CIGARETTE SMOKING AS THE MAJOR CAUSE OF LUNG CANCER

PART I

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'A custom . . . dangerous to the lungs.'
James I of England: *Counterblaste to Tobacco.*

Comparisons of the cancer incidence in primitive African races with that in westernized groups, suggest that at least 80% of the cancers of these Western groups are attributable to their way of life.[27, 74] It is not therefore surprising that a common Western habit should be found to be carcinogenic. Further research into aetiology will probably implicate many other customs, now assumed to be innocuous.

The first recognition of an environmental carcinogen was the observation in 1775 by Percival Pott[80] of scrotal cancer in chimney-sweeps. This usually exceedingly rare cancer was frequent in sweeps: Earle[26] recorded a man, his brother, father, and grandfather, all sweeps, who died from it. Pott attributed it to exposure to soot, deducing that products of combustion could cause cancer after a long latent period. It took nearly 150 years before the carcinogenicity of soot was demonstrated experimentally by Passey.[77] The carcinogen has not yet been identified (though information on coal tars and carbon blacks would no doubt apply also to tars in the soot of chimneys). Although the evidence is essentially statistical, and chimney-sweep's cancer has seldom been reported outside of England,[99] Pott's conclusions are unchallenged.

The discovery that the products of combustion of tobacco are also carcinogenic is much more recent. Because in South Africa widespread ignorance of the cigarette smoking — lung cancer hypothesis is combined with active criticism, the question deserves detailed examination. South African statistics will be presented to emphasize its local significance.

THE MEANING OF 'CAUSE'

'A universe in which cause and effect always have a one-to-one correspondence with each other would be easier to understand, but it is obviously not the kind we inhabit.' Cornfield *et al.*[25]

In saying that Percival Pott discovered the cause of scrotal cancer in chimney sweeps or that cigarette smoking causes lung cancer, I should explain what is meant by the term 'cause' in this context. The statement that a factor is related causally to the development of a particular cancer implies no more than that this factor forms part of the complex of circumstances that sometimes results in the cancer, and that in its absence fewer cancers would have developed. It does not imply that exposure to the factor invariably induces this cancer, nor that every cancer developing in its presence is caused by the factor. It is also granted that the cancer may develop in the absence of the factor and be prevented by removal of other factors, so that there may be other causes.

The following postulates support a causal relationship between a factor and a type of cancer:

I. In the presence of the factor there should be an increased incidence or a relative risk of cancer (i.e. the ratio of two conditional probabilities). The recognition of the increased risk is simplified if the cancer is characteristically of a specific histologic type, or has a specific anatomic site.

II. The risk should vary with dosage (after allowing for the appropriate latent period). The relation to dosage can be shown by retrospective or prospective methods in the presence of: *(a)* varying degrees of exposure, *(b)* comparisons between continued exposure and arrested exposure, *(c)* sex differences in exposure, and *(d)* secular changes in incidence and exposure.

These are best demonstrated *within populations,* but similar correlations should be demonstrable *between populations* as well. The latter correlations may be less close, for there are usually more variables between populations than within populations.

III. The site affected should have been exposed to the factor.

IV. The factor should be capable of producing cancer of the same or comparable sites in susceptible experimental animals.

The case is strengthened if the chemical carcinogen can be identified, and its nature and dosage is compatible with existing knowledge regarding carcinogenesis.

It is not essential that all these postulates be fulfilled. Thus, if several factors are involved, secular changes may fail to show the expected correlation [postulate II (d)], e.g. although cancer of the oesophagus shows a striking correlation with exposure to tobacco within a population, in westernized groups the disease has become rarer in the last 50 years while exposure to tobacco has been increasing. This suggests counterbalancing by a concurrent diminution in other causal factors.

The third postulate may be very difficult to prove, since the site of exposure may not be obvious. Thus in cases of industrial bladder cancer caused by 2-naphthylamine, the skin

may have been constantly exposed to the chemical, without skin cancer developing. The metabolic changes involved required much study before the susceptibility of the bladder could be explained, although once again the association between the disease and occupational exposure was so obvious that none doubted its causal nature. Arsenical cancers have yet to be produced in laboratory animals (postulate IV).

These postulates resemble those used by Koch for the identification of a parasite as the cause of a disease. They include in addition the effects of variation in dosage and latent period.

For comparison, and because it has been suggested that Koch 'did not tabulate any "laws" such as are often quoted at the present day',[44] a translation of Koch's statement of these postulates is given here:

'If it can be proved, however:
firstly, that the parasite is encountered in every single case of the particular disease, and indeed in circumstances which correspond to the pathological changes and the clinical course of the disease,
secondly, that the parasite occurs in no other disease as an accidental and non-pathogenic parasite,
and thirdly, that the parasite, absolutely isolated from the body and subcultured in sufficiently frequent pure cultures, is capable of producing the disease anew,
then it can no longer be an accidental coincidence of the disease, but in this case no other relationship between parasite and disease can be imagined except that the parasite is the cause of the disease.'[62]

Today immunological confirmation is added. Koch's postulates are not always fulfilled for every bacterial disease. Leprosy was attributed to the leprosy bacillus without confirmation by culture or transmission to animals. The enteric fevers are not associated with a single organism. The diphtheria bacillus has not been isolated from the heart lesions, nor is *Bacillus botulinus* isolated from cases of botulism.

Inescapably the evidence for the aetiology of human cancer is statistical, but similarly 'the evidence on which we establish a bacterium as a cause of a disease is essentially statistical'.[101] For those who feel statistical proof is insufficient, it may be sobering to remember that bacteriology is based on the intelligent interpretation of similar statistical associations.

A GENUINE INCREASE IN LUNG CANCER

> 'The immunity of the mucous membrane of . . . the trachea, bronchi and lungs from primary cancer is remarkable; with the exception of the heart, there is no organ in the body which is so rarely occupied by a primary malignant tumour as the lung. In the few cases recorded as primary cancer of the lung there is good ground for the belief that the disease arose in the mucous glands of the bronchi.' Bland-Sutton.[11]

At the turn of the century, cancer of the lung, like cancer of the scrotum, was a rare disease. Some of this rarity was probably attributable to misdiagnoses, e.g. oat-cell carcinomas were termed oat-cell sarcomas, and many mediastinal cancers, pneumonias or lung abscesses may have been missed bronchogenic cancers. Nevertheless, after allowing for these errors, the overall incidence of lung cancer must still have been low.

Increase in Deaths Attributed to Lung Cancer

Deaths from lung cancer certified in England and Wales (Table I) have increased at a rate far exceeding that accountable on increases in population or age distribution. Many have doubted if this increase is real, but no one has put forward an adequate alternative explanation. Some claimed it could be explained by poor diagnosis in the early days. If so, then doctors in those days failed to recognize more than 95% of cases of lung cancer. Furthermore, the sex ratio has been changing, so, on the explanation of past poor diagnosis, diagnosis must have been improving at a different rate in males compared with females. Present deaths from cancer of the lung outnumber the total deaths from all lung diseases in the early days and are increasing in England and Wales by about 1,000 per year. It is noteworthy that the sex ratio in 1961 is lower than that of 1957, suggesting that the number of female cases of lung cancer has begun to increase relatively faster than the number of male cases. This suggests an increased exposure of females to a cause for which the exposure of males was previously relatively greater.

TABLE I. LUNG CANCER DEATHS BY SEX (ENGLAND AND WALES, 1907-1960)

Year	Men	Women	Total	Sex ratio
1907..	164	133	297	1·23 : 1
1917..	250	152	402	1·64 : 1
1927..	666	290	956	2·30 : 1
1937..	2,914	927	3,841	3·14 : 1
1947..	7,667	1,620	9,287	4·73 : 1
1957..	16,430	2,689	19,119	6·11 : 1
1961..	19,460	3,350	22,810	5·81 : 1

South African White death certificates for primary lung cancer (Table II) over a 10-year period from 1949 to 1958 have also increased, and male deaths have more than doubled. Standardized death rates have risen. In females the increase in standardized rates is less obvious, although there is a suggestion of a rise in the period 1956 - 1958, compared with the figures before 1952. Those who would explain all this on improved diagnosis are obliged to conclude that diagnoses in males (but not in females) have improved 200% since 1949, although no new instruments or techniques have been developed (they may, however, have become more accessible). These death certificates have been shown by Dean[28] to be reasonably accurate. 88% of those he sampled from 1947 to 1956 having had verification by bronchoscopy and biopsy, by thoracotomy, lobectomy, pneumonectomy, and very often by necropsy. The remainder (12%) had been investigated radiologically.

TABLE II. PRIMARY LUNG CANCER DEATHS (I.S.C. 162) IN WHITE MALES AND FEMALES (SOUTH AFRICA, 1949-1958[76])

Year	Males		Females	
	No.	Standardized death rate	No.	Standardized death rate
1949..	176	17·55	57	5·33
1950..	200	19·54	77	7·05
1951..	260	25·20	68	5·93
1952..	256	24·12	69	5·84
1953..	284	26·94	79	6·74
1954..	337	30·83	72	5·85
1955..	334	30·06	62	4·90
1956..	376	33·30	98	7·58
1957..	366	32·01	101	7·54
1958..	380	32·51	91	6·57

Secular Changes in Age-specific Death Rates

The curve of mortality by age from lung cancer shows an unusual maximum at the ages 55 - 64, distortion which Kennaway and Waller[61] and Case[15] have shown to be the natural reflection of increasing rates for each successive cohort of persons born since 1871. This confirms similar cohort studies for the Netherlands,[64] Switzerland, and Canada.[73]

This curve of mortality, it may be noted, cannot be explained on air pollution alone, for either all age groups should be equally exposed to a recent contaminant, or older groups would be more exposed than younger ones.

Kreyberg[65] has shown that this type of curve applies only to type-1 carcinomas of the lung (large- and small-cell and squamous-cell carcinomas) and does not apply to his second type, the adenocarcinomas.

Increase in Lung Cancer in Necropsies on White South African Gold Miners

The legislation relating to the examination and compensation of gold miners has provided a remarkable series of postmortem studies. All miners who have not had full compensation are examined after death to assess the degree of silicosis and the presence or absence of tuberculosis. The final amount of compensation is based on the autopsy findings. In consequence there is little opposition to postmortem examination — on the contrary, the bereaved relatives are usually eager to ensure that it is carried out. This material deserves intensive study. Available figures show that the frequency of lung cancer in miners at necropsy corresponds closely to that in Johannesburg non-mining males, and that the degree of silicosis does not affect the risk of lung cancer at any given period.

This necropsy material is unusual in offering a representative sample of the population at risk. Examination in the early days was largely by naked eye, and cases of bronchogenic carcinoma with cavitation may well have been missed (in both mining and non-mining series). Lung cancer has increased in both miners and non-miners at approximately the same rate (Tables III and IV). The latest figures for miners are startling: in the period January 1957 to October 1962 lung cancer accounted for 35·9% of all cancers found at postmortem examination.

TABLE III. FREQUENCY OF LUNG CANCER IN NECROPSIES ON WHITE MINERS

Years	*Dates*	*Necropsies*	*Lung cancers*		*Reference Nos.*
			No.	*%*	
15 ..	1.8.1920-31.7.1935	3,117	22	0·7	94
10 ..	1935-1945	550	—	3·6	6, 95, 96
5 ..	1957-1962	800	61	7·6	16

TABLE IV. FREQUENCY OF LUNG CANCER IN NECROPSIES ON NON-MINERS, JOHANNESBURG GENERAL HOSPITAL

Years	*Dates*	*Necropsies*	*Lung cancers*		*Reference Nos.*
			No.	*%*	
11½ ..	1924-1935	1,393	13	0·9	94
10 ..	1935-1945	750	30	4·0	6, 95, 96

Details of histologic types are available for two samples of miners, viz. 1941 - 1948 and 1957 - 1962. These indicate that the increase is in Kreyberg type-1 tumours; the figures for type 2 are too small to be significant (Table V).

Increase in Undiagnosed Cases of Lung Cancer

If the increase is attributed to improved diagnosis the number of undiagnosed cases of lung cancer should be falling. An opportunity of examining undiagnosed lung cancer is given by material from the National Hospital, Queen Square, London. In a study of secondary tumours of the brain, Proctor,[51] of the South African Institute for Medical Research, noted the proportion arising from a previously undetected primary lung cancer. The frequency of lung cancer in this group is thus a measure of original failure to recognize the primary site. The number of undiagnosed lung cancers (Table VI) increased 8-fold from the period before 1918 to the period 1934 - 1953. The only possible conclusion is that the increase in lung cancer is genuine.

TABLE V. HISTOLOGIC CLASSIFICATION (KREYBERG'S) OF LUNG CANCERS SEEN AMONG MINERS, IN ABSOLUTE NUMBERS, AND AS PERCENTAGES OF ALL NECROPSIES

	1.8.1941-31.7.1948[95, 96]	*1957-1962*[16]
Total necropsies ..	2,103	800
Lung cancers of type 1 ..	38	55
Lung cancers of type 2 ..	6	6
Ratio of type 1 : type 2 ..	6·3 : 1	9·2 : 1
Percentage of type 1 ..	1·7	6·9
Percentage of type 2 ..	0·3	0·8

TABLE VI. LUNG CANCER AS A PROPORTION OF METASTATIC TUMOURS IN THE BRAIN (NATIONAL HOSPITAL, QUEEN SQUARE, LONDON[81])

	Carcinoma of the bronchus	*Increase*
Walshe, up to 1918 ..	33·3	1 x
Elkington, 1919-1933 ..	52·9	2 x
Proctor, 1934-1953 ..	79·0	8 x

ASSOCIATION OF LUNG CANCER WITH CIGARETTE SMOKING

> 'A mortal disease, which demands decades for its development, and probably as lengthy efforts for its prevention, is now rapidly increasing because of widespread addiction . . . to a Red Indian habit . . . The real extent of this catastrophe is hitherto only realized by a limited number of workers . . .' J. Clemmesen[17]

Many noted the increase in lung cancer,[25] and suggested that it was associated with various possible factors, such as air pollution, tarred streets, war gases, influenza and cigarette smoking.[93] In 1931 Hoffman[58] pointed out the change in mortality from 0·7 per 100,000 in 1915 to 1·9 per 100,000 in 1927, and rejected attempts to explain it away on improvements in diagnosis. He concluded cautiously that 'the increase in cancer of the lungs observed in this and many other countries, is, in all probability, to a certain extent directly traceable to the more common practice of cigarette smoking and the inhalation of cigarette smoke'. Proof of the association required studies of a different type.

Retrospective and Prospective Studies

Since 1928 a succession of independent studies of the habits of patients with lung cancer compared with patients of the same age without lung cancer has demonstrated an increased risk in smokers. Lombard and Doering's figures in 1928[70] were only suggestive, but by now there are over 30 studies based on the restrospective investigation of patients. This holds for groups with relatively low lung-cancer incidence (e.g. Johannesburg Bantu) as well as for those in whom it is high. Six prospective studies involving follow-up of persons of known habits[53] also show an increased risk in smokers.

The type of material smoked affects the risk. In one comparison of standardized rates for lung cancer[31] from Hammond and Horn's study (Table VII), cigar smokers showed no increased risk, but in the whole group of cigar smokers there was a 350% increase of type-1 carcinomas.[56] Pipe smokers showed an intermediate increase, and those who smoked cigarettes only had the greatest risk. It is noteworthy that cigarette smokers are the group most likely to inhale smoke. Hammond and Garfinkel[35]

TABLE VII. STANDARDIZED DEATH RATES PER 100,000 PER YEAR FROM LUNG CANCER IN MEN IN RELATION TO TYPE OF TOBACCO SMOKED[31]

Men	*Non-smokers*	*Cigars*	*Pipes*	*Cigarettes and pipes or cigars*	*Cigarettes only*
Doctors, 35+ years old (Doll and Hill)	10	?	39	67	135
USA men, 50-69 years old (Hammond and Horn)	13	13	39	98	127

showed that deep inhaling occurred in about 24% of cigarette smokers, but in only 3% of pipe smokers and 1·5% of cigar smokers.

Much has been made of the fact that Doll and Hill found no significant difference in the history of inhaling between cases (65% inhaled) and controls (67%). They did, however, find that males with peripheral growths had a significantly greater history of inhalation than males with central growths.[33]

Fisher[46] re-examined the original material and showed that patients with lung cancer inhaled significantly less than controls. The material unfortunately did not distinguish pipe and cigar smokers. Further examination of later material showed that, among lighter smokers, patients with lung cancer gave a significantly greater history of inhaling.[31] Heavy smokers apparently inhale whether they realize it or not.[32]

Three subsequent studies have shown that among cigarette smokers the relative risk of lung cancer is greater among inhalers than among non-inhalers, when age, type, and amount of smoking are held constant.[25]

The increased risk of lung cancer in smokers relates only to one group, viz. Kreyberg's type 1. No comparable sex differences or increase can be noted in the frequency of tumours of type 2 involving the mucous glands of the trachea, the carcinoids, the adenocarcinomas and adenomas of the lung, and brochiolar and alveolar-cell carcinomas.[65, 104] It is noteworthy that this was the type of tumour that Bland-Sutton reported as typical of lung cancer in 1903 (muco-epidermoid carcinomas are classified as epidermoid).

The risk of lung cancer of type 1 increases with the amount smoked (Table VIII), until the man smoking 40 and more per day shows a risk 64 times that of one who has never smoked. The well-known difference in breast-cancer susceptibility between married and unmarried women amounts to a 35% increase in risk in unmarried women.[69] The heavy cigarette smoker, according to Hammond and Horn, faces a 6,400% increase in lung cancer.[58]

TABLE VIII. RISK OF LUNG CANCER (EXCLUSIVE OF ADENOCARCINOMA) IN MEN, RELATED TO AMOUNT SMOKED[56]

Smoking history	*Deaths*	*No. at risk*	*Rate/ 100,000 man-years*
Never smoked	4	32,392	3·4
Former cigarette smoker. Not smoking	15	10,095	44·0
Former regular cigarette smoker. Smoking occasionally ..	2	1,322	49·3
Fewer than 10 cigarettes / day	13	7,647	51·4
10-19 / day	50	26,370	59·3
20-39 / day	60	14,292	143·9
40 + / day	22	3,100	217·3

In Table IX Doll and Hill's results are given as the fractional risk of dying from lung cancer in the following decade for various age groups.[86] In non-smokers this fraction was too small to measure. The risk increases by age group, with the amount smoked.

TABLE IX. FRACTIONAL RISK OF DYING FROM LUNG CANCER, IN DECADES FROM AGE 35 TO AGE 74[86]

Decade	*Non-smokers*	*Number of cigarettes smoked*		
		1-14/day	*15-24/day*	*25 or more/day*
35–44 ..	—	—	—	1 in 833
45–54 ..	—	1 in 244	1 in 182	1 in 172
55–64 ..	—	1 in 159	1 in 51	1 in 23
65–74 ..	—	1 in 34	1 in 21	1 in 17

Some have assumed that the risk of dying from lung cancer is alternative to other risks of dying; in fact it is added to other risks (Table X). Not only does smoking increase the risk of lung, larynx, mouth, oesophageal and bladder cancer, but it also increases the risk of dying from coronary thrombosis and many chronic lung diseases. The increase is relatively (but not absolutely) greatest in the case of cancer of the lung. In the United Kingdom a smoker of 40 and more cigarettes per day has added a risk of lung cancer which approaches the non-smoker's total risk of dying from any cancer.

TABLE X. FRACTIONAL RISK OF DYING FROM ALL CAUSES IN DECADES FROM AGE 35 TO AGE 74[86]

Decade	*Non-smokers*	*Number of cigarettes smoked*		
		1-14/day	*15-24/day*	*25 or more/day*
35–44 ..	1 in 90	1 in 64	1 in 65	1 in 23
45–54 ..	1 in 27	1 in 18	1 in 14	1 in 10
55–64 ..	1 in 8	1 in 6	1 in 5	1 in 4
65–74 ..	1 in 3	1 in 2	1 in 2	1 in 2

The Effect of Abandoning Smoking

The risk in those who give up smoking is reduced when compared with that in those who continue to smoke (Table VIII). Within the first five years after ceasing to smoke the risk is about one-third of that expected, and thereafter falls still lower, suggesting that smoking is co-carcinogenic as well as carcinogenic, for co-carcinogens shorten the latent period.

Relative risk of Lung Cancer in South African White Males

Dean[29] published the results of a retrospective survey of smoking habits in White males, aged 45 - 64, dying from lung cancer, matched with controls for year of death, quinquennial age group, birthplace group and place of residence before death. Letters were sent to the widows and families. Replies were obtained in respect of 54% of cases and 51% of controls.

The results are given in Table XI, with the relative risk by smoking habits. The risk increases with the amount of cigarettes smoked, that of smokers of pipes only being less than that of smokers of cigarettes only. The South African-born group of 'all other smokers' has the highest risk of all main groups, although less than that of smokers of over 25 cigarettes per day.

TABLE XI. RELATIVE RISK OF DYING FROM LUNG CANCER IN WHITE SOUTH AFRICAN MALES 45-64 YEARS OLD, BY SMOKING HABITS AND BIRTHPLACE, 1947-1956 (CALCULATED FROM DEAN—TABLE II[29])

	Non-smokers	Cigarette smokers: 1-20	25-45	50+ per day	Total	Pipe only	Other	Total smokers	Total deaths
South African born									
Cases	10	50	136	72	258	44	121	423	433
Percentage	2·3	11·6	31·4	16·6	59·6	10·2	27·9	97·7	100·0
Controls	52	119	106	30	255	61	96	412	464
Percentage	11·2	25·7	22·8	6·5	55·0	13·2	20·7	88·8	100·0
Relative risk of lung-cancer deaths	1	2·2	6·7	12·5	5·3	3·8	6·6	5·3	—
United Kingdom born									
Cases	2	23	92	30	145	5	18	168	170
Percentage	1·2	13·5	54·1	17·6	85·3	2·9	10·6	98·8	100·0
Controls	9	49	66	15	130	10	22	162	171
Percentage	5·3	28·7	38·6	8·8	76·0	5·8	12·9	94·7	100·0
Relative risk of lung-cancer deaths	1	2·1	6·3	9·0	5·0	2·2	3·7	4·7	—

In the British-born South Africans lung-cancer rates were 44% higher than those of South African-born males in this age group, but the relative risks were very similar (Table XI).

The relative risks among cigarette smokers here are undoubtedly less than those obtaining in England and Wales and in the USA, but the trends are similar. Dean[29] concluded that 'in both South Africa and the United Kingdom the elimination of air pollution from urban areas would substantially reduce the incidence of lung cancer even if no change occurred in smoking habits'. He did not compare the effects of eliminating air pollution with those of eliminating smoking habits; his figures show that these habits cause a 500% increase in risk.

In view of the dependence of Dean's statistics on evidence from the widows or families, and the low percentage of responses, it would not seem justified to attempt absolute calculations of risk. Comparison of rural and urban groups is hampered by the small number of rural cases, but the rural death rates are much lower than the urban. This Dean attributes to atmospheric pollution. It may as easily be explained by less dangerous smoking habits in the country, the combination of smoking with atmospheric pollution in the towns, or a tendency for rural lung-cancer patients to migrate to cities before death. Certainly South Africa shows a very striking difference in male lung-cancer mortality by size of magisterial districts[76] (Table XII), as well as between cities (Table XIII).

TABLE XII. STANDARDIZED MORTALITY RATIOS* FOR LUNG CANCER IN SOUTH AFRICA BY REGION

Magisterial districts by population for each sex separately	Males	Females
South Africa		
<1,000	63·00	49·94
1,000–10,000	66·02	95·89
10,000–100,000	119·70	97·46
>100,000	154·81	119·55
Whole country	99·86	100·67
Cape		
<1,000	66·24	64·22
1,000–10,000	64·17	105·15
10,000–100,000	114·18	115·37
>100,000	—	109·35
Whole of the Cape	85·48	106·33
Natal		
<1,000	42·19	—
1,000–10,000	80·24	85·37
10,000–100,000	182·39	92·78
>100,000	—	—
Whole of Natal	146·66	87·51
Transvaal		
<1,000	70·42	126·58
1,000–10,000	68·64	89·47
10,000–100,000	98·69	89·49
>100,000	154·81	126·71
Whole of the Transvaal	108·00	103·03
Orange Free State		
<1,000	68·43	25·97
1,000–10,000	60·25	83·14
10,000–100,000	81·66	107·76
>100,000	—	—
Whole of the Orange Free State	64·71	83·32

* In males based on the years 1949, 1950, 1952, 1955, 1956 and 1957. In females based on the years 1949, 1950, 1952, 1953, 1954, 1956 and 1957.[76]

TABLE XIII. STANDARDIZED MORTALITY RATIOS* FOR LUNG CANCER IN SOUTH AFRICAN CITIES**

	Males	Females
Port Elizabeth	82·83	116·85
East London	104·82	94·94
Cape Town	135·15	109·35
Durban	203·08	102·12
Pietermaritzburg	87·39	53·08
Johannesburg	154·81	126·71
Pretoria	114·55	85·74
Bloemfontein	81·66	107·76

* These ratios are calculated for each sex separately and do not permit of comparisons between the sexes.
** Based on the same material as that used in Table XII.[76]

Precancerous Lesions in Smokers

Precancerous lesions in the bronchi show a similar association with cigarette smoking (Table XIV).[2] Loss of cilia in the bronchi should encourage retention of inhaled carcinogens.

Giving up smoking is associated with disappearance of precancerous lesions.

TABLE XIV. FREQUENCY OF PRECANCEROUS CHANGES IN LUNGS AT POSTMORTEM EXAMINATIONS: MEN 40-59 YEARS[2]

Group of subjects	*Sections with entirely atypical cells, and cilia absent* %	*Sections with some atypical cells, and cilia absent* %	*Sections with 3 or more cell rows, and cilia present* %
Deaths not due to lung cancer:			
1. Subjects never smoked regularly	—	—	7·3
2. Subjects smoked less than 1 package per day ..	1·0	16·9	34·4
3. Subjects smoked 1 or more packages per day ..	4·5	17·4	59·9
Deaths due to lung cancer ..	19·4	19·6	80·3

Butt length

A mere count of cigarettes purchased is an inaccurate measure of the amount of tar retained. This varies with the type of cigarette (Table XV), the depth and frequency of inhalation per cigarette, and finally the length of butt discarded. The length of butt does not merely reduce the amount smoked by the proportion thrown away—shorter butts are associated with a much greater tar intake. This is a major difference between South Africa and England, where the average butt lengths are 23 - 26 mm.[28] and 18 mm.[34] respectively. Furthermore, during the 1930s in England and Scotland it was common practice for men to stick a pin into the butt when it became too hot to hold, in order to get the maximum value out of the 'Wild Woodbine' that was then the poor man's solace.[88] The habit of smoking discarded butts, indulged in by many South African Bantu and Coloured people (who also employ the pin method), has been blamed for the lung-cancer susceptibilities of these groups, which appear to be greater than expected on their smoking history.[57]

TABLE XV. TAR PRODUCTION IN DIFFERENT USA BRANDS[102] (IN MG. PER CIGARETTE)

Brand	*National sales position*	*Tar production*
Chesterfield	6	39·8
Pall Mall	2	35·1
Camel	1	30·2
Lucky Strike	3	28·6
Salem	10	26·0
Winston	4	23·0
Viceroy	8	21·4
L & M	7	21·3
Marlboro	9	20·3
Kent	5	17·7

Secular Changes in Cigarette Smoking

Before World War I, cigarettes accounted for a small fraction of tobacco usage. The increase in tobacco consumption in the USA is more than accounted for by the increase in cigarette consumption (Table XVI).

South African figures show a similar rate of increase between 1920 and 1957 (Table XVIIa). The figures for Whites are available for a shorter period (Table XVIIb) and again indicate an increase in cigarette smoking.

Fairly close correlation exists between lung-cancer mortality and the current tobacco consumption of a country; this becomes closer and the regression line passes through zero if the correlation is made with tobacco consumption 20 years previously.[73]

Not surprisingly, because the correlation coefficient is not 1·0, some points lie off the regression line. South African and USA lung-cancer mortality rates, for example, are less than expected. Differences in type of tobacco, tar production, puff frequency, butt length, use of filters, cost of cigarettes, or purloining by servants, may easily explain such anomalies. The high lung-cancer death rates in England and Wales are associated with high cost of tobacco, which encourages more economical use. The lung-cancer rates for Scotland are higher still.

The adoption of smoking by women in Western countries has been relatively delayed by comparison with men, and the death rates in women are consistent with this. Where allowance is made for the latent period and the amount smoked, the risk in women smokers is virtually that of men of similar smoking habits. Among non-smokers no sex difference in susceptibility need be postulated,[25,52] and the sex differences by dosage are not significant.

Tar Production

Although figures for tar production by South African cigarettes have not been forthcoming, I am told that South African brands differ from those of the same name published in Table XV. Hammond[51] holds that the smoker has a right to know the tar and nicotine content of the smoke of the various brands, just as the purchaser has a right to know the fibre content of a fabric. He recom-

TABLE XVI. TOBACCO PRODUCTS, UNSTEMMED PROCESSING WEIGHT* IN LB.: CONSUMPTION PER PERSON OVER 14 YEARS OF AGE (USA 1880 - 1954)[72]

Year	*Cigarettes*		*Cigars*	*Smoking tobacco***	*Chewing tobacco*	*Snuff*	*Total*
	lb.	*% of total*	*lb.*	*lb.*	*lb.*	*lb.*	*lb.*
1880	0·047	0·87	1·36	0·73	3·15	0·12	5·41
1890	0·18	2·47	1·78	1·12	3·99	0·22	7·29
1900	0·16	2·15	1·99	1·42	3·56	0·30	7·43
1910	0·41	4·77	2·19	2·17	3·35	0·47	8·59
1920	1·89	21·80	2·45	1·50	2·36	0·47	8·67
1930	3·84	43·39	1·67	1·44	1·47	0·43	8·85
1940	5·16	56·58	1·36	1·50	0·74	0·36	9·12
1950	9·36	78·26	1·18	0·59	0·49	0·34	11·96
1954	9·84	80·66	1·23	0·41	0·40	0·32	12·20

* Unstemmed processing weight represents weight before stems are removed. It does not include non-tobacco materials such as sugar, honey and liquorice, added during manufacture.

** The category 'smoking tobacco' includes tobacco used in roll-your-own cigarettes. During 1933 - 40 this tobacco amounted to 46% of the smoking-tobacco category, but by 1950 - 54 it is estimated that it had dropped to around 32%.

TABLE XVIIA. CONSUMPTION OF TOBACCO GOODS IN SOUTH AFRICA (TOTAL POPULATION)[91]

Year	Cigarettes (million lb.)	Cigars and cigarillos (million lb.)	Other (million lb.)	Snuff (million lb.)	Total (million lb.)	Consumption per adult	
						Cigarettes	lb.
1920	3·3	0·2	10·1	0·1	13·7	380	3·4
1927	4·9	0·1	11·0	0·1	16·1	470	3·4
1937	9·1	0·1	12·6	0·1	21·9	630	3·7
1947	18·0	0·1	15·0	0·1	33·2	1,100	4·5
1957	25·2	—	22·4	—	47·6	1,300	5·4

TABLE XVIIB. CONSUMPTION OF TOBACCO GOODS IN SOUTH AFRICA (WHITE POPULATION ONLY)[91]

Year	Cigarettes (million lb.)	Cigars and cigarillos (million lb.)	Other (million lb.)	Total (million lb.)	Consumption per adult	
					Cigarettes	lb.
1937	7·3	0·2	4·4	11·9	2,380	8·5
1947	13·0	0·1	4·3	17·4	3,480	10·2
1957	16·4	neg.	3·6	20·0	3,720	10·0

mends that this information should be given on the label, and that cigarettes of high nicotine and tar content should receive discriminatory taxation. If manufacturers object that tar production is not exactly equivalent to carcinogenicity, a more direct estimate of carcinogenicity might be chosen.

The average heavy smoker who inhales, retains 90% of the tar in his lungs, and thus can be shown to retain 300 G. of tar a year, i.e. over half-a-pound. The retention is no doubt mainly temporary, but the amount of tar and carcinogen it contains is theoretically quite sufficient to produce cancer.

Carcinogens in Cigarette Smoke

Some of the carcinogens found in cigarette smoke are listed in Table XVIII. The first, 3.4-benzpyrene,[105] is the usual index of amount of carcinogen present, but others

TABLE XVIII. CARCINOGENS FOUND IN SMOKE[1, 97, 102]

Benzo(a)pyrene (3.4-benzpyrene)
Dibenzo(a,h)anthracene (1.2.5.6-dibenzanthracene)
Benzo(b)fluoranthene (3.4-benzfluoranthene)
Benzo(j)fluoranthene (10.11-benzfluoranthene)
Benzo(a)anthracene (1.2-benzanthracene)
Chrysene
Benzo(e)pyrene (1.2-benzpyrene)
Benzo(g,h,i)perylene (1.12-benzperylene)
Benzo(k)fluoranthene (11.12-benzfluoranthene)
Benzo(c)phenanthrene
6.7-cyclopenteno-1.2-benzanthracene

occur, and the total quantity of 3.4-benzpyrene should not be equated with total carcinogen. The output of carcinogens depends on the temperature of pyrolysis. Where this is below 650° C. the output is greatly reduced.

Cancer-promoting Agents in Cigarette Smoke

A second important group of factors consists of cancer-promoting agents—co-carcinogens—which render a small dose of carcinogen effective in a much shorter time. Probably the most important of many co-carcinogens present in cigarette smoke are phenolic substances (0·9% of the condensate); in addition some promoting activity is shown by the acid fraction of the smoke.[106] Wynder[102] has shown that this fraction can potentiate weak doses of other carcinogens applied to mouse skin.

Free Radicals in Cigarette Smoke

These are commoner in the fresh smoke and disappear as smoke becomes staler. Free radicals are important in carcinogenesis by irradiation. Their precise contribution to carcinogenesis from cigarette smoke has yet to be defined.

Ciliostasis by Cigarette Smoke

Certain pharmacological constituents of smoke arrest the motility of cilia.[5] This is detectable in human bronchial epithelium in tissue culture in as short a time as five minutes. This forms a new segment of the problem, since both laboratory experimentation and smoking experience show that tobacco smoke interferes with the normal cleansing mechanism of the bronchi. The smoker's cough is worse in the morning, for the night's rest gives his cilia time to recover. Ciliostatics will promote retention of all inhaled carcinogens.

The chemistry and pharmacology of cigarette smoke is completely consistent with the hypothesis that smoking is carcinogenic.

Experimental Evidence

The last postulate for a causal association between cigarette smoke and cancer requires that cigarette tar and its fractions produce cancer in the experimental animal (postulate IV). The usual test for surface carcinogenicity is the mouse skin. When cigarette tar is applied to the mouse in adequate concentration, i.e. 50% strength, it produces skin cancers. In more dilute doses the number of cancers is greatly reduced. Cigarette tar is evidently a weak carcinogen.

Direct inhalation of smoke from the lighted cigarette is not possible with small animals, but the injection of cigarette tar from 40 cigarettes into the lung of a rat will produce cancer.[10]

Cigarette smoke condensate has been applied repeatedly to the mucosal surface of the bronchi of 85 dogs after tracheal fenestration.[112] This has produced precancerous changes (20 cases), carcinoma-*in-situ* (2 cases), and invasive carcinoma (1 case)—the last after 5 applications only. None of these changes was seen in the control dogs subjected to rubbing manipulations of the bronchial mucosa.

(*To be continued*)