Smoking and Carcinogenesis

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Relative importance of genetic and environmental factors

Medical students are taught that diseases may be either genetically or environmentally determined. In practice factors of both kinds interact in the causation of most diseases and this is true for cancers for which smoking appears to be a risk factor. In the case of lung cancer, the importance of environmental factors predominates and that of these, cigarette smoking is the most important single factor. Tokuhata and Lilienfeld in 1963 reported significantly more lung cancer and other respiratory diseases among the brothers and sisters of 270 patients than among the brothers and sisters of 270 matched controls. However the adequacy of the matching process is questionable in that the lung cancer patients had significantly more brothers and sisters than the controls. Theoretically a study of identical smoking-discordant identical twins would be an ideal way of comparing the relative contribution of smoking habits and genetic factors in the causation of lung cancer. However, identical twins are difficult to find and smoking-discordant identical twins are very rare indeed. So far, in an on-going study of this kind in Sweden (Cederlof et al, 1977) there have been too few deaths from lung cancer for any conclusion to be drawn, although among the study population generally, smoking has been associated with enhanced lung cancer risk.

Genetic factors

Many different polycyclic aromatic hydrocarbons are present in tobacco smoke. In the body some of these may be converted to active carcinogens by enzymes of the so-called aryl hydrocarbon hydroxylase (AHH) type. Genetically-determined variation in AHH-inducibility has been proposed as a determinant of lung cancer risk in smokers (Kellermann et al, 1973) and higher AHH-inducibility in circulating lymphocytes of smokers with lung cancer than in comparable healthy smokers has recently been confirmed by Emery et al (1978). A possibly related finding is that the blood lymphocytes of smokers with lung cancer are more susceptible to genetic damage on exposure to tobacco tar than lymphocytes from healthy heavy smokers (Hopkin and Evans, 1980).

Slide 1	Summarises what I have said about the role of genetic factors

Cancers associated with smoking

Table 1 is taken from the 1979 US Surgeon General's report on Smoking and Health. It summarizes data from 8 prospective studies concerning the association between cigarette smoking and risk of various cancers.

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The findings suggest that cigarette smokers put themselves at increased risk not only of lung cancer but also of cancers of the larynx, buccal cavity, pharynx, oesophagus, urinary bladder and pancreas. There is no unequivocal evidence of enhanced risk of cancers of the kidney, stomach, colon or rectum.

With the exception of the urinary bladder and pancreas, all the sites for which there is definitely or probably an enhanced cancer risk are ones that are directly exposed to tobacco smoke or tar and it is probable that carcinogens of the polycyclic aromatic hydrocarbon type along with related heterocyclic compounds and tumour promoters are largely responsible. The enhanced risk of cancers of the bladder and pancreas involves no such direct exposure to tar. Carcinogenic aramotic amines absorbed from smoke and carried to these sites in the blood stream may be the culprits in this case.

Why are pipe and cigar smokers at much less risk?

Pipe and cigar smokers are less at risk of developing lung cancer than cigarette smokers despite the fact that the tars obtained by smoking pipe and cigar tobaccos are at least as carcinogenic for mouse skin as cigarette tar (Table 2)

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Part of the explanation according to the US Surgeon General (1979) is that the average pipe smoker and the average cigar smoker, in the United States at least, is a relatively light smoker. Also, since the risks of buccal and larynx cancers are similar in pipe, cigar and cigarette smokers, the lower risk of lung cancer in pipe and cigar smokers may be due to their inhaling less smoke into their lungs than cigarette smokers.

Most smokers indulge in the habit because they enjoy the pharmacological effects of nicotine. In the alkaline smoke of cigars and of heavily fermented air-

cured cigarettes, nicotine is present as the free base. As such, it can be absorbed directly through the epithelium of the mouth and nasal cavity (Armitage and Turner, 1970). By comparison, the nicotine in the acidic smoke of 100% flue-cured tobacco cigarettes, as typically smoked in the United Kingdom, is present in conjugated form. Only if such smoke is taken into the lungs is nicotine absorbed in amounts sufficient to give rise to pharmacological effects. Furthermore, inhaling smokers obtain their nicotine in pulse doses each time they take smoke into their lungs, whereas, in non-inhaling cigar smokers, blood, nicotine levels rise slowly and steadily during continued smoking. It has been suggested that the neuropharmacological effects of pulse-doses of nicotine are different from those of nicotine absorbed slowly via the epithelial lining of the mouth and upper respiratory tract. If this is true, then it is to be expected that a cigarette smoker who is used to inhaling and thereby getting pulse doses of nicotine would continue to inhale if he switched to cigars. Unfortunately the only evidence that this happens in practice (Turner et al, 1977) was open to criticism (Roe and Lee, 1978). In any event most authorities seem to be agreed that if a cigarette smoker switched to cigars and continued to inhale the same amount of smoke each day as he did before he switched he would probably be as much at risk of developing lung cancer as if he had continued smoking cigarettes.

Air-cured fermented tobacco and flue-curred tobacco differ both in type of leaf and in chemical composition. Flue-cured tobaccos contain more sugar. Elson and Betts (1972) suggested that the amount of sugar in tobacco determines the acidity of the smoke. They also reported that the initially acidic smoke of a 100% flue-cured tobacco cigarette gets even more acidic as the cigarette burns down whereas the initially less acidic smoke of oriental or blended cigarettes becomes more alkaline as the cigarette burns down. This must mean that the nicitone in the smoke of a flue-cured tobacco cigarette becomes less available as the butt shortens whereas the reverse is true for an air-cured tobacco cigarette. Obviously the subject is one of considerable complexity.

Synergism between tobacco smoking and other environmental factors in lung cancer aetiology

Presently in the United States the Chemical Industry and the Tobacco Industry are preparing for war against each other. The spark which led to this situation was the launching by the Occupational Safety and Health Administration (OSHA) of generic proposals to control the use of possibly carcinogenic substances in industry. OSHA's proposals were based on the scientifically unsound conclusion that, in future, 20-40% of cancer in the United States will be occupationally-linked

(Bridbord et al, 1978; Lancet, 1978; Lancet, 1980; Peto, 1980). Industry responded by quoting the assessments of eminent scientists that occupational factors are unlikely to be responsible for more than 2 - 6% of all cancers whereas smoking is the most important single cause of cancer in males in most Western countries (Higginson and Muir, 1979) and of premature death generally (McGinty, 1979). Table 3 summarises the conclusions of the American Health Foundation Conference (1980) regarding the contributions of smoking and other factors to overall cancer risk. Smoking is blamed for between 25 and 35% of all cancers in males and between 5 and 10% of all cancers in females.

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The nux of the problem is illustrated by a comparison of the risks of lung cancer in smoking and non-smoking asbestos workers.

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The same kind of apparent synergism has been reported in uranium miners and is being actively looked for in other industries where workers are exposed to dusts and fumes.

Approaches to the reduction of cancer risk from smoking

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There are two possible kinds of approach to the reduction of cancer risk from smoking. The first is to ban or very strongly discourage (e.g. by prohibitive taxation) smoking. The second is to endeavour to make smoking safer. Most people agree that a total ban of smoking is not a practical solution. It would merely create a black market and encourage crime in the same way as prohibition of alcohol did in the United States. Lesser bans, such as the banning of advertising have seemingly had relatively little effect on cigarette sales in countries which have adopted this course. In the United Kingdom cigarette smoking which was once practiced equally by men of all social classes has become more common among the lower social classes than the upper ones (Table 5). Consequently, the over-zealous banning of smoking in public places is at risk of

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being socially devisive. It is arguable that it is easier for professional people who have interesting work and many opportunities to express their personalities to quit smoking than for people lower down the social order, whose work is tedious and whose life-style offer litter scope for self-expression. It is, thus, not surprising that most active anti-smoking campaigners belong to the upper strata of society.

Irrespective of the extent to which smoking should be discouraged altogether, it has always been my view that every effort should be made to develop safer cigarettes. Most smokers indulge in the habit because they enjoy the pharmacological effects of nicotine. Nicotine can both stimulate and improve powers of concentration and soothe anxiety. It is not itself a carcinogen and it is unlikely that its nitrosation to nitrosonornicotine contributes significantly to the overall carcinogenicity of smoke. Tobacco smoke may thus be regarded as a delivery system for nicotine, nicotine itself being more or less harmless and the vehicle constituting the cancer hazard.

Cigarettes can theoretically be made safer either by reducing the amount of tar or by improving the quality of the tar that they produce while keeping the dose of nicotine they deliver at a level adequate to satisfy the smoker.

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There is plenty of evidence that many smokers adjust the amount of smoke they inhale so as to provide the dose of nicotine which they desire (Ashton, et al, 1979; Russell, 1978). For these smokers it may solve nothing to reduce both tar and nicotine delivery by equal extents. Hence, a way has to be found to reduce the tar without affecting the nicotine. Technically this is possible to do especially if the lack of taste of low tar cigarettes can be compensated for by the use of added flavours. One of the attractions of the tobacco substitute known as New Smoking Material, or NSM for short, was that it produced not only less tar per gram of unsmoked material, but the tar produced possessed demonstrably less carcinogenic activity for mouse skin (Clapp et al, 1977). I personally believe that it was a great mistake that Governmental Health authorities in Britain did not back the use of substitutes by offering some price advantage to the consumer. The commercial failure of tobacco substitutes has undoubtedly slowed progress in the development of safer cigarettes.

Animal models

The epidemiological evidence of association between smoking and lung cancer is arguably so strong that there is no need to attempt to prove that smoking causes cancer by experiments on animals. However, animal models are needed in relation to new product development. For instance, it is obviously important to establish that proposed flavouring agents are safe to inhale and that entirely newly formulated products exhibit no novel toxicity and are not for some unexpected reason more carcinogenic than traditional ones.

During the past few years considerable advances have been made in the field of inhalation smoke toxicology. It is now possible to expose small laboratory rodents to measured doses of inhaled tobacco smoke and many ways of measuring of response quantitatively are now available. However, certain fundamental problems remain. Firstly, it is not possible to mimic closely either the mode of exposure or the extent of exposure of the heavy human cigarette smoker. The laboratory rodent is an obligatory nose-breather and its nose is more effective as a filter of particulate matter than the human nose. The exposure via the nose of rodents is thus not a very good model of the human smoker who inhales smoke via the mouth. The 'dedicated' human smoker can indulge in the habit for as much as 16 hours a day on 7 days a week, avoiding death from carbon monoxide or nicotine poisoning by suspending exposure from time to time as necessary. For humane and logistic reasons the exposure of small rodents cannot be extended for more than a few hours per day and rates of obligatory exposure have to be kept down because of the risk of fatal nicotine and carbon monoxide poisoning.

Mice are unsuitable models because they are prone to develop benign

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and malignant

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adenomatous tumours in high incidence spontaneously. The results of an early experiment by Essenburg (1952) (Table 6).

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are thus impossible to interpret.

Dontenwill et al (1973) reported a dose-related increase in precancerous and cancerous lesions of the larynx in hamsters in response to inhaled cigarette smoke, but they saw very few lung tumours in the same animals.

In our own studies (Davies et al, 1975) we saw aggregates of golden-brown macrophages - sometimes called 'smoke-cells' - and areas of cuboidal or columnar metaplasia of alveolar epithelium, usually in the vicinity of terminal bronchioles.

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Later, squamous metaplasia of alveolar epithelium became a prominent feature of the response of some rats to smoke exposure.

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However, only 4 out or over 400 exposed rats developed pulmonary neoplasms and in only one of these was the tumour aggressively malignant. Later Dalbey et al (1980) reported a significant excess of lung tumours in smoke-exposed rats compared with sham exposed controls, but the excess was small and most of the additional tumours were benign adenomas. A feature of both these rat experiments was a significant reduction in the smoke-exposed groups of tumours associated with excessive prolactin release (i.e. prolactinomas of the pituitary gland and mammary tumours). It would seem that the stress associated with smoke exposure protected the animals from the development of these neoplasms. The fact that the incidence of pulmonary tumours was very low in both these studies suggests that the rat could not be used to compare the smokes from different cigarettes for carcinogenic potency. Only if it were

shown that the incidences of lesser changes (e.g. squamous metaplasia) that occur in smoke exposed rats are correlated with lung cancer risk could rats be used for this purpose.

Most of the tumours reported by Auerbach et al (1970) in smoke-exposed dogs were bronchiolo-alveolar lesions. Also their method of exposing the dogs via a tracheostomy to undiluted smoke would not nowadays be acceptable on humane grounds for the mere purpose of developing a putatively safer cigarette for humans.

All in all, the hamster larynx model is seemingly the best available inhalation animal model at present, and it is interesting that the results of studies comparing the smokes of different cigarettes using this model are similar to those of studies in which smoke condensates prepared from the same cigarettes are applied repeatedly to mouse skin with the production of benign and malignant squamous tumours. This similarity in response is consistent with the view that most of the carcinogenic activity of tobacco smoke resides in the particulate rather than the vapour phase of the smoke - in other words, most of the carcinogenicity is in the tar.

Falling lung cancer incidences may be due to improved cigarettes that deliver less tar

During recent years there have been two encouraging observations. Firstly, lung cancer mortality rates are falling in younger groups, both in males and females, and this is despite the fact that the incidence of smoking has been increasing in women. Table 7 shows what has been happening in the United Kingdom.

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It is tempting to believe that this fall in risk is associated with the reduction in tar deliveries of cigarettes that has been occurring (Table 8)

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The second encouraging observation is contained in a report by Auerbach et al (1979). These workers compared the pathological changes in the lungs of men who died during two different periods - 1955-60 and 1970-77 - matching the men for numbers of cigarettes smoked per day. They found that the incidence and severity of changes in the lungs that are possible precursors of malignant change (e.g. cellular atypia) was much higher in the pair member who died in the earlier period

than in the pair member who died in the later period.

These two sets of observations provide grounds for hoping that the changes that have occurred in cigarettes of the most popular brands in the United Kingdom, including the provision of filters and reduction of tar delivery, are already having beneficial effects on lung cancer statistics. Even if no further improvements were made there is probably still a lot of 'benefit' in the pipeline from the tar reduction that has already occurred. Of course, one cannot be sure that other factors - in particular reduced air-pollution - have not contributed to the improved situation with regard to lung cancer, but personally I do not believe that other factors provide the whole explanation, and I am very hopeful that, with further reduction in tar delivery and with further improvements in tar quality, the problem of smoking-associated respiratory tract cancer will diminish substantially before the end of the present century.

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Table 1

Cancers associated with cigarette smoking

(US Surgeon General, 1979)

ICD*	Site of Cancer	Risk of death compared with non-smokers +
Definite		
162-3	Lung, Bronchus	4.5 - 15.9
161	Larynx	6.1 - 13.1
140-1	Buccal cavity	1.0 - 13.0
145-8	Pharynx	2.8 - 12.5
Probable		
150	Oesophagus	0.7 - 6.6
181	Urinary Bladder	1.0 - 6.0
157	Pancreas	1.6 - 2.7
Possible		
180	Kidney	1.1 - 1.6
151	Stomach	0.8 - 2.3
152-3	Intestines including Colon	0.5 - 1.4
154	Rectum	0.6 - 2.7

* International Classification of Diseases Code Number(s)

\+ In 8 different prospective studies.

Table 2

Mortality Ratios for lung cancer in 4 prospective studies in males

(US Surgeon General, 1979)

Study	Non-smoker	Pipe smoker	Pipe & Cigar smoker	Cigar smoker	Cigarette smoker
Hammond & Horn (1958)	1.0	3.0	-	1.0	10.7
Doll & Peto (1976)	1.0	-	5.8	-	14.0
Best & McGregor (1966)	1.0	4.3	-	2.9	14.9
Kahn (1966)	1.0	1.8	1.7	1.6	12.1

Table 3

ASSESSMENT OF RISK FACTORS FOR CANCER

CONCLUSIONS FROM AHF CONFERENCE, 1979 BASED MAINLY ON USA & UK DATA

Major Factors	Risk Attributable
Nutrition	Up to 50 %
Smoking	25 to 35 % in males; 5 to 10 % in females
Minor Factors	
Alcohol	3 %
Occupation	6 % in males; 2 % in females
Ionizing radiation	Less than 3 %
Ultraviolet radiation	Less than 2 %
Minimal Factors	
Food additives	
Drugs	
General air pollution	
Water pollution	
Immunological factors	
Other Factors	
Genetic factors	
Viruses	

Table 4

LUNG CANCER MORTALITY BY ASBESTOS EXPOSURE AND CIGARETTE SMOKING

(Hammond and Selikoff, 1979)

Asbestos exposure	History of cigarette smoking	Death rate (per 100,000p.a)	Mortality ratio
–	–	11.3	1.0
+	–	58.4	5.2
–	+	122.6	10.8
+	+	601.6	53.2

Table 5

Cigarette Consumption by Males of Different Social Classes

(from Todd, 1976)

Social Class (occupation)		1958	1974
I	Professional	76	44
II	Intermediate	76	66
III	Skilled	82	76
IV	Semiskilled	70	76
V	Unskilled	78	99

Table 6

Induction of lung tumours in mice exposed to cigarette smoke by inhalation

(After Essenberg, Science, 1952, 116, 561-2)

Treatment	Number of mice	Number of mice with lung tumours at 12 months	Percentage
Smoke Chamber	23	21	91.3
Control Chamber	32	19	59.4

Table 7

PERCENT CHANGE IN LUNG CANCER DEATH RATES 1966-70 TO 1971-75

(England & Wales)

Age Group	Men	Women
35-39	- 22%	- 16%
40-44	- 17%	- 17%
45-49	- 4%	+ 16%
50-54	- 7%	+ 17%
55-59	- 6%	+ 24%
60-64	- 5%	+ 30%
65-69	- 2%	+ 23%
70-74	+ 9%	+ 23%
75-79	+ 21%	+ 24%
80-84	+ 26%	+ 31%
85+	+ 26%	+ 26%
All ages	+ 7%	+ 27%

From Trends in Mortality, 1951-75
Her Majesty's Stationery Office
London, 1978

Table 8

Recent trends in sales-weighted tar levels of plain and filter cigarettes in the UK (mg/cig)

	Plain	Filter	All
1965	35.0	29.3	31.4
1971	27.7	19.8	21.3
1977	24.7	16.5	17.3