf, R., Friberg, L., Hrubec, Z. & Lorich, U. (1975) *The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity. A Ten-year Follow-up in a Probability Sample of 55 000 Swedish Subjects, Age 18–69*, Part 1 and Part 2, Stockholm, Department of Environmental Hygiene, The Karolinska Institute

Chapman, S. (1985) Stop-smoking clinics: A case for their abandonment. *Lancet*, ***i***, 918–920

Cox, D.R. (1972) Regression models and life tables (with discussion). *J. R. Soc. Biostat.*, ***34***, 187–200

Doll, R. & Peto, R. (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. *Br. med. J.*, ***274***, 1525–1536

Doll, R., Gray, R., Hafner, B. & Peto, R. (1980) Mortality in relation to smoking: 22 years' observations on female British doctors. *Br. med. J.*, ***280***, 967–971

Dorn, H.F. (1959) Tobacco consumption and mortality from cancer and other diseases. *Public Health Rep.*, ***74***, 581–593

Epstein, F.H. (1984) Lessons from falling coronary heart disease mortality in the United States. *Postgrad. Med. J.*, ***60***, 15–19

Feinleib, M. (1984) Changes in cardiovascular epidemiology since 1950. *Bull. N. Y. Acad. Med.*, ***60***, 449–464

Friedman, G.D., Dales, L.G. & Ury, H.K. (1979) Mortality in middle-aged smokers and nonsmokers. *New Engl. J. Med.*, ***300***, 213–217

Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M.H. & Wingard, D.L. (1985) Effects of passive smoking on ischemic heart disease mortality of nonsmokers: a prospective study. *Am. J. Epidemiol.*, ***121***, 645–650

Gsell, O., Abelin, T. & Wieltchnig, E. (1979) Smoking and mortality of Swiss physicians: Results after 18 years of observation (Ger.). *Bull. schweiz. Akad. med. Wiss.*, ***35***, 71–82

Hammond, E.C. (1966) Smoking in relation to the death rates of one million men and women. In: Haenszel, W., ed., *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases (Natl Cancer Inst. Monograph No. 19)*, Bethesda, MD, National Cancer Institute, pp. 127–204

Hammond, E.C. & Garfinkel, L. (1969) Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. *Arch. Environ. Health,* ***19,*** 167–182

Hammond, E.C. & Horn, D. (1958) Smoking and death rates – Report on forty-four months of follow-up of 187 783 men: II Death rates by cause. *J. Am. med. Assoc.,* ***166,*** 1294–1308

Hirayama, T. & Hamano, Y. (1981) Smoking and mortality from major causes of death (Jpn.) *Eisei No Shibyo,* ***28,*** 3–18

Hjermann, I., Velve Byre, K., Holme, I. & Leren, P. (1981) Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo study group of a randomized trial in healthy men. *Lancet,* ***ii,*** 1303–1310

Jajich, C.L., Ostfeld, A.M. & Freeman, D. H., Jr (1984) Smoking and coronary heart disease mortality in the elderly. *J. Am. med. Assoc.,* ***252,*** 2831–3834

Kahn, H.A. (1966) The Dorn study of smoking and mortality among U.S. veterans: Report on eight and one-half years of observation. In: Haenszel, W., ed., *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases (National Cancer Institute Monograph No. 19),* Bethesda, MD, National Cancer Institute, pp. 1–125

Kannel, W.B. & Gordon, T. (1974) *The Framingham Study, Section 30. Some Characteristics Related to the Incidence of Cardiovascular Disease and Death: 18-year Follow-up (Department of Health, Education, and Welfare Publication No. NIH 74–599),* Washington DC

Keys, A. (1980) *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease,* Cambridge, MA, Harvard University Press

Kuller, L., Meilahn, E. & Ockene, J. (1985) Smoking and coronary heart disease. In: Connor, W.E. & Bristow, J.D., eds, *Coronary Heart Disease: Prevention, Complications, and Treatment,* Philadelphia, PA, J.B. Lippincott

McGill, H.C., Jr (1979) Potential mechanisms for the augmentation of atherosclerosis and atherosclerotic disease by cigarette smoking. *Prev. Med.,* ***8,*** 390–403

McMillan, G.C. (1978) Atherogenesis: The process from normal to lesion. In: Chandler, A.B., Eurenius, K., McMillan, G.C., Nelson, C.B., Schwartz, C.J., Wessler, S., eds, *The Thrombotic Process in Atherogenesis,* New York, Plenum Press, pp. 3–10

Multiple Risk Factor Intervention Trial (1982) Risk factor changes and mortality results. *J. Am. med. Assoc.,* ***248,*** 1465–1477

Paffenbarger, R.S., Jr, Wing, A.L. & Hyde, R.T. (1978) Physical activity as an index of heart attack risk in college alumni. *Am. J. Epidemiol.,* ***108,*** 161–175

Paffenbarger, R.S., Jr, Hyde, R.T., Wing, A.L. & Steinmetz, C.H. (1984) A natural history of athleticism and cardiovascular health. *J. Am. med. Assoc.,* ***252,*** 491–495

Puska, P., Tuomilehto, J., Salonen, J., Neittaanmaki, L., Maki, J., Virtamo, J., Nissinen, A., Koskela, K. & Takolo, T. (1979) Changes in coronary risk factors during a comprehensive five-year community programme to control cardiovascular diseases (North Karelia project). *Br. med. J.,* ***ii,*** 1173–1178

Rogot, E. & Murray, A.J. (1980) Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Rep.,* ***95,*** 213–222

Rose, G., Hamilton, P.J.S., Colwell, L. & Shipley, M.J. (1982) A randomised controlled trial of anti-smoking advice: 10-year results. *J. Epidemiol. Commun. Health,* ***36,*** 102–108

Rosenberg, L., Kaufman, D.W., Helmrich, S.P., Miller, D.R., Stolley, P.D. & Shapiro,

S. (1985) Myocardial infarction and cigarette smoking in women younger than 50 years of age. *J. Am. med. Assoc.*, ***253***, 2965–2969

Strong, J.P. & Richards, M.L. (1976) Cigarette smoking and atherogenesis in autopsied men. *Atherosclerosis*, ***23***, 451–476

US Department of Health and Human Services (1983) *The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General*, Washington DC, Public Health Service, Office on Smoking and Health

US Department of Health, Education, and Welfare (1964) *Smoking and Health Report of the Advisory Committee to the Surgeon General of the Public Health Service (PHS Publication* No. 1103), Washington DC, US Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control

Weir, J.M. & Dunn, J.E., Jr (1970) Smoking and mortality: a prospective study. *Cancer*, ***25***, 105–112

World Health Organization European Collaborative Group (1982) Multifactorial trial in the prevention of coronary heart disease: 2. Risk factor changes at two and four years. *Eur. Heart J.*, ***3***, 184–190

SMOKING AND RESPIRATORY DISEASE EXCLUDING LUNG CANCER

H. PEACH

Department of Community Medicine,
United Medical and Dental Schools, St Thomas' Campus
London SE1 7EH, UK

INTRODUCTION

This paper is concerned with a group of diseases which, in the 1950s, would have been called 'chronic non-specific respiratory disease' (Ciba Foundation Guest Symposium, 1959) namely, chronic obstructive lung disease, chronic mucus hypersecretion and asthma. Specific airway diseases such as tuberculosis, sarcoidosis, pneumoconiosis and diseases of the pulmonary interstitium are excluded. Chronic obstructive lung disease, often referred to as chronic obstructive airways disease or chronic obstructive pulmonary disease, is an important burden in terms of morbidity and mortality in many economically developed countries. Chronic mucus hypersecretion, which describes a chronic productive cough independent of airflow limitation and was previously called simple and mucopurulent bronchitis (Thurlbeck, 1977), may not itself lead to mortality (Peto *et al.*, 1983) but is important in terms of morbidity.

Table 1 shows the deaths and admissions to hospital in the UK due to 'chronic bronchitis and emphysema', a term which embraces both chronic mucus hypersecretion and chronic obstructive lung disease. There is little doubt that death rates from bronchitis and emphysema are related to the number of cigarettes smoked. However, the increase in cigarette smoking over the decades before 1956 did not result in correspondingly more deaths from bronchitis, as happened with lung cancer. In the 25 years before 1956, death rates from bronchitis in men remained fairly constant, while in women there was a steady decline. Since then, the death rates in men have shown an accelerating decline. Since 1978, the decline in death rates among men and women have appeared to accelerate even more (Fig. 1), but this may be a recent certification artefact. Generally, diagnosis and methods of certification for respiratory disease have probably been more stable in the UK than in most countries, and the marked drop in mortality rates over time probably reflects a real fall in disease incidence. This fall is probably due to improvements in living standards, improvements in the control of air pollution, and possibly decreasing tar delivery from cigarettes.

Table 1. Mortality and hospital discharges for chronic bronchitis and emphysema in England and Wales, 1981[a]

	Rates per 10 000 population				
	All ages	25–44 years	45–64 years	65–74 years	75+ years
Mortality					
Men	53.03	0.73	31.29	198.32	647.00
Women	18.60	0.28	10.92	43.46	141.74
Hospital discharges					
Men	97.27	3.94	83.44	371.82	729.91
Women	40.59	4.01	46.14	96.18	167.81

[a] From Office of Population Censuses and Surveys (1981a, b)

MUCUS HYPERSECRETION

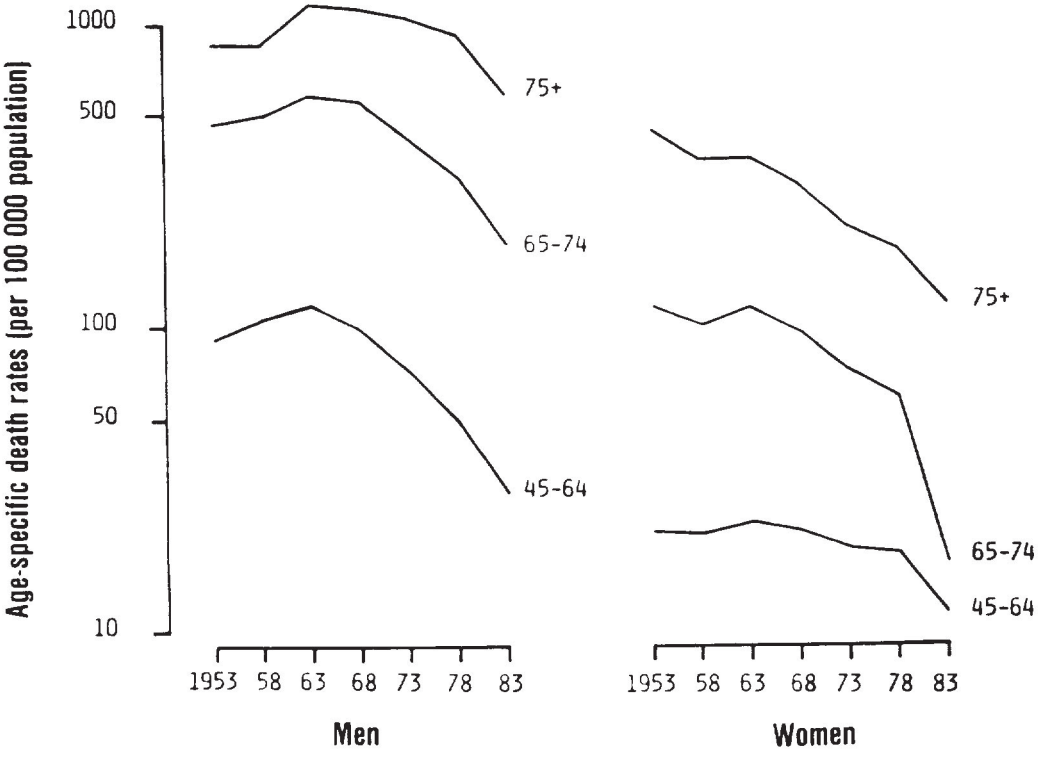
Surveys from many countries show that cigarette smokers cough more often and produce more phlegm than do nonsmokers. Even teenagers who smoke more than five cigarettes a day cough almost as much as adult cigarette smokers (Addington *et al.*, 1970; Seely *et al.*, 1971). The risk increases with number of cigarettes smoked, earlier age of starting to smoke, and depth of inhalation. That cough and phlegm usually disappear or diminish when cigarette smoking is given up shows that smoking is the main cause of these symptoms. At all ages, cigarette smokers have more chest illnesses than nonsmokers (Finklea *et al.*, 1971; Colley *et al.*, 1973). Cough, expectoration, and recurrent respiratory infections lead to much absence from work and are often treated with expensive antibiotics. Airways obstruction is often more severe during an infective episode but recovery is usual, and these episodes do not seem to accelerate the progression of chronic obstructive lung disease (Fletcher & Peto, 1977). Pipe and cigar smokers are much less affected than are cigarette smokers by cough, phlegm and recurrent chest infection (Boudik *et al.*, 1970; Comstock *et al.*, 1970; Mueller *et al.*, 1971). Morning phlegm has been found to be commoner in smokers of nonfilter cigarettes than in smokers of filter-tipped cigarettes (Rimington, 1972).

OBSTRUCTIVE LUNG DISEASE

Obstructive lung disease is as specifically related to smoking as is lung cancer. Forced expiratory volume in one second (FEV_1) falls gradually and irreversibly over several decades among both nonsmokers and smokers. The range of rates of loss of FEV_1 is much wider among smokers than nonsmokers. Some smokers suffer such unusually rapid rates of loss of FEV_1 that, if they continue to smoke, they will first become disabled, once their FEV_1 falls to about one litre, and then killed by their obstructive lung disease. If such people stop smoking their FEV_1 will not recover but their subsequent rate of loss of FEV_1 will usually revert to about that seen in nonsmokers. Thus, if susceptible smokers stop well before they are disabled, they will not die from chronic obstructive lung disease.

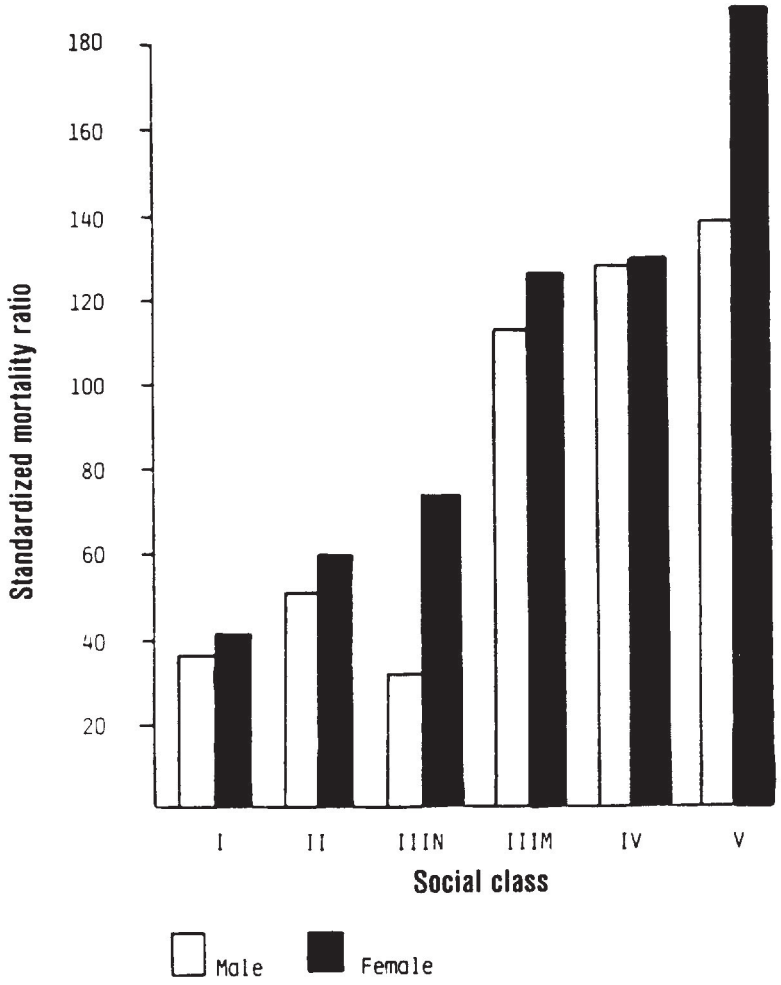
That there was no rise in death rates from chronic bronchitis and emphysema following the rise in tobacco consumption indicated that extrinsic factors must exist that alone or in

Fig. 1. Age and age-specific mortality rates for chronic bronchitis and emphysema in England and Wales, 1953–1983 (from Holland, 1984)



conjunction with smoking are responsible for some of the mortality from chronic bronchitis and emphysema. Studies in the UK and elsewhere have shown that chronic obstructive lung disease is more common among poorer groups in a population than among the economically better off (Reid, 1963). This appears to reflect general environmental exposures rather than specific occupational factors, since married women classified by their husband's socioeconomic status also have an excess of chronic bronchitis and emphysema (Fig. 2). Such factors might include poor housing conditions, domestic overcrowding, or indoor and outdoor air pollution, but they have never been precisely identified. Acute episodes of high-level particulate air pollution can exacerbate symptoms in susceptible groups in a population such as the elderly, the chronically ill, and, possibly also, young children. Similarly, the long-term chronic effects of exposure to high levels of air pollution have been well documented. Both these aspects of air pollution were thoroughly reviewed by Holland *et al.* (1979). In many countries, the introduction of measures to control particulate air pollution has meant that this is now a less important factor than it was in the past, except in particular populations occupationally or otherwise exposed to high levels of local pollution. It must be emphasized that, at present, only the effects of tobacco are reliably known to be of substantial importance and amenable to change.

Fig. 2. Mortality among men (□) and women (■) aged 15–64 years from chronic bronchitis and emphysema by social class in England and Wales, 1970–1972 (from Holland, 1984); N, nonmanual; M, manual



CHILDREN, RESPIRATORY DISEASE AND SMOKING

Although cough and phlegm usually disappear or diminish when cigarette smoking is given up, and the rate of loss of FEV_1 will usually revert to about that seen in nonsmokers, priority in prevention should not be given to persuading adults with chronic mucus hypersecretion or chronic obstructive lung disease to stop smoking. It is better to dissuade children from ever taking up the habit or at least from becoming regular smokers. Traditionally, smoking has been the habit of adults, but, since the late 1950s, it has been established that a measurable proportion of school children smoke regularly. Estimates of

Table 2. Annual incidence (per 100 infants) of 'bronchitis' or pneumonia in the first year of life[a]

Parental asthma or wheeze	Parental smoking habit			
	Neither	One	Both	Habit changed
Neither	6.7	9.6	13.7	8.7
One	8.9	18.0	22.3	7.4
Both	14.3	13.6	39.3	30.0

[a] From Leeder *et al.* (1976)

the prevalence of smoking one or more cigarettes per week among school children, vary from 7% of boys aged 10–11 years to over 16% in two populations of boys aged 11–14 years and up to 20–40% in youths of 14–17 years (Bewley *et al.*, 1973). The role of cigarette smoking in the development of respiratory disease in childhood has more relevance to attempts to persuade children from ever taking up the habit than has rates of decline of FEV_1 in middle age.

Holland *et al.* (1969a) followed a cohort of 2000 children born between 1963 and 1965 in Harrow, a suburb in north-west London. A one in three random sample had 'crying' ventilatory function tests performed using a pneumotachograph. Of the original 623 who had these initial tests, ventilatory function measured each year was available for 487 at the age of five. No events before, during or immediately after pregnancy had an effect on incidence of respiratory illness or on ventilatory function up to six weeks of age, and ventilatory function was not affected by any other environmental or familial factors. No large or consistent differences in 'crying' ventilatory function were found between children who subsequently suffered from pneumonia or bronchitis and those who did not (Colley *et al.*, 1976), which suggests that children who suffer from pneumonia or bronchitis in early life do not start life with a defective respiratory system.

The factors which appeared to be most closely associated with 'bronchitis' or pneumonia in the first year of life were a history of asthma or wheeze in the parents and parental smoking habits. If both these factors were present, the annual incidence of 'bronchitis' and pneumonia per 100 infants was 39.3, compared to 6.7 where neither existed (Table 2). A higher incidence of 'bronchitis' and pneumonia was also associated with parental cough or phlegm. This association may have resulted from shared genetic susceptibility to respiratory disease, parents and children living in the same home environment, or to cross-infection within the family. Work in France (Liard *et al.*, 1982) showed that wheezy bronchitis was strongly related to mother's cigarette consumption but simple bronchitis was not. This supports the hypothesis that passive inhalation of cigarette smoke irritates the child's lung and facilitates the spread of infection to the lower respiratory tract.

In the Harrow study, the main factors influencing the incidence of 'bronchitis' and pneumonia and other respiratory symptoms during the first five years of life were similar to those which affected disease incidence in the first year of life. However, ventilatory function, measured as peak expiratory flow rate (PEFR) using the Wright Peak Flow Meter, at the age of five was related to past history of bronchitis and pneumonia (the

earlier the onset of disease, the greater the effect of past history) and also to the history of asthma, but not to parental smoking habits (Leeder *et al.*, 1976).

The normal practice of school medical examinations at the ages of five, 11 and 15 years was utilized in the Kent studies, which began in 1964 (Holland *et al.*, 1969a,b). The parents of 4707 children were interviewed. Examination of the children included PEFR measurements. Older children answered questions about respiratory symptoms and smoking habits. Re-examinations, when parents were asked about their child's respiratory illnesses over the preceding 12 months, took place at the age of 11 years for those aged five at the start of the study, and at 14 for those aged 11 at the start of the study. Prevalence of respiratory tract symptoms was found to be influenced by area of residence, parent's social class, age and sex, and particularly smoking habits; even exsmokers had more symptoms of cough and phlegm production than those who had never smoked. In contrast, PEFR was significantly influenced by area of residence, parent's social class, number of siblings and past history of bronchitis, pneumonia and asthma but not smoking.

Only 1978 children could be traced at the time of the first re-examination, and because the percentage loss varied between area and social class groups it was not possible to use the data to draw conclusions about the relationship between respiratory disease and social and environmental factors. However, it was possible to establish that children with a history of 'bronchitis', pneumonia or asthma before the age of five years (partly caused by parental smoking) were more likely to have 'bronchitis', wheezy chest and phlegm production at the age of 11. Children with reported symptoms at 11 also had on average a lower PEFR at 11 and at five. Those who had had low ventilatory function at the age of five were more likely to have respiratory symptoms and low ventilatory function at 11.

The most recent follow-up of the children in the Kent cohort was in 1974–1975. The relative risks of reporting respiratory symptoms in children with an early history of 'bronchitis', asthma or pneumonia was unchanged for those at ages five, 11 and 15. Thus, once a child's respiratory system has been compromised by early disease, there appears to be a lasting increased risk of having persistent symptoms.

Further evidence is needed to link factors experienced in early life with the development of chronic disease in much later life. It is unlikely that a single birth cohort could be satisfactorily followed from birth to old age. For example, a 1946 cohort was difficult to follow because the numbers remaining in 1966 had dwindled so that the reliability of conclusions was reduced (Douglas & Waller, 1966). Nonetheless, the study showed that a relationship between lower respiratory tract infection and air pollution levels exists until at least the age of 15. In 1966 it was only possible to collect data from 3899 of the original sample, then aged 20 (Colley *et al.*, 1973). The major finding of the 20-year follow-up was that prevalence of cough during the day or night was most closely related to current smoking habits and to a history of lower respiratory tract illnesses before the age of two. In the most recent follow-up, it was possible to collect data from 2088 men and women aged 25 (Kiernan *et al.*, 1976). At this age certain changes in the factors affecting respiratory symptom prevalence appeared to have taken place, namely that the association of cough prevalence with past history of respiratory illness and current smoking was even stronger.

Studies of respiratory disease in childhood have thus demonstrated that the environmental factors which are associated with respiratory disease in adults, for example air pollution, past respiratory illness and smoking, are also present amongst children. The relationship of respiratory disease in childhood to that developed in adults is more tenuous. No

good prospective studies have yet been completed or undertaken to demonstrate the link, and merely showing that the same factors are responsible for disease at both ages is insufficient to prove that there is any real association. From a prevention viewpoint, it is not necessary to wait until such a link is demonstrated, because respiratory disease in children is more relevant than respiratory disease in adults to persuading children not to take up smoking. Smoking habits are associated with bronchitis and pneumonia in teenagers, and young adults and antismoking campaigns could emphasize this. However, respiratory disease in childhood is also related to infection in earlier years. It is quite possible that we may be able to treat respiratory infection in the early years better and thus perhaps avoid some of the troubles of later childhood. But also, if it could be shown that those children with respiratory infections were susceptible to chronic bronchitis and emphysema in later life, campaigns directed toward preventing those children from taking up cigarette smoking may be even more effective.

The Medical Research Council Derbyshire smoking study was the first longitudinal study of children's smoking to be performed in the UK (Banks *et al.*, 1978). At the start of the study in 1974, questionnaires were administered to children aged 11–12 years. These children were followed up until 1978. Factors which induce children to take up smoking are many and varied, but considerable importance seems to be attached to parental and sibling smoking, especially for the same sex. The fact that parental smoking is also associated with bronchitis and pneumonia among children under five years of age and that children's smoking habits are associated with bronchitis and pneumonia in teenagers and young adults suggest that antismoking efforts could be directed at the family rather than at adults or children separately.

LESS HAZARDOUS SMOKING

If children cannot be dissuaded from taking up smoking, the next best thing is to persuade adults to stop smoking. Various surveys of British men carried out in the 1950s and early 1960s have recently yielded sufficient data on deaths from chronic obstructive lung disease to show that the single original forced expiratory volume in one second (FEV_1) measured when these men were in their fifties can be used to predict reliably which men would have a high risk of death from chronic obstructive lung disease during the subsequent 20 years (Peto *et al.*, 1983). Antismoking campaigns directed toward these men could be very effective. However, the age-standardized chronic obstructive lung disease death rates per 100 000 British doctors who smoked 1–14, 15–24 and 25+ cigarettes a day were 51, 78 and 114 respectively, suggesting that if people cannot cease smoking, diminution of the dose might produce diminution of the effect (Doll & Peto, 1976).

Because of this dose-response relationship, it has also been suggested that the smoking of cigarettes in a lower tar group would be less deleterious to the lungs. Several studies have suggested that there might be a direct relationship between reduction in the tar yield of cigarettes and a reduced prevalence of cough (Comstock *et al.*, 1970; Freedman & Fletcher, 1976; Fletcher *et al.*, 1976; Dean *et al.*, 1978; Schenker *et al.*, 1982), and phlegm production (Rimington, 1972; Hawthorne & Fry, 1978; Higenbottam *et al.*, 1980). Fewer studies have examined the potential importance of tar yield for change in pulmonary function. One prospective study (Comstock *et al.*, 1970) found that smokers of nonfilter

cigarettes, compared to those smoking filter-tipped cigarettes, had a lower FEV_1 at entry into the study but a smaller reduction of FEV_1 after five years. However, in another longitudinal survey, multiple regression analysis did not show any significant association between tar yield and lung function (Sparrow *et al.*, 1983). Cross-sectional surveys also indicate no relationship between pulmonary function and the use of filter-tipped *versus* nonfilter cigarettes (Beck *et al.*, 1981) or cigarette tar yield (Higenbottam *et al.*, 1980).

It has been suggested that mucus hypersecretion and chronic airflow obstruction are essentially distinct lung diseases (Fletcher *et al.*, 1976; Peto *et al.*, 1983), and it is possible that they might differ in their susceptibility to tar intakes. However, it would be premature to conclude that tar intake might not be an important factor in chronic airflow obstruction. Firstly, cross-sectional studies cannot define the natural history of a disease. Secondly, Fletcher *et al.* (1976) suggested that approximately eight years are necessary to establish rates of change of FEV_1 with sufficient confidence even to distinguish between smokers and nonsmokers. Thirdly, there is usually no information on the lung function of smokers at the time they change from high- to low-tar cigarettes. It is possible that similar function differences may exist in subjects who choose between high- and low-tar cigarettes as have been observed in adults choosing to smoke or not (Tashkin *et al.*, 1983).

Government tables of the tar yields of cigarettes in the UK advise committed smokers to choose a cigarette in a lower tar group. In 1971–1973, data on smoking habits including cigarette brand smoked, phlegm production and lung function were recorded on factory workers as part of the Heart Disease Prevention Project (HDPP) (Rose *et al.*, 1980). Assessment of their 1984 smoking habits, phlegm production and lung function permitted

Table 3. Characteristics of cigarette smokers at the start of the Heart Disease Prevention Project[a]

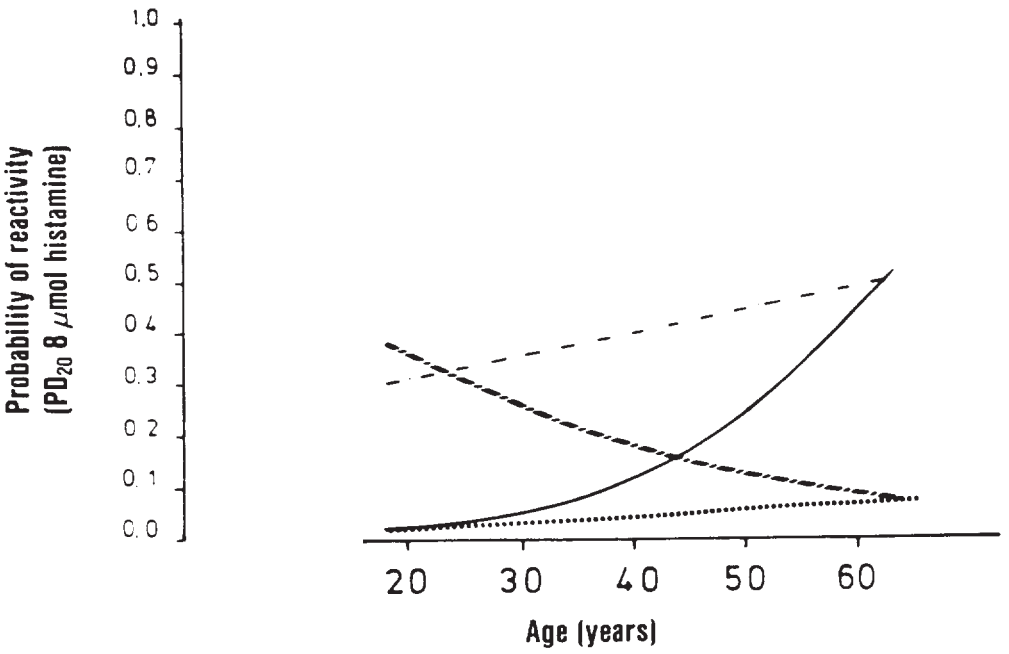
Variable	Type of cigarette smoked 1971–1984: mean (SE)					
	Same tar group		Dropped one tar group		Dropped two tar groups	
Age (years)	47.5	(0.44)	48.0	(0.27)	48.3	
Social class[b] I-III NM (%)	28.2		21.8		27.3	
IIIM-V (%)	71.7		78.3		72.8	
Cigarettes/day	17.4	(0.73)	17.7	(0.56)	18.5	(0.79)
Tar yield (mg/cigarette)	19.7	(0.20)	22.5	(0.23)	23.0	(0.39)
Nicotine yield (mg/cigarette)	1.28	(0.02)	1.44	(0.02)	1.47	(0.03)
Inhale (%)	87		86		94	
Morning phlegm usually (%)	28		32		37	
FEV, % FVC[c]	77.5	(0.59)	77.2	(0.40)	78.0	(0.66)
FEV,[c] (litres)	3.1	(0.05)	3.0	(0.03)	3.1	(0.05)
FVC[c] (litres)	4.0	(0.05)	3.9	(0.04)	4.0	(0.03)
Number	145		322		132	

[a] From Peach *et al.* (1986)

[b] Social class in the UK is divided into six categories: I, II, III nonmanual (NM), III manual (M), IV and V, on the basis of present occupation

[c] FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV, % FVC, the ratio of FEV_1 to FVC expressed as a percentage

Fig. 3. Mean prevalence of bronchial reactivity according to age, atopic status and smoking history; (–·–·) current smokers, 3-mm mean skin-weal diameter; (------) nonsmokers, 3-mm mean skin-weal diameter; (——) current smoker, 0-mm mean skin-weal diameter; (·····) non-smoker, 0-mm mean skin-weal diameter



a comparison between cigarette smokers who had changed tar groups with those who had not.

Table 3 shows the age, social class, smoking habits, phlegm production and mean pulmonary function levels of men at the start of the HDPP. Smokers who subsequently changed to a lower tar group smoked cigarettes with higher tar and nicotine yields in 1971. If high-tar cigarettes were particularly deleterious, men who smoked them might have had more phlegm and poorer lung function before they changed tar groups. A comparison between men changing and not changing to a cigarette in a lower tar group would then be biased. However, there was no difference in mean pulmonary function levels (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC] and the ratio of FEV_1 to FVC expressed as a percentage) between these types of smoker in the HDPP. There was a tendency for the prevalence of phlegm at the start of the study to increase from 28% among men who always smoked a cigarette in the same tar group to 37% among those who subsequently dropped two or more tar groups, but this trend was not significant. Although smokers who changed tar groups did not differ in phlegm production and pulmonary function before they changed, a comparison with non-changers could still be biased if the effects of smoking the higher-tar cigarettes were long-term. Only a controlled trial in which 'middle'-tar cigarette smokers, who are unwilling to stop smoking, are allocated at random to smoke a cigarette of the same or a lower tar group will provide definitive evidence of the potential benefit of changing tar groups on respiratory disease.

ASTHMA

Bronchial reactivity is beginning to appear as an important cause of continuing deterioration in patients with chronic obstructive lung disease. Barter *et al.* (1974) and Barter and Campbell (1976) showed that the deterioration in FEV_1 over a four-year period was related to the degree of bronchial reactivity. Mann (1976) related the improvement in FEV_1 of patients who stopped smoking to the bronchial reactivity measured by a bronchial challenge with 0.15 mg methacholine. Patients with the most bronchial reactivity had the best response, suggesting that increased bronchial reactivity is an important factor in lowering FEV_1. This bronchial reactivity is not in the asthmatic range and does not appear to be related to atopic status. However, the role of tobacco products as allergens is only just beginning to be assessed. Burney and his colleagues (personal communication) carried out tests of bronchial reactivity to histamine in 511 subjects randomly selected from a population who had returned questionnaires on respiratory symptoms. Bronchial reactivity was associated with positive skin tests to common allergens and with smoking history (Fig. 3). Both of these effects were in turn affected by the age of the subjects, the skin sensitivity being the more important determinant of reactivity in the young, and smoking the more important in older subjects. If bronchial reactivity is to be taken as the defining characteristic of asthma, it must follow that cigarette smoking is commonly associated with this condition.

REFERENCES

Addington, W.W., Carpenter, R.L., McCoy, J.E., Duncan, K.A. & Mogg, K. (1970) The association of cigarette smoking with respiratory symptoms and pulmonary function in a group of a high school students. *Oklahoma State med. Assoc.*, ***63***, 525–529

Banks, M.H., Bewley, B.R., Bland, J.M., Dean, J.R. & Pollard, V. (1978) Longterm study of smoking by secondary schoolchildren. *Arch. Dis. Child.*, ***53***, 12–19

Barter, C.E. & Campbell, A.H. (1976) Relationship of constitutional factors in cigarette smoking to decrease in the one second forced expiratory volume. *Am. Rev. resp. Dis.*, ***113***, 305–314

Barter, C.E., Campbell, A.H. & Tandon, M.K. (1974) Factors affecting the decline of FEV_1 in chronic bronchitis. *Aust. N. Z. J. Med.*, ***4***, 339

Beck, G.J., Doyle, C.A. & Schachter, E.N. (1981) Smoking and lung function. *Am. Rev. resp. Dis.*, ***123***, 149–155

Bewley, B.R., Day, I. & Idle, L. (1973) *Smoking by Children in Great Britain: A Review of the Literature*. London, Social Science Research Council, Medical Research Council

Boudik, F., Goldsmith, J.R., Teichman, V. & Kaufmann, P.C. (1970) Epidemiology of chronic bronchitis in Prague. *Bull. World Health Organ.*, ***42***, 711

Ciba Foundation Guest Symposium (1959) Terminology, definitions and classification of chronic pulmonary emphysema and related conditions. *Thorax*, ***14***, 286–299

Colley, J.R.T., Douglas, J.W.B. & Reid, D.D. (1973). Respiratory disease in young adults: influence of early childhood lower respiratory tract illness, social class, air pollution and smoking. *Br. med. J.*, ***3***, 195–198

Colley, J.R.T., Holland, W.W., Leeder, S.R. & Corkhill, R.T. (1976) Respiratory

function of infants in relation to subsequent respiratory disease: an epidemiological study. *Bull. Eur. Physio-Pathol.*, **12**, 651–657

Comstock, G.W., Brownlow, W.J., Stone, R.W. & Startwell, P.E. (1970) Cigarette smoking and changes in respiratory findings. *Arch. Environ. Health*, **20**, 50–57

Dean, G., Lee, P.N., Todd, G.F., Wicken, A.J. & Sparks, D.N. (1978) Factors related to respiratory and cardiovascular symptoms in the United Kingdom. *J. Epidemiol. Community Health*, **32**, 86–96

Doll, R. & Peto, R. (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. *Br. med. J.*, **ii**, 1525–1536

Douglas, J.W.B. & Waller, R.E. (1966) Air pollution and respiratory infection in children. *Br. J. prev. soc. Med.*, **20**, 1–8

Finklea, J.F., Hasselbad, V., Sadifer, S.H., Hammer, D.I. & Lowrimore, G.R. (1971) Cigarette smoking and acute non-influenzal respiratory disease in military cadets. *Am. J. Epidemiol.*, **93**, 457–462

Fletcher, C.M. & Peto, R. (1977) The natural history of chronic airflow obstruction. *Br. med. J.*, **i**, 1645–1648

Fletcher, C., Peto, R., Tinker, C. & Speizer, F.E. (1976) *The Natural History of Chronic Bronchitis and Emphysema. An Eight-year Study of Early Chronic Obstructive Lung Disease in Working Men in London*, New York, Oxford University Press

Freedman, S. & Fletcher, C.M. (1976) Changes of smoking habits and cough in men smoking cigarettes with 30% NSM tobacco substitute. *Br. med. J.*, **i**, 1427–1430

Hawthorne, V.M. & Fry, J.S. (1978) Smoking and health: the association between smoking behaviour, total mortality and cardio-respiratory disease in west central Scotland. *J. Epidemiol. Community Health*, **32**, 260–266

Higenbottam, T., Shipley, M.J., Clark, T.J.H. & Rose, G. (1980) Lung function and symptoms of cigarette smokers related to tar yield and number of cigarettes smoked. *Lancet*, **i**, 409–412

Holland W.W. (1984) 'Chronic bronchitis – what has to be done. What should we do next? An epidemiologist's dreams', Ninth Annual Theodore L. Badger Lecture delivered at Harvard Medical School 26 November, 1984

Holland, W.W., Halil, T., Bennett, A.E. & Elliott, A. (1969a) Factors influencing the onset of chronic respiratory disease. *Br. med. J.*, **ii**, 205–208

Holland W.W., Halil, T., Bennett, A.E. & Elliott, A. (1969b) Indications for measures to be taken in childhood to prevent chronic respiratory disease. *Milbank Mem. Fund Q.*, **48**, 215–227

Holland, W.W., Bennett, A.E., Cameron, I.R., Florey, C.V., Leeder, S.R., Schilling, R.S., Swan, A.V. & Waller, R.E. (1979) Health effects of particulate pollution: reappraising the evidence. *Am. J. Epidemiol.*, **110**, 525–659

Kiernan, K.E., Colley, J.R.T., Douglas, J.W.B. & Reid, D.D. (1976) Chronic cough in young adults in relation to smoking habits, childhood environment and chest illness. *Respiration*, **33**, 236

Leeder, S.R., Corkhill, R.T., Wysocki, M.J., Holland, W.W. & Colley, J.R.T. (1976) Influence of personal and family factors on ventilatory function of children. *Br. J. prev. soc. Med.*, **30**, 219–224

Liard, R., Perdrizet, S. & Reinert, P. (1982) Wheezy bronchitis in infants and parents' smoking habits. *Lancet*, **i**, 334–335

Mann, J.S. (1976) *Cigarette Smoking and Lung Function,* MD thesis, University of Sydney

Mueller, R.E., Keble, D.L., Plummer, J. & Walker, S.H. (1971) The prevalence of chronic bronchitis, chronic airway obstruction and respiratory symptoms in a Colorado city. *Am. Rev. resp. Dis.*, ***103,*** 209–228

Office of Population Censuses and Surveys (1981a) *Mortality Statistics in England and Wales,* London, Her Majesty's Stationery Office

Office of Population Censuses and Surveys (1981b) *Hospital Inpatient Statistics in England and Wales,* London, Her Majesty's Stationery Office

Peach, H., Hayward, D.M., Ellard, D.R., Morris, R.W. & Shak, D. (1986) Phlegm productions and lung function among cigarette smokers changing tar groups during the 1970s. *Epidemiol. Commun. Health* (in press)

Peto, R., Speizer, F.E., Cochrane, A.L., Moore, F., Fletcher, C.M., Tinker, C.M., Higgins, I.T.T., Gray, R.G., Richards, S.M., Gillilard, J. & Norman-Smith, B. (1983) The relevance in adults of airflow obstruction but not of mucus hypersecretion to mortality from chronic lung disease: 20-year results from prospective surveys. *Am. Rev. resp. Dis.*, ***128,*** 491–500

Reid, D.D. (1963) *The Epidemiology of Chronic Bronchitis,* Edinburgh, Royal College of Physicians of Edinburgh

Rimington, J. (1972) Phlegm and filters. *Br. med. J.*, ***ii,*** 262–264

Rose, G., Heller, R.F., Pedoe, H.T. & Christie, D.G.S. (1980) Heart disease prevention project: a randomised controlled trial in industry. *Br. med. J.*, ***i,*** 747–751

Schenker, M.B., Samet, J.M. & Speizer, F.E. (1982) Effect of cigarette tar content and smoking habits on respiratory symptoms in women. *Am. Rev. resp. Dis.*, ***125,*** 684–690

Seely, J.E., Zuskin, E. & Bouhuys, A. (1971) Cigarette smoking: objective evidence for lung damage in teenagers. *Science,* ***172,*** 741–743

Sparrow, D., Stafos, T., Bosse, R. & Weiss, S. (1983) The relationship of tar content to decline in pulmonary function in cigarette smokers. *Am. Rev. resp. Dis.*, ***127,*** 56–58

Tashkin, D.P., Clark, V.A., Coulson, A.H., Bourque, L.B., Simmons, M., Reems, C., Detels, R. & Rokaw, S. (1983) Comparison of lung function in young non-smokers and smokers before and after initiation of the smoking habit: a prospective study. *Am. Rev. resp. Dis.*, ***128,*** 12–16

Thurlbeck, W.M. (1977) Aspects of chronic airflow obstruction. *Chest,* ***72,*** 3

CHEMICAL CONSTITUENTS AND BIOACTIVITY OF TOBACCO SMOKE

D. HOFFMANN & E.L. WYNDER

Naylor Dana Institute for Disease Prevention,
American Health Foundation,
Valhalla, NY 10595, USA

INTRODUCTION

The occurrence of cancer of the respiratory tract and of the upper digestive tract is causally related to smoking of cigarettes, cigars, pipes and *bidis*, while malignant tumours of the bladder, renal pelvis and pancreas are causally related to smoking of cigarettes (IARC, 1986). Epidemiological studies have demonstrated an association of tobacco chewing with cancer of the oral cavity (IARC, 1985). These conclusions have been supported by a large number of bioassays. The application of tobacco extracts, the inhalation of tobacco smoke and the application of tobacco smoke condensate induce cancer in laboratory animals (Wynder & Hoffmann, 1967; Hoffmann *et al.*, 1983; IARC, 1985, 1986). It has been the joint task of chemists and biologists to identify those components in tobacco and tobacco smoke that contribute to their carcinogenic effects. However, it would be an insurmountable task to evaluate each of the more than 2500 constituents in tobacco leaf and more than 3900 compounds in tobacco smoke for possible tumorigenic effects (Table 1). Therefore, the research programme has to be limited to the identification of those tumorigenic and carcinogenic agents that can account for most of the carcinogenic activity of tobacco products. Despite this limitation, remarkable progress has been made by the laboratory scientists. This progress is well reflected in the reduced carcinogenic potential of 'low-tar' cigarettes (IARC, 1986). In evaluating the carcinogenic risk of environmental tobacco smoke exposure (passive smoking), the knowledge of the physicochemical nature of sidestream and mainstream smoke and the principles of chemical carcinogenesis were the primary data bases which led the IARC (1986) to conclude that 'passive smoking gives rise to some risk of cancer.'

THE PHYSICOCHEMICAL NATURE OF TOBACCO SMOKE

The combustion of tobacco products leads to the formation of mainstream smoke (MS) and sidestream smoke (SS). MS is generated during puff-drawing in the burning cone and

Table 1. Estimates of constituents in tobacco smoke (≃3900 known compounds)

Major classes of compounds[a]	No
Amides, imides, lactones	240
Carboxylic acids, anhydrides	240
Lactones	150
Esters	475
Aldehydes	110
Ketones	520
Alcohols	380
Phenols	285
Amines	200
N-Nitrosamines	22
N-Heterocyclics	920
Hydrocarbons	755
Nitriles	105
Carbohydrates	45
Ethers	310
Total	4865

[a] Some compounds contain multiple functional groups, thus this list exceeds 3900

hot zones of cigarettes and cigars; it travels through the tobacco column and out of the mouthpiece. SS is formed between puffing and is emitted from the smouldering coal into the ambient air.

The data presented throughout this review are derived from machine-smoking under standardized laboratory conditions (Brunnemann *et al.*, 1976a; International Committee for Cigar Smoke Study, 1974). However, it has to be realized that machine-smoking parameters can differ substantially from the puff-drawing parameters of smokers, especially in the case of cigarettes with low nicotine delivery (Herning *et al.*, 1981).

About 30% of the total effluents of MS originate from the tobacco, the remainder comes from the air drawn through the cigarette. When leaving the mouthpiece, undiluted smoke from a nonfilter cigarette contains about 5×10^9 particles per millilitre, with a median particle size of about 0.4 μm (Keith & Tesh, 1965; Carter & Hasegawa, 1975).

The pH of tobacco smoke is of major significance, since it influences the degree of protonation and, therefore, the proportion of nicotine and other basic components in the vapour phase. This determines the inhalability of MS (Armitage & Turner, 1970). At about pH 5.4, all nicotine in tobacco smoke is monoprotonated and resides in the particulate phase (Fig. 1). The pH of the MS of air-cured tobaccos and of cigars increases with ascending number of puffs. Consequently, the smoke of these products contains proportionately larger amounts of nicotine in the vapour phase. The smoke pH of cigarettes filled with flue-cured tobaccos or with tobacco blends, on the other hand, decreases slightly or remains rather constant (Fig. 2; Brunnemann & Hoffmann, 1974).

The total MS of a cigarette weighs about 400–500 mg. More than 92% of the total is made up of 400–500 individual gaseous components with nitrogen (≃58%), oxygen (≃12%),

Fig. 1. Degree of protonation of nicotine in relation to pH (pH = pKa log $1 - \alpha/\alpha$ (Henderson-Hasselbach))

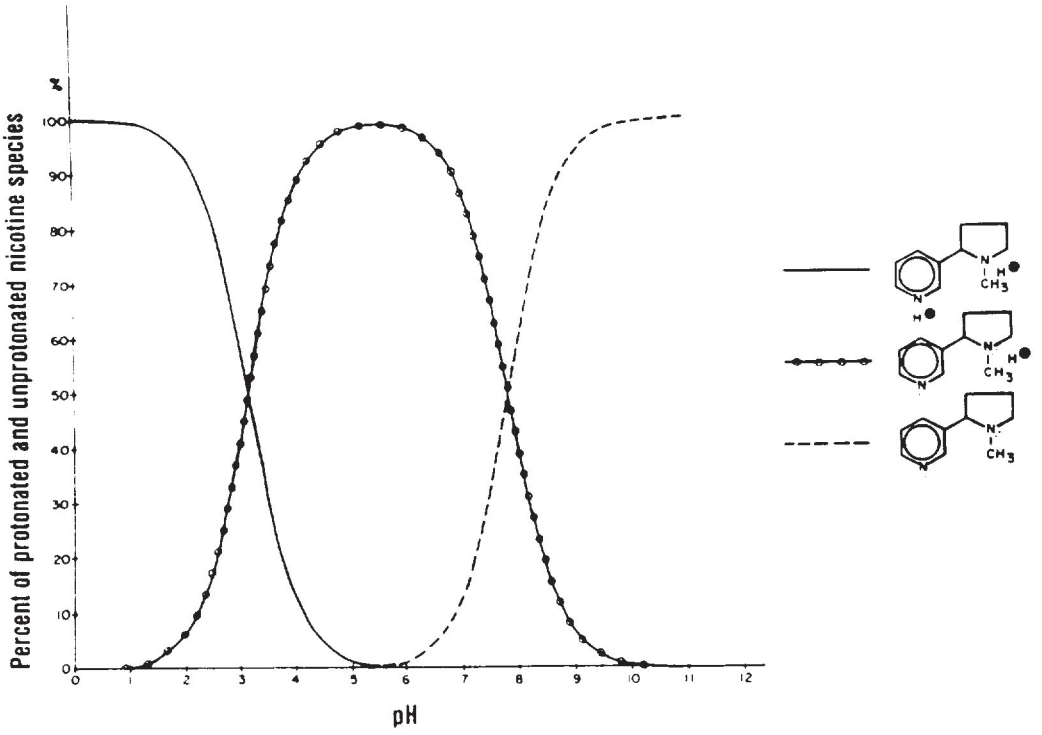


Fig. 2. pH of total mainstream smoke of various tobacco products: (1) little cigar I; (2) little cigar II; (3) cigar; (4) Kentucky reference cigarette (84 mm); (6) blended cigarette without filter (84 mm)

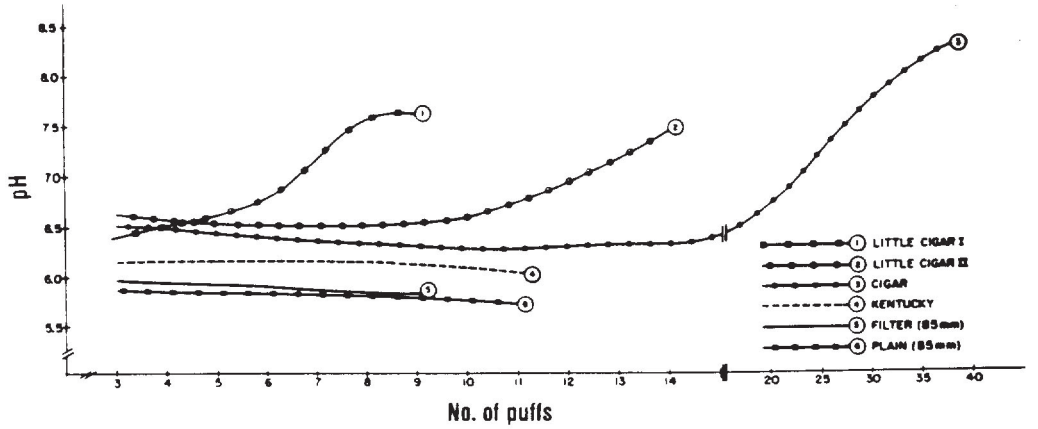
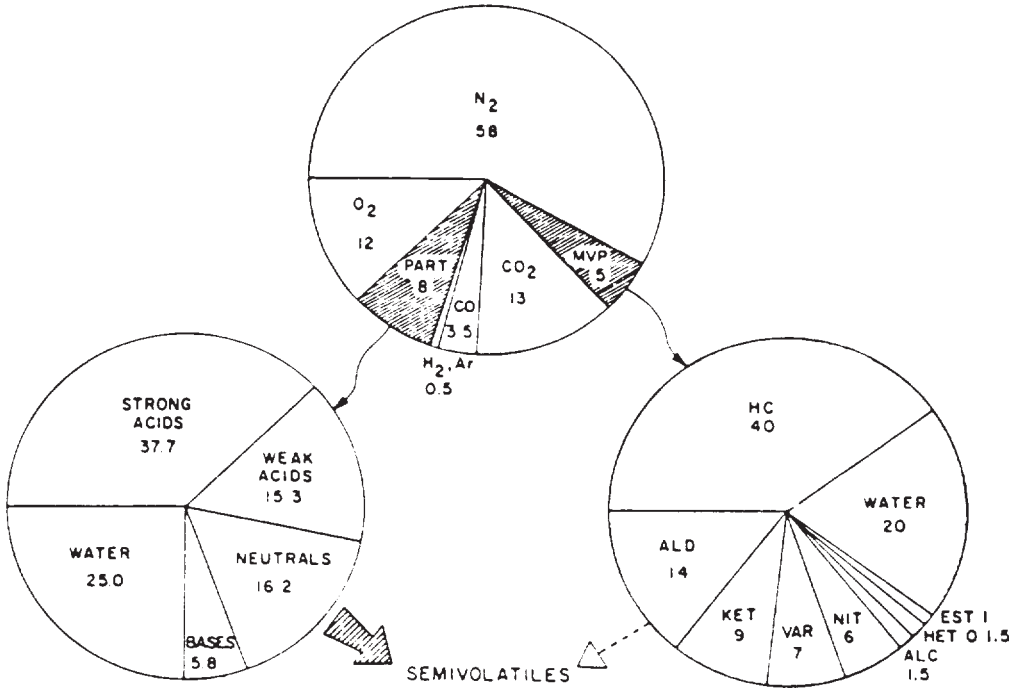


Fig. 3. Approximate chemical composition of mainstream smoke (from Norman, 1977)



carbon dioxide (≃13%) and carbon monoxide (≃3.5%) as major constituents. The remainder is comprised of other vapour phase components and of compounds constituting the particulate phase (Fig. 3; Norman, 1977).

VAPOUR PHASE

Bioassays with total smoke have indicated that the majority of the genotoxic and cocarcinogenic agents reside in the particulate phase (Dontenwill *et al.*, 1973; Hoffmann *et al.*, 1979). Thus, specific methods have been developed for the quantitative determination of smoke particulates. The most widely applied technique is the Cambridge filter method, utilizing a glass fibre filter pad which retains 99.7% of all particles with diameters of >0.1 μm (Dube & Green, 1982). This manner of trapping does not effect a strict separation of the solid and gaseous components in the physicochemical sense, nevertheless, it permits reproducible, quantitative determination of the particulate matter in the smoke of cigarettes, cigars and pipes and analysis of the major vapour phase components by gas chromatography. In addition to nitrogen, oxygen, carbon dioxide and carbon monoxide, the vapour phase contains hydrogen, methane and other hydrocarbons, volatile aldehydes and ketones, nitrogen oxides, hydrogen cyanide and volatile nitriles and at least an additional 400–450 minor constituents (Keith & Tesh, 1965; Wynder & Hoffmann, 1967; Brunnemann & Hoffmann, 1982).

Table 2. Major toxic and tumorigenic agents in the vapour of freshly generated smoke of a nonfilter cigarette[a]

Agent	Conc./cigarette	Biol. effect[b]
Carbon monoxide	10–23 mg	T
Acetaldehyde	0.5–1.2 mg	CT
Nitrogen oxides (NO_x)	50–600 μg	T
Hydrogen cyanide	150–300 μg	CT, T
Ammonia	50–170 μg	T
Acrolein	50–100 μg	CT
Benzene	20–50 μg	HC
Formaldehyde	5–100 μg	C
2-Nitropropane	0.2–2.2 μg	C
Hydrazine	24–43 ng	C
Urethane	20–38 ng	C
Vinyl chloride	1.3–16 ng	HC

[a] Does not include volatile *N*-nitrosamines
[b] Abbreviations: T, toxic agent; CT, ciliatoxic agent; HC, human carcinogen; C, carcinogen

Fig. 4. Hamburg II smoke inhalation device for Syrian golden hamsters

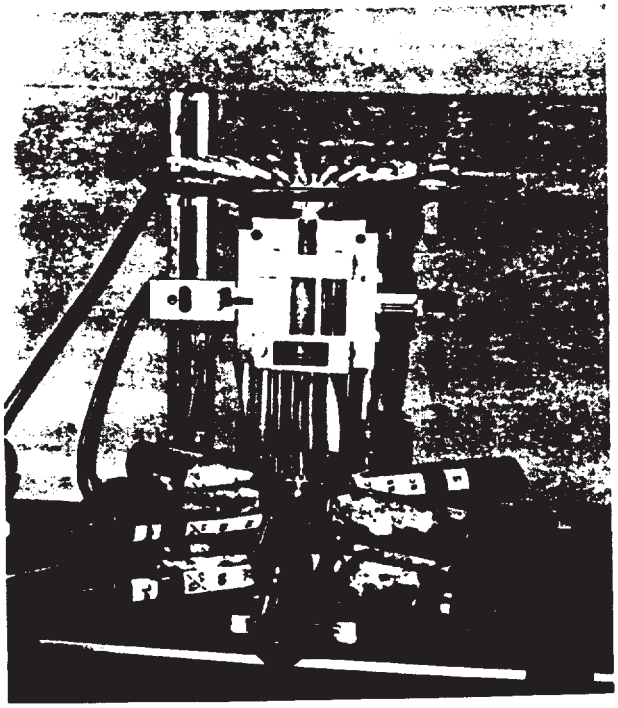


Table 2 presents a listing of the major known toxic and tumorigenic agents in the vapour phase of cigarette smoke. Each of the volatile smoke constituents was quantitatively assessed by analytical methods that had to be specifically developed for their determination in the smoke of cigarettes or cigars. Despite the presence of volatile carcinogens in the vapour phase of tobacco smoke, currently available bioassays – and here mainly inhalation experiments with hamsters (Fig. 4) – have not been sensitive enough to induce tumours by administering the vapour phase as such, aside from the induction of lung adenoma in mice (Mohr & Reznik, 1978).

PARTICULATE PHASE

While the vapour phase by itself is not tumorigenic in most of the inhalation assays, and the total smoke induces benign and malignant tumours in the upper respiratory tract of rats and hamsters (Dontenwill *et al.*, 1973; Hoffmann *et al.*, 1979), evidence from contact carcinogenesis studies indicates that the particulate phase contains most of the known tumorigenic and carcinogenic agents of tobacco smoke. Tobacco smoke particulates

Fig. 5. Fractionation of cigarette 'tar'; C, relative carcinogenic activity; P, relative tumour-promoting activity

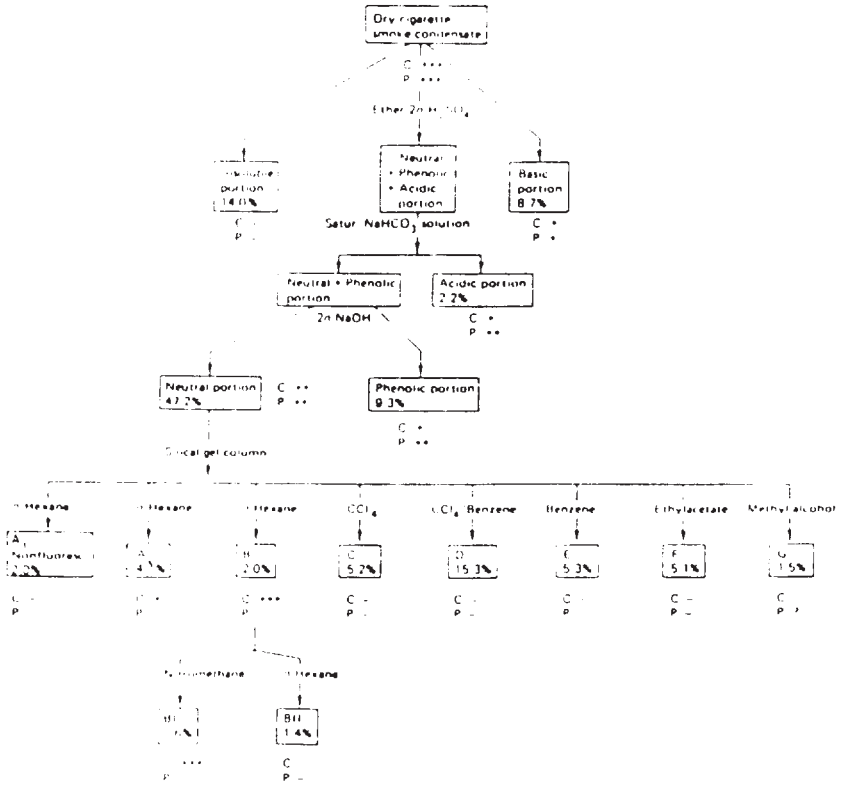
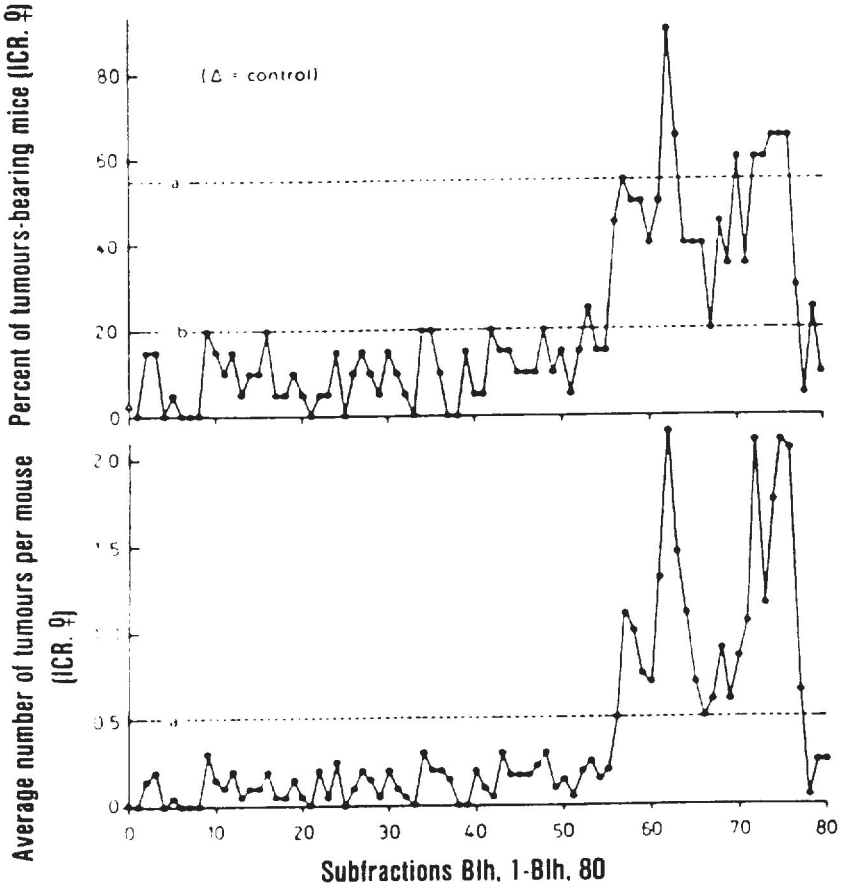


Fig. 6. Tumour-initiating activities of 80 end-fractions from BI subfractions. Each end-fraction was tested on 20 mice, negative control, no initiator: 1% croton oil as promoter; line a, fractions with activities significantly above those in negative control group ($p < 0.05$); line b, fractions with strong tumour-initiating activity ($p < 0.05$ above those in line a)



('tars') have consistently and in a dose-related response, induced benign and malignant tumours in the skin of mice and rabbits, and in the connective tissue and bronchial epithelium of rats (Wynder & Hoffmann, 1967; Mohr & Reznik, 1978; Hoffmann *et al.*, 1979; IARC, 1986).

Tumour initiators and cocarcinogens

The findings from bioassays with tobacco 'tars' have led to more detailed and systematic testing on mouse skin of the various fractions and subfractions of the particulate phase (Fig. 5; Hoffmann & Wynder, 1971). The only fractions found to have significant activity as complete carcinogens were the neutral fraction and its subfractions B and BI. A further breakdown of subfraction BI, which amounted to 0.6% of the total particulate phase, led

Table 3. Major compounds identified in neutral subfractions BIh 56–66 of the particulate phase of cigarette smoke

- Chlorinated hydrocarbon insecticides
  - DDD
  - *o,p'*-DDD
  - DDT
  - *o,p'*-DDT
  - DDM (DDD-HCl)
  - DDE (DDT-HCl)
  - *Trans*-4,4'-Dichlorostilbene
- *N*-Alkylcarbazoles
  - 9-Methylcarbazole
  - 9-Ethylcarbazole
  - 1,9-, 2,9-, 3,9- and 4,9-Dimethylcarbazole
- Fluoranthenes
  - Fluoranthene
  - 1-, 2-, 3-, 7- and 8-Methylfluoranthene
  - X-Ethylfluoranthene(s)
  - x,x'-Dimethylfluoranthenes
  - Benzo[*mno*]fluoranthene
- Benzofluorenes
  - 11*H*-benzo[*a*]fluorene
  - 11*H*-benzo[*b*]fluorene
  - 7*H*-benzo[*c*]fluorene
- 17*H*-cyclopenta[*a*]phenanthrene
  - 17*H*-cyclopenta[*a*]phenanthrene
  - x-Methyl-17*H*-cyclopenta[*a*]phenanthrene
  - x-Ethyl-17*H*-cyclopenta[*a*]phenanthrene
- x-Phenylindene
- Pyrenes
  - Pyrene
  - 1-, 3- and 4-Methylpyrene
  - x,x'-Dimethylpyrene(s)

Table 4. Major compounds identified in neutral subfractions BIh 71–78 of the particulate phase of cigarette smoke

- Chrysenes
  - Chrysene
  - 1-, 2-, 3-, 4-, 5- and 6-Methylchrysene
  - x,x'-Dimethylchrysene(s)
  - x-Ethylchrysene(s)
- Benz[*a*]anthracenes
  - Benz[*a*]anthracene
  - x-Methylbenz[*a*]anthracene
- Benzo[*c*]phenanthrenes
  - Benzo[*c*]phenanthrene
  - x-Methylbenzo[*c*]phenanthrene
- Benzopyrenes
  - Benzo[*a*]pyrene
  - x-Methylbenzo[*a*]pyrenes
  - Benzo[*e*]pyrene
- Benzofluoranthenes
  - Benzo[*b*]fluoranthene
  - Benzo[*j*]fluoranthene
  - Benzo[*k*]fluoranthene
  - Ideno[1, 2, 3,-*cd*]pyrene
- Dibenzopyrenes
  - Dibenzo[*a, h*]pyrene (?)
  - Anthanthrene
- Perylene
- Benzo[*ghi*]perylene

to a highly carcinogenic concentrate, BIh (representing 0.09% of the 'tar') and this, in turn, was chromatographically separated to yield 80 end fractions. Upon testing as tumour initiators on mouse skin (Fig. 6), end fractions BIh 56–66 and BIh 71–78 were found to be highly active. Their chemical analysis revealed that they consisted primarily of polynuclear aromatic hydrocarbons, many of which are known carcinogens in laboratory animals (Tables 3 and 4; Hoffmann & Wynder, 1971). Application to mouse skin of these highly active end fractions in doses proportionate to their occurrence in the total particulate

Table 5. Carcinogens and cocarcinogens in the smoke of a nonfilter cigarette

Agent	Relative carcinogenic activity	ng/cigarette
Carcinogens		
Benzo[*a*]pyrene	+++	10–50
5-Methylchrysene	+++	0.6
Dibenz[*a,h*]anthracene	++	40
Benzo[*b*]fluoranthene	++	30
Benzo[*j*]fluoranthene	++	60
Dibenzo[*a,i*]pyrene	++	present
Indeno[1,2,3-*cd*]pyrene	+	4
Benz[*a*]anthracene	+	40–70
Chrysene	+	40–60
Benzo[*e*]pyrene	?	5–40
Dibenz[*a,j*]acridine	++	3–10
Dibenz[*a,h*]acridine	+	0.1
Dibenzo[*c,g*]carbazole	+	0.7
Cocarcinogens		
Pyrene		50–200
Fluoranthene		100–260
Benzo[*g h i*]perylene		60
4,4'-Dichlorostilbene		1 500
Catechol		25 000–360 000
3-Methylcatechol		11 000–20 000
4-Methylcatechol		15 000–21 000
4-Ethylcatechol		10 000–24 000

matter did not lead to tumour induction. Yet, co-application of the active neutral subfractions with the inactive phenolic fraction of the particulate matter led to a tumour yield which accounted for approximately 65–75% of that induced with the total 'tar'. This indicated that the phenolic fraction had cocarcinogenic activity, and further studies showed that catechols were the major cocarcinogens in the phenolic portion (Hecht *et al.*, 1981). Catechol itself is the most abundant phenol in tobacco smoke, amounting to 26–360 μg per cigarette (Wynder & Hoffmann, 1967; Brunnemann *et al.*, 1976b). Table 5 lists the major epithelial carcinogens and cocarcinogens identified in the smoke of a non-filter cigarette.

Organ-specific carcinogens

Tobacco smoke contains, in addition to contact carcinogens and cocarcinogens, several organ-specific carcinogens. This supports the epidemiological observation that cigarette smoking is an important factor in the etiology of cancer of the oesophagus, pancreas, renal pelvis and urinary bladder (IARC, 1986). Table 6 lists the known organ-specific carcinogens in cigarette smoke. Polonium-210 (0.03–1.0 pCi/cigarette) has been incriminated as a possible contributing factor for the increased risk for cancer of the lung in cigarette smokers (Radford & Hunt, 1964; Harley *et al.*, 1980). The presence of aromatic amines in

Table 6. Organ-specific carcinogens in cigarette smoke

Carcinogen	ng/cigarette
N-Nitrosodimethylamine	1–180
N-Nitrosoethylmethylamine	1–40
N-Nitrosodiethylamine	0.1–28
N-Nitrosopyrrolidine	2–110
N-Nitrosopiperidine	0–9
N-Nitrosodiethanolamine	0–40
N'-Nitrosonornicotine	120–3700
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	120–950
N'-Nitrosoanabasine	40–400
2-Toluidine	30–160
2-Naphthylamine	4.3–27
4-Aminobiphenyl	2.4–4.6
Nickel	20–3000
Polonium-210	0.03–1.0 pCi

Table 7. Estimated exposure of US residents to nitrosamines[a]

Source of exposure	Nitrosamines[b]	Primary exposure route	Daily intake (μg/person)	
Beer	NDMA	Ingestion	0.34	
Cosmetics	NDELA	Dermal absorption	0.41	
Cured meat; cooked bacon	NPYR	Ingestion	0.17	
Scotch whisky	NDMA	Ingestion	0.03	
Cigarette smoking	VNA[c]	Inhalation	0.3	
	NDELA	Inhalation	0.5	
	NNN	Inhalation	6.1	16.2[d]
	NNK	Inhalation	2.9	
	NAT+NAB	Inhalation	7.2	

[a] From National Research Council (1981)
[b] NDMA, *N*-nitrosodimethylamine; NDELA, *N*-nitrosodiethanolamine; NPYR, *N*-nitrosopyrrolidine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, *N'*-nitrosoanatabine; NAB, *N'*-nitrosoanabasine
[c] VNA, volatile nitrosamines (NDMA + *N*-nitrosomethylethylamine + *N*-nitrosodiethylamine + NPYR)
[d] Tobacco-specific nitrosamines

smoke has been associated with the increased risk for bladder cancer in cigarette smokers (Doll, 1972).

The *N*-nitrosamines are the major group of organ-specific carcinogens in tobacco products. They are formed during the processing of tobacco and during smoking by *N*-nitrosation of secondary and tertiary amines. Tobacco smoke contains volatile, non-volatile and tobacco-specific *N*-nitrosamines (TSNA; Table 6). It has been estimated that US residents receive the highest degree of exposure to nitrosamines from cigarette smoking (Table 7). In fact, the concentration of these compounds in tobacco smoke exceeds by

Fig. 7. Tobacco alkaloids and nitrosamines which can be formed from them. With the exception of NNA, all of these compounds are present in tobacco and tobacco smoke

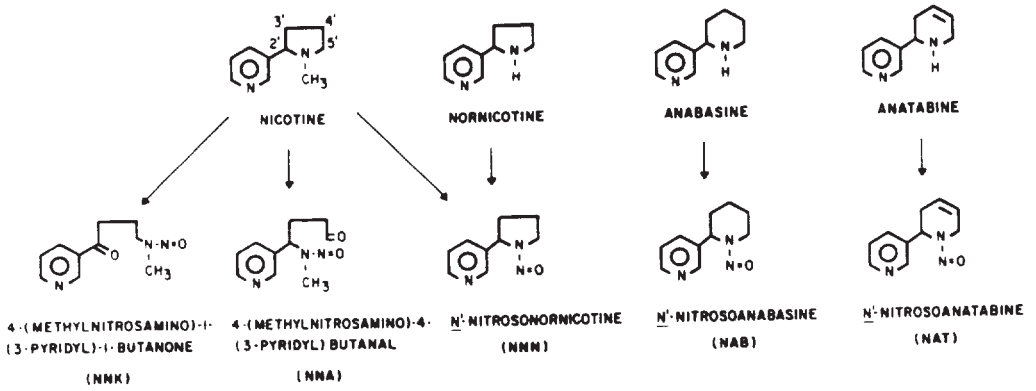


Table 8. *N*-Nitrosamines in cigarette smoke from different varieties of tobacco (ng/cigarette) [a]

N-Nitrosamine	Burley tobacco	Bright tobacco	French black tobacco
N-Nitrosodimethylamine	11–180	0.5–13.2	29–143
N-Nitrosomethylamine	9.1–13	>0.1	2.7–12
N-Nitrosodiethylamine	4–25	nd–1.8 [b]	0.6–6
N-Nitrosopyrrolidine	52–76	6.2	25–110
N'-Nitrosonornicotine	3700	620	590
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	320	420	220
N'-Nitrosoanatabine	4600	410	200
N'-Nitrosoanabasine	400	40	nd–150 [b]

[a] From Hoffmann *et al.*, 1984a
[b] nd, not detected

at least two orders of magnitude the levels of nitrosamines reported in any other consumer product or respiratory environment, except for a few, very limited occupational settings (National Research Council, 1981).

The most abundant nitrosamines in tobacco smoke are the TSNA. They are formed from nicotine and the minor tobacco alkaloids (Fig. 7). In the smoke, 25–45% of the TSNA originate by transfer from the tobacco, the remainder is formed by pyrosynthesis during smoking (Adams *et al.*, 1983; Hoffmann & Hecht, 1985). The single most important factor for the smoke yields of nitrosamines is the nitrate content of tobacco (Adams *et al.*, 1984), thus the smoke of air-cured tobacco is significantly richer in the nitrosamines (Table 8; Hoffmann *et al.*, 1984a). Utilization of cigarette blends with stems and ribs, which are the portions of the tobacco leaf with the greatest abundance of nitrate, can substantially elevate the nitrosamine content of the smoke (Brunnemann *et al.*, 1983).

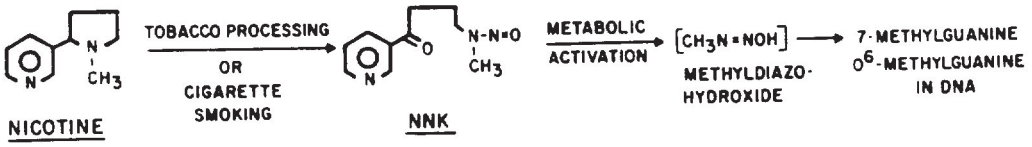
The nicotine-derived *N*-nitrosamines, *N'*-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), are by far the most powerful carcinogens in

Table 9. Carcinogenicity of tobacco-specific nitrosamines[a]

Nitrosamine[b]	Species and strain	Route of application	Principal target organs	Dose
NNN	A/J mouse	i.p.	Lung	0.12 mmol/mouse
	F344 rat	s.c.	Nasal cavity, oesophagus	0.2–3.4 mmol/rat
		oral	Oesophagus, nasal cavity	1.0–3.6 mmol/rat
	Sprague-Dawley rat	oral	Nasal cavity	8.8 mmol/rat
	Syrian golden hamster	s.c.	Trachea, nasal cavity	0.9–2.1 mmol/hamster
NNK	A/J mouse	i.p.	Lung	0.12 mmol/mouse
	F344 rat	s.c.	Nasal cavity, lung, liver	0.2–2.8 mmol/rat
	Syrian golden hamster	s.c.	Trachea, lung, nasal cavity	0.9 mmol/hamster 0.005 mmol/hamster
NAT	F344 rat	s.c.	None	0.2–2.8 mmol/rat
NAB	F344 rat	oral	Oesophagus	3-12 mmol/rat
	Syrian golden hamster	s.c.	None	2 mmol/hamster
NNA	A/J mouse	i.p.	None	0.12 mmol/mouse

[a] From Hoffmann and Wynder, 1985
[b] NNN, *N*'-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, *N*'-nitrosoanatabine; NAB, *N*'-nitrosoanabasine; NNA, 4-(methylnitrosamino)-4-(3-pyridyl)butanal

Fig. 8. Scheme linking nicotine, the major tobacco alkaloid and habituating factor in tobacco, to formation of the promutagenic DNA adduct O^6-methylguanine



tobacco smoke, inducing carcinoma in mice, rats and Syrian golden hamsters (Table 9). Perhaps the most important observation is that NNK induces benign and malignant tumours in laboratory animals not only in the upper respiratory tract but also in the lung. In hamsters, a single application of 1 mg of NNK suffices to induce lung tumours. In rats, NNK induces also liver tumours, nasal cavity tumours, and a high incidence of squamous-cell carcinoma and adenocarcinoma in the lungs of males and, at a significantly lower rate, in females (Hoffmann *et al.*, 1984b; Hoffmann & Hecht, 1985). Although we are presently lacking definite evidence, it may be presumed that NNN and NNK are also formed endogenously when a smoker inhales the precursors, nitrogen oxides and nicotine, as smoke constituents. The inhalation of smoke from a single cigarette provides up to 600 μg of nitrogen oxides and up to 2 mg of nicotine. The known catalytic effects of thiocyanate for *N*-nitrosation (Boyland *et al.*, 1971) favour these reactions in smokers who have elevated

levels of thiocyanate in the saliva and in blood (IARC, 1986), owing to the detoxification of hydrogen cyanide, inhaled as a smoke constituent in amounts of up to 500 μg per cigarette (Brunnemann *et al.*, 1977).

A most stimulating observation lies in the fact that NNK is metabolically activated by α-hydroxylation, yielding methyldiazohydroxide. This unstable compound is known to alkylate guanine in DNA to 7-methylguanine and O^6-methylguanine *in vitro* as well as *in vivo*. Thus, we know today, that nicotine is not only the major habituating agent in tobacco but that it is also a precursor for the powerful carcinogen NNK. Figure 8 depicts the pathway of NNK formation from nicotine. Metabolic activation leads to α-hydroxylation of NNK which gives rise to methyldiazohydroxide. The latter methylates DNA to the promutagenic DNA adduct, O^6-methylguanine (Hoffmann & Hecht, 1985).

ENVIRONMENTAL TOBACCO SMOKE

Since 1981, a number of epidemiological studies have indicated a possible correlation between uptake of environmental tobacco smoke ('passive smoking') and an increased risk for cancer. The IARC concluded: 'The observations on nonsmokers that have been made so far are compatible with either an increased risk from "passive" smoking or an absence of risk. Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens leads to the conclusion that passive smoking gives rise to some risk of cancer.' (IARC, 1986).

A comparison of the constituents of mainstream (MS) and sidestream (SS) smoke reveals that these combustion effluents are similar but not the same (Table 10). The differences become particularly apparent when one compares the chemical composition of undiluted MS and SS. Considering that 35–40% of the tobacco is burned during puff-drawing and the remainder during smouldering, one would expect, in the case of a non-filter cigarette, that the release of smoke compounds in the SS would be 50–100% greater

Table 10. Comparisons of mainstream (MS) and sidestream (SS) smoke of cigarettes (physicochemical data)

Parameters	MS	SS
Peak temperature during formation (°C)	~900	~600
pH (total aerosol) [a]	6.0–6.2	6.4–6.6
Particle size (μm)	0.1–1.0	0.01–0.1
Median diameter	0.4	
Smoke dilution (vol. %) [b]		
Carbon monoxide	3–5	≃1
Carbon dioxide	8–11	≃2
Oxygen	12–16	16–20
Hydrogen	15–3	≃0.5

[a] 85 mm nonfilter cigarette
[b] At a distance of 10 mm from the burning coal

Table 11. Distribution of compounds in mainstream smoke (MS) and sidestream smoke (SS) of nonfilter cigarettes

Compound	MS	SS/MS
Vapour phase		
Carbon monoxide	10–23 mg	2.5–4.7
Carbon dioxide	20–40 mg	8–11
Benzene	20–50 μg	10
Formaldehyde	5–100 μg	0.1–~50
Acrolein	50–100 μg	8–15
Acetone	100–250 μg	2–5
Hydrogen cyanide	400–500 μg	0.1–0.25
Hydrazine	24–43 ng	3.0
Ammonia	50–170 μg	40–170
Methylamine	11.5–28.7 μg	4.2–6.4
Nitrogen oxides	50–600 μg	4–10
N-Nitrosodimethylamine	10–180 ng	20–100
N-Nitrosopyrrolidine	2–110 ng	6–30
Particulate phase		
Particulate matter	15–40 mg	1.3–1.9
Nicotine	1–2.5 mg	2.6–3.3
Phenol	60–140 μg	1.6–3.0
Catechol	100–350 μg	0.6–0.9
Hydroquinone	110–300 μg	0.7–0.9
Aniline	360 ng	30
2-Toluidine	30–160 ng	19
2-Naphthylamine	4.3–27 ng	30
4-Aminobiphenyl	2.4–4.6 ng	31
Benz[*a*]anthracene	40–70 ng	2–4
Benzo[*a*]pyrene	10–40 ng	2.5–3.5
N'-Nitrosonornicotine	120–3700 ng	0.5–3
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	120–950 ng	1–4
Cadmium	100 ng	7.2
Nickel	20–3000 ng	13–30
Polonium-210	0.03–1.0 pCi	?

than in the MS. However, this is not the case. As seen in Table 11, compounds generated by reduction reactions are formed in significantly higher yields and those formed by oxidation occur in lower yields during smouldering (SS formation) than during puff-drawing (MS formation). These differences are primarily due to the depletion of oxygen inside the burning cone during smouldering as opposed to only a partial oxygen deficiency during puff-drawing. Excessive formation of SS compounds is greatest for ammonia, amines including aromatic amines and, especially, for the volatile carcinogenic *N*-nitrosamines (VNA).

The high yields of VNA in SS explain the fact that they are detectable in smoke-polluted environments in spite of extensive dilution by air. The qualitative and quantitative differences of MS and SS composition and the effects of ageing of SS constituents in the environment make it clear that smoke polluted indoor-air cannot be regarded as 'diluted mainstream smoke'.

REDUCTION OF SMOKE CONSTITUENTS

One of the earliest and yet most important observations in the association of cancer risk and smoking was that of a dose-response relationship (Wynder & Graham, 1950; Doll & Hill, 1954; Hammond & Horn, 1958). Therefore, during the last two to three decades, a reduced exposure to tobacco smoke by modifying the smoke yields of cigarettes was

Fig. 9. US sales-weighted average tar and nicotine yields (adapted from Norman, 1982); RT, reconstituted tobacco; ET, expanded tobacco; F, cigarettes with filter tips; numbers, lengths of filter tips

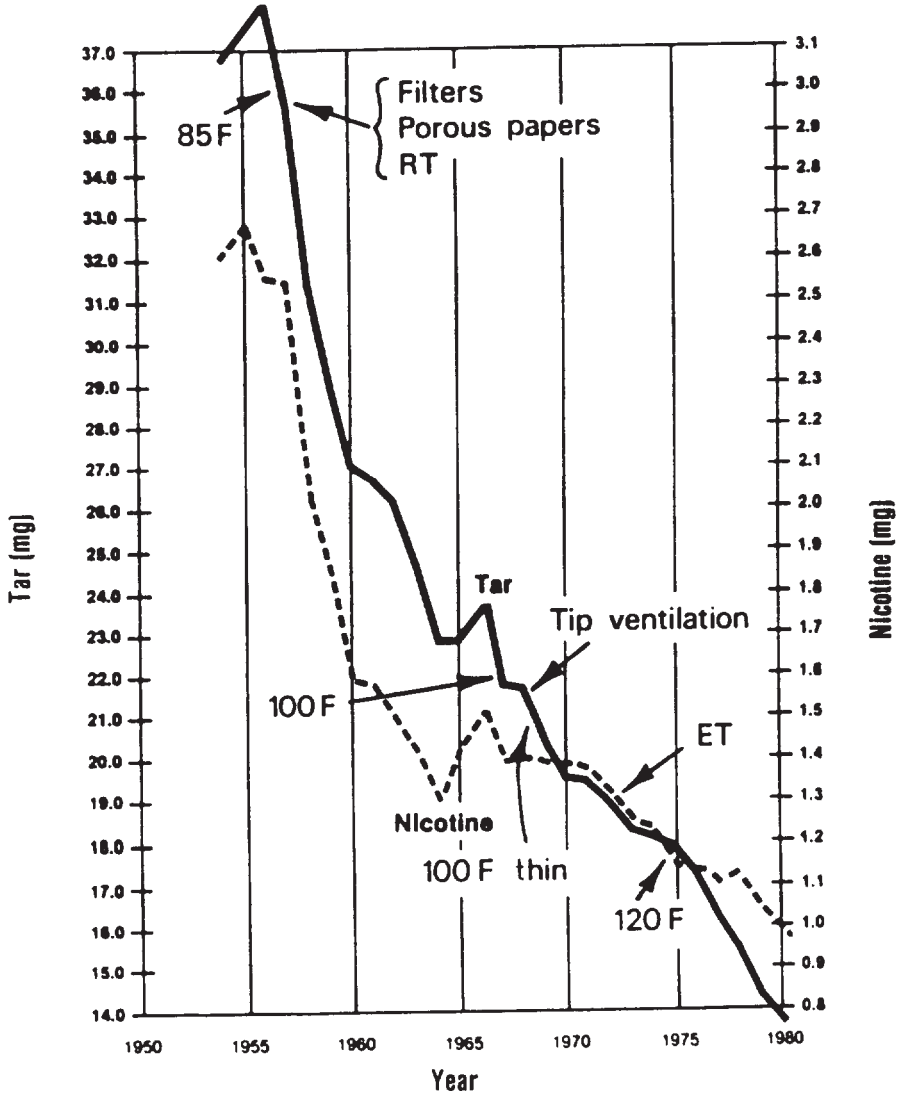


Table 12. Reductions of biological activity of smoke from experimental cigarettes[a]

Methods[b]	Smoke constituents			Selective reduction of biological activity[c]		Remarks
	'Tar'	Nicotine	Benzo[*a*]pyrene	Carcinogenicity	Tumour promotion	
Agricultural aspects						
Tobacco type (Bright-Burley)[d]	+	+	+	+	+	
New cultivars	+	+	+		?	
Fertilization (nitrate)	+	+	+	+	?	
Tobacco processing						
Cut	±	±	±	±?	?	
Use of tobacco midribs	+	+	+	++	++	
Reconstituted tobacco sheets (RTS)[e]	+	+	+	++	±	Some RTS give high CO
RTS-paper process	++	+	+	++	±	
Expanded tobacco laminae	+	++	+	±?	±	
Expanded tobacco midribs	+	++	+	++	?	
Cigarette production						
Paper porosity	+	+	+	±	?	
Cellulose acetate filters	+	+	+	±	±	
Charcoal filters[f]	+	+	+	±	±	
Perforated filters	++	++	++	±	±	Smoker's compensation

[a] From Wynder and Hoffmann (1982)

[b] Methdology known to be applied to commercial US cigarettes. Reductions: ++, >50%; +, significant; ±, insignificant; ±?, questionable; ?, unknown

[c] Comparison of gram-to-gram 'tar' on mouse skin tests and/or hamster smoke inhalations

[d] Replacing Bright with Burley tobaccos

[e] Data given for RTS relate to those not made by the paper process

[f] Reductions of 'tar', nicotine, benzo[*a*]pyrene (and other nonvolatiles) and volatile *N* nitrosamines are, in general, greater with cellulose acetate filters than with charcoal filters.

regarded as one significant step towards diminishing the cancer risks associated with smoking. Measures to reduce the smoke yields included changes in the cultivation of tobacco, breeding and selection of new varieties, homogenized leaf curing, incorporation of stems and ribs into the tobacco blends, use of reconstituted and expanded tobaccos, and modification of wrappers and filter tips.

The most obvious results of these changes in the make-up of cigarettes have been reflected in a trend of declining sales-weighted average 'tar' and nicotine levels in the smoke of cigarettes since 1955. This trend has been observed in many countries.

In the USA, sales-weighted average 'tar' and nicotine values have dropped from 38 mg and 2.7 mg, respectively, in 1956 to 13 mg 'tar' and 1.0 mg of nicotine (Tobacco Institute, 1984). Figure 9 graphically documents the decline in 'tar' and nicotine while denoting the technical modifications that have contributed to the reduction of smoke yields of cigarettes (Norman, 1982).

For our own studies (Wynder & Hoffmann, 1967; Hoffmann & Wynder, 1976) and for studies by the US National Cancer Institute (1980), experimental cigarettes were made in which specific parameters were changed. The smoke of these cigarettes was analysed and the resulting 'tars' were assayed for carcinogenicity and tumour-promoting activity on mouse skin. The most encouraging results in respect to a selective reduction of tumorigenicity were observed for cigarettes made entirely of reconstituted tobacco, of stems and ribs, of expanded tobacco and of expanded stems and ribs (Table 12). In smoke inhalation studies with modified cigarettes, significant declines in activity were also observed in respect of tumours in the larynx of hamsters (Dontenwill, 1974).

We consider these changes in the make-up of cigarettes and a significant reduction of the tumorigenic potential of the resulting smoke as significant progress, although we need to acknowledge that the smoker of cigarettes with a low nicotine content tends to compensate by smoking more intensely (Herning *et al.*, 1981).

The IARC (1986) concluded that 'in a few countries, in which smoking has been established for many years, a substantial reduction in mortality from lung cancer has been observed in young and middle-aged men, which is greatest in the youngest age groups. This has occurred at a time when the number of cigarettes smoked by young men in these countries has remained approximately constant. No substantial cause (or cofactor) has so far been identified that offers a plausible explanation for the observed magnitude of the reduction of risk for lung cancer, other than changes in cigarette design which include reduction in tar content.'

SUMMARY

Tobacco smoke contains more than 3900 constituents. In this presentation we have summarized our present knowledge as to the physicochemical nature of tobacco smoke and specific agents therein. Emphasis has been placed on the discussion of formation and identification of toxic and, especially, of tumorigenic agents in tobacco smoke. In the concluding Table 13 we have listed those smoke constituents in the mainstream smoke of cigarettes that we regard as important contributors to the toxic and carcinogenic potential of tobacco smoke. This judgement is based on extensive laboratory studies. Finally, data

Table 13. Biologically active agents in mainstream smoke[a]

Smoke constituent	Conc./cigarette	Biological effect[b]
Total particulate matter	15–40 mg	T, HC
Carbon monoxide	10–23 mg	T
Nicotine	1.0–2.5 mg	T
Acetaldehyde	0.5–1.2 mg	CT
Acetone	100–250 μg	CT
NO_x	50–600 μg	T
Formic acid	80–600 μg	CT
Hydrogen cyanide	400–500 μg	CT, T
Catechol	140–500 μg	CoC
Ammonia	50–130 μg	T
Benzene	20–50 μg	HC
Acrolein	50–100 μg	CT
Acrylonitrile	3.2–15.0 μg	C
Phenol	60–140 μg	TP
Formaldehyde	5–100 μg	C
Carbazole	1 μg	C?
2-Nitropropane	0.2–2.2 μg	C
N'-Nitrosonornicotine	120–3700 ng	C
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	120–950 ng	C
N'-Nitrosoanabasine	120 ng	C?
N-Nitrosodiethanolamine	0–40 ng	C
N-Nitrosopyrrolidine	2–110 ng	C
N-Nitrosodimethylamine	2–180 ng	C
N-Nitrosomethylethylamine	0.1–40 ng	C
N-Nitrosodiethylamine	0.1–28 ng	C
N-Nitrosodi-*n*-propylamine	0–1 ng	C
N-Nitrosodi-*n*-butylamine	0–3 ng	C
N-Nitrosopiperidine	0–9 ng	C
N-Nitrosopyrrolidine	2–42 ng	C
Hydrazine	24–43 ng	C
Urethane	20–38 ng	C
Vinyl chloride	1.3–16 ng	HC
Benz[*a*]anthracene	40–60 ng	C
Benzo[*a*]pyrene	10–50 ng	C
5-Methylchrysene	0.6 ng	C
Dibenz[*a*, *j*]acridine	3–10 ng	C
2-Naphthylamine	4.3–27 ng	HC
4-Aminobiphenyl	2.4–4.6 ng	HC
2-Toluidine	30–160 ng	C
Polonium-210	0.03–1.0 pCi	

[a] Quantitative data refer to nonfilter cigarettes

[b] Abbreviations: T, toxic agent; HC, human carcinogen; CT, ciliatoxic agent; CoC, cocarcinogen; TP, tumour promoter; C, animal carcinogen

are presented in support of the concept that product modification can reduce the carcinogenic potential of cigarettes. However, it must be emphasized that the only safe way to avoid the cancer risks associated with smoking is to refrain from smoking.

ACKNOWLEDGEMENTS

We greatly appreciate the extensive contributions of our colleagues J.D. Adams, K.D. Brunnemann, S.S. Hecht, E.J. LaVoie and A.S. Rivenson. We thank B. Stadler, D. Conroy and I. Hoffmann for their editorial assistance.

Our studies in tobacco carcinogenesis are supported by Grants CA-17613, CA-29580, and CA-35667 from the National Cancer Institute, US Department of Health and Human Services. This is No. XXXIII of the series '*A Study of Tobacco Carcinogenesis*'.

REFERENCES

Adams, J.D., Lee, S.J., Vinchkoski, N., Castonguay, A. & Hoffmann, D. (1983) Chemical studies on tobacco smoke. 73. On the formation of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone during smoking. *Cancer Lett.*, ***17***, 339–346

Adams, J.D., Lee, S.J. & Hoffmann, D. (1984) Carcinogenic agents in cigarette smoke and the influence of nitrate on their formation. *Carcinogenesis*, ***5***, 221–223

Armitage, A.K. & Turner, D.M. (1970) Absorption of nicotine in cigarette and cigar smoke through the oral mucosa. *Nature*, ***226***, 1231–1232

Boyland, E., Nice, E. & Williams, K. (1971) The catalysis of nitrosation by thiocyanate in saliva. *Food Cosmet. Toxicol.*, ***9***, 639–643

Brunnemann, K.D. & Hoffmann, D. (1974) The pH of tobacco smoke. *J. Food Cosmet. Toxicol.*, ***12***, 115–124

Brunnemann, K.D. & Hoffmann, D. (1982) Pyrolytic origins of major gas phase constituents of cigarette smoke. *Recent Adv. Tob. Sci.*, ***8***, 103–140

Brunnemann, K.D., Hoffmann, D., Wynder, E.L. & Gori, G.B. (1976a) *Determination of tar, nicotine, and carbon monoxide in cigarette smoke. A comparison of international smoking conditions.* In: Wynder, E.L., Hoffmann, D. & Gori, G.B., eds, *Smoking and Health. I. Modifying the Risk for the Smoker (US Dept of Health, Education, and Welfare Publ. No. (NIH) 76–1221)*, Washington DC, pp. 441–449

Brunnemann, K.D., Lee, H.-C. & Hoffmann, D. (1976b) Chemical studies on tobacco smoke XLVII. On the quantitative analysis of catechols and their reduction. *Anal. Lett.*, ***9***, 939–955

Brunnemann, K.D., Yu, L. & Hoffmann, D. (1977) Gas chromatographic determination of cyanide and cyanogen in tobacco smoke. *J. anal. Toxicol.*, ***1***, 38–42

Brunnemann, K.D., Masaryk, J. & Hoffmann, D. (1983) Role of tobacco stems in the formation of *N*-nitrosamines in tobacco and cigarette mainstream and sidestream smoke. *J. Agric. Food Chem.*, ***31***, 1221–1224

Carter, W.L. & Hasegawa, I. (1975) Fixation of tobacco smoke aerosols for size distribution studies. *J. Colloid Interface Sci.*, ***53***, 134–141

Doll, R. (1972) *Cancers related to smoking.* In: *Proceedings of the 2nd World Conference on Smoking and Health*, London, Pitman Medical, pp. 10–23

Doll, R. & Hill, A.B. (1954) The mortality of doctors in relation to their smoking habits; a preliminary report. *Br. med. J.*, ***i***, 1451–1455

Dontenwill, D.P. (1974) *Tumorigenic smoke inhalation studies in inbred Syrian hamsters.* In: Karbe, E. & Park, J.F., eds, *Experimental Lung Cancer – Carcinogenesis and Bioassays*, New York, Springer, pp. 331–359

Dontenwill, W., Chevalier, H.J., Harke, H.P., Lafrenz, U., Reckzeh, G. & Schneider, B. (1973) Investigations on the effects of chronic cigarette smoke inhalation in Syrian golden hamsters. *J. natl Cancer Inst.* **5,** 1781–1832

Dube, M.F. & Green, C.R. (1982) Methods of collection of smoke for analytical purposes. *Recent Adv. Tob. Sci.*, **8,** 42–102

Hammond, E.C. & Horn, D. (1958) Smoking and death rates – report on forty-four months of follow-up in 187 783 men. II. Death rates by cause. *J. Am. med. Assoc.*, **166,** 1294–1308

Harley, N.H., Cohen, B.S. & Tso, T.C. (1980) *Polonium-210: A questionable risk factor in smoking-related carcinogenesis.* In: Gori, G.B. & Bock, F.G., eds, *A Safe Cigarette? (Banbury Report No. 3)*, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, pp. 93–104

Hecht, S., Carmella, S., Mori, H. & Hoffmann, D. (1981) A study of tobacco carcinogenesis. XX. Role of catechol as a major cocarcinogen in the weakly acidic fraction of smoke condensate. *J. natl Cancer Inst.*, **66,** 163–169

Herning, R.I., Jones, R.T., Bachman, J. & Mines, A.H. (1981) Puff volume increases when low-nicotine cigarettes are smoked. *Br. med. J.*, **283,** 187–189

Hoffmann, D. & Hecht, S.S. (1985) Perspectives in cancer research. Nicotine-derived *N*-nitrosamines and tobacco-related cancer: Current status and future directions. *Cancer Res.*, **45,** 935–944

Hoffmann, D. & Wynder, E.L. (1971) A study of tobacco carcinogenesis. XI. Tumor initiators, tumor accelerators, and tumor promoting activity of condensate fractions. *Cancer*, **27,** 848–864

Hoffmann, D. & Wynder, E.L. (1976) *Selective reduction of tumorigenicity of tobacco smoke. III. The reduction of polynuclear aromatic hydrocarbons in cigarette smoke.* In: Wynder, E.L., Hoffmann, D. & Gori, G.B., eds, *Smoking and Health. I. Modifying the Risk for the Smoker. (US Department of Health, Education and Welfare Publ. No. (NIH) 76–1221)*, Washington DC, pp. 495–504

Hoffmann, D., Rivenson, A., Hecht, S.S., Hilfrich, J., Kobayashi, N. & Wynder, E.L. (1979) Model studies in tobacco carcinogenesis with the Syrian golden hamster. *Prog. exp. Tumor Res.*, **24,** 370–390.

Hoffmann, D., Wynder, E.L., Rivenson, A., LaVoie, E.J. & Hecht, S.S. (1983) Skin bioassays in tobacco carcinogenesis. *Prog. exp. Tumor Res.*, **26,** 43–67

Hoffmann, D., Brunnemann, K.D., Adams, J.D. & Hecht, S.S. (1984a) *Formation and analysis of N-nitrosamines in tobacco products and their endogenous formation in tobacco consumers.* In: O'Neill, I.K., von Borstel, R.C., Miller, C.T., Long, J. & Bartsch, H., eds, *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57)*, Lyon, International Agency for Research on Cancer, pp. 743–762

Hoffmann, D., Rivenson, A., Amin, S. & Hecht, S.S. (1984b) Dose-response study of the carcinogenicity of tobacco-specific *N*-nitrosamines in F344 rats. *J. Cancer Res. clin. Oncol.*, **108,** 81–86

IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals*

to Humans, Vol. 37, *Tobacco Habits Other than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines*, Lyon

IARC (1986) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon

International Committee for Cigar Smoke Study (1974) Machine smoking of cigars. *Coresta Inf. Bull.*, ***1***, 31–34

Keith, C.H. & Tesh, P.G. (1965) Measurement of the total smoke issueing from a burning cigarette. *Tob. Sci.*, ***9***, 61–64

Mohr, U. & Reznik, G. (1978) Tobacco carcinogenesis. *Lung Biol. Health Dis.*, ***10***, 263–367.

National Research Council (1981) *The Health Effects of Nitrate, Nitrite and N-Nitroso Compounds*, Washington DC, National Academy Press, p. 529

Norman, V. (1977) An overview of the vapor phase, semivolatile and nonvolatile components of cigarette smoke. *Recent Adv. Tob. Sci.*, ***3***, 28–58

Norman, V. (1982) Changes in smoke chemistry of modern day cigarettes. *Recent Adv. Tob. Sci.*, ***8***, 141–177

Radford, E.P. & Hunt, V.R. (1964) Polonium-210, a volatile radioelement in cigarettes. *Science*, ***143***, 247–249

Tobacco Institute (1984) *US Sales-weighted Average Tar and Nicotine Yield*, Washington, DC, p. 2

US National Cancer Institute (1980) *Towards a Less Hazardous Cigarette (Report No. 5)*, Bethesda, MD, p. 29

Wynder, E.L. & Graham, E.A. (1950) Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. A study of six hundred and eighty-four proved cases. *J. Am. med. Assoc.*, ***143***, 329–336

Wynder, E.L. & Hoffmann, D. (1967) *Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis*, New York, Academic Press, p. 730

Wynder, E.L. & Hoffmann, D. (1982) *Tobacco*. In: Schottenfeld, D. & Fraumeni, J. F., Jr, eds, *Cancer Epidemiology and Prevention*, Philadelphia, W.B. Saunders Co., pp, 277–292