CIGARETTE SMOKING AS THE MAJOR CAUSE OF LUNG CANCER

PART III

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CONCLUSIONS

'All grocerdom screamed. When it had done screaming, it acquiesced.' Clive Bell[7]

The Grounds for Rejecting a Hypothesis

In modern science a hypothesis stands until an alternative is proposed which fits the facts even better. If two rival hypotheses fit equally well, a crucial experiment must be devised to indicate conclusively that one is correct. Absolute proof of hypothesis is a contradiction in terms, for, when such proof is available, the hypothesis becomes a fact. To demand absolute proof, as if it were a characteristic of all good hypotheses, is folly; it is not available for even the theory of gravitation.

In the meanwhile, the facts to explain[75] are:

1. The age-adjusted lung-cancer mortality has increased tremendously in the last 30 years.

2. This increase affects males more than females.

3. This increase involves certain histologic types only (Kreyberg's type 1).

4. Cigarette smoking has also increased in all countries where this rise in lung cancer has been noted, and the increase in cigarette smoking has preceded the increase in lung cancer by some decades.

5. Within a population at a given time the risk of lung cancer in males and females is proportional to the amount smoked and falls off with cessation of smoking.

6. Carcinogens and co-carcinogenic factors are present in smoke.

7. Cigarette tar is carcinogenic when applied in comparable dosage to the lungs or skin of suitable animals.

The hypothesis is open to modification, e.g. cigarette smoking itself is not strictly the factor held responsible, but (excluding certain occupational groups) *the major cause of lung cancer in civilized countries is held to be the inhalation into the bronchi of carcinogenic and co-carcinogenic substances derived from cigarette smoke and, to a lesser extent, from pipe and cigar smoke*. In this form it remains the only explanation of the facts.

Some critics apparently feel under no obligation to provide an alternative hypothesis, and merely attempt to cast doubt on single items of evidence. The strength of a chain is the strength of its weakest link, they argue—demolish one link and the whole theory can be rejected.

In the first place, in medicine we normally have to act on reasonable grounds, without waiting for absolute certainty. Greenwood[49] wrote that 'the scientific purist, who will wait for medical statistics until they are nosologically exact, is no wiser than Horace's rustic waiting for the river to flow away'.

In the second place, evidence does not form a chain that can be broken at one link. It is more like the threads that bound Gulliver to the ground in Lilliput—flimsy though the individual threads might have been, their combined strength was irresistible. It is the consistency between data, derived from many sources, that validates this hypothesis.

Finally, where a crucial requirement has been demanded, and met, the hypothesis that fits ought to be accepted. This has not happened. Berkson, for example, attributed the greater smoking habits of lung-cancer patients to bias even in prospective surveys, i.e. he suggested that patients who were going to develop lung cancer would say they smoked more than they actually did. This bias,

if present, should have 'worn off' in 3 - 5 years.[8] The passage of time, therefore, should show lung cancer appearing more frequently in those of lower smoking habits. This has not occurred, and the original postulate of bias falls away. Doll and Hill[32] showed this bias was not present in patients incorrectly diagnosed as having lung cancer, so it is doubtful if this bias existed in their retrospective study. The critic, however, has not changed his ground.

The failure of Doll and Hill to demonstrate increased inhalation among lung-cancer patients was regarded as crucial. It has now been demonstrated in other series. Will the critic believe the demonstration to be as crucial as he once claimed his objection was?

Unless objections are no longer a matter of logic, and are now matters of personal reputation, the critic should state his objections clearly, the alternative hypothesis that he favours and what crucial experiment, within reason, would be accepted. The ideal experiment would be to take a group of 100,000 schoolboys, randomly subdivided and ordered to adopt particular smoking habits, and follow them for the next 60 years. This is not a practical proposal. Short of this, however, it seems that everything possible has been done, and the hypothesis that holds cigarette smoking is the major cause of the present pandemic of lung cancer remains the only explanation that fits the facts. It is the most thoroughly substantiated of all hypotheses regarding the aetiology of any human cancer, and all postulates have been amply fulfilled. From the theoretical viewpoint, it merely extends Pott's demonstration, now nearly two centuries old, that cancer may result from exposure to the products of combustion.

The hypothesis has been vigorously attacked, but the major opposition has come from what Bross[13] has termed 'hit and run' critics, who attempt to discredit the association without seriously putting forward any counter hypothesis. The techniques of 'factifuging'[62] have been most effectively applied.

This opposition is not wholly unexpected, however unjustified it may be. It has been shown, even among medical men in England[82] and Holland,[109] that the intensity of disbelief is greater in smokers. From these published figures, and also from my findings in local medical students,[76] it is evident that the evaluation of the association between smoking and lung cancer is affected by the smoking habits of the subject. Since this bias exists, public statements discrediting the evidence or advocating delay should be prefaced with a statement whether the speaker smokes, or has a vested interest in tobacco—be it shareholding, employment, the prosperity of his relatives or political pressure. Such frankness is not without precedent: it was a noteworthy feature of the debate in the House of Lords on 22 March 1962.[116]

RECOMMENDATIONS

> 'Health cannot be imposed upon a people; it must be won in partnership with them.' F. Brockington[12]

The obvious recommendation to the smoker is to give it up, and to the non-smoker, not to begin. People do not necessarily follow good advice, however, so it behoves the tobacco companies to render their products less noxious. Since they must perforce experiment on their customers, they will have to base the changes on reasonable grounds, and not vainly ask for proof. Subsequent changes in lung-cancer mortality will demonstrate the efficiency of the alterations. Elimination of carcinogens, co-carcinogens, and ciliostatics would seem an obvious measure. This may be attempted by selection of tobacco, alteration in processing, reduction in temperature of combustion[60,102] (to below 650° C.), reduction in phenolic and acid fractions of the smoke, and identification and elimination of ciliostatic agents. Reduced production of carcinogens, co-carcinogens and ciliostatics should be reinforced by selective filtration (other modifications may be demanded to reduce the risk of coronary thrombosis and chronic bronchitis). It is a tremendous problem, and offers plenty of scope for immediate action and research, once the industry abandons its present struthious behaviour.

Frank admission of the dangers of a product need not mean industrial suicide. The liquor industry has never denied the association between alcohol and drunkenness—and also received a million-rand grant for research from the South African Government.

The proper course of action will need great wisdom, experience and skill. It is possible to dispose of some suggested methods immediately. Control of a habit-forming drug cannot be left to individual choice. It cannot be left to the tobacco industry and its shareholders—who to my knowledge have done nothing in this country so far towards either censoring advertising or acknowledging the danger of their product. The companies, furthermore, produce the products that the public requires, and the farmers in turn produce the tobacco that the companies require. A change in demand can only come about slowly.

State action in some form is inevitable, and the Public Health Act No. 36 of 1919, as amended,[18] makes adequate provision for this in Section 3 (1) which reads:

> 'The functions of the Department of Health shall be . . . the prevention, limitation, or suppression of . . . preventable diseases . . .' as well as 'to promote or carry out researches and investigations in connection with the prevention or treatment of human diseases'.

To justify action by responsible bodies, an official statement is needed on the reality of this association, which the British Ministry of Health describes as 'demonstrating, "crushingly and irrefutably", that smoking, above all cigarette smoking, was the cause of the vast majority of cases of lung cancer'.[43]

Health education is urgently necessary, although the immediate results of educational campaigns are disappointing.[34] The small voice of health education cannot compete with the lavishly endowed blare of advertising media, and will never be able to compete unless cigarette companies are obliged to provide a sum of money for anti-smoking advertisements equal to that which they spend in extolling their products. Long-term effects may be expected, however, and have already been demonstrated in a reduction of smoking among doctors, who are best able to see the results.[86] Even here, however, it has been slow. Suggestions that propaganda be directed at adolescents, while adults continue to smoke unabatedly, are naïve.

Simple taxation of tobacco does not reduce consumption, and will only encourage the habits of economy that

no doubt help to make the British lung-cancer mortality so high.

Deserving of consideration are three measures. The first is differential taxation, least on cigars, and varying with the tar production or carcinogenicity of cigarettes. This might stimulate improvement of the brands as well as an alteration in smoking habits.

The second is a printed statement on each packet[54] giving the nicotine and tar content of the smoke, so that the customer can know what he is purchasing.

Finally, there is limitation of advertising. If not done voluntarily by the tobacco companies, it should be State-enforced. It is difficult to convince youth of dangers 20 or 30 years ahead, in the face of all the subtleties of modern advertising, suggesting that cigarette smoking—at least of a particular brand—is a mark of success, maturity, popularity, or appreciation by either beautiful girls or handsome men. Advertising revenue also biases information services. Not all newspapers keep their news and advertising sections in watertight compartments, and statements relating to the incrimination of cigarette smoking are usually followed up closely by counter-arguments, in type as bold, though the reasoning be trivial.

Differential taxation would lead to the anomalous situation that the most expensive brands would probably be the worst for the customer. It remains to be seen whether the snob value of higher prices would be counteracted by the knowledge that this price increase was produced by taxation, intended to discriminate against a more harmful product. This would of course be supported by the manufacturer's label giving the content of noxious material in the smoke.

An informed shift in public demand is necessary to incline industry and farming in the direction of a safer product.

It will be argued that tar content is not an exact measure of carcinogenicity. It is, however, a good measure, and cigarettes which produce less tar are generally less carcinogenic than those which produce more.[111] When a better practical index of cancer risk is agreed upon, it can be used. The label on the packet might then be changed from '6 mg. smoke condensate per cigarette' to 'The smoke from 4 of these cigarettes will produce cancer in 50% of the rats (or mice) injected'. Whether the increase in precision will be welcome to the industry remains to be seen.

Improvement will require a sensible acknowledgement of facts by the public, industry, and State health agencies. The only policies with a hope of success are those that make it easy to do the safe thing, and difficult—and much more expensive—to inhale carcinogens.

The size and the economic importance of the tobacco industry as producers of revenue and advertising, seem to have weighed too much with governments. Official inaction before the mountain of evidence relating to tobacco smoking stands in marked contrast to the prompt and radical action of the USA Government[41] whose Secretary of Health, Education and Welfare impounded cranberries contaminated with traces of the weed-killer amino-triazol, refusing to impose tolerance levels (e.g. the suggested level of 1 part per million). A single experiment showed that this substance gave rise to adenocarcinomas of the thyroid in rats fed for 2 years on a diet containing 100 parts per million. At 50 parts per million only adenomas developed. There were certainly no grounds for believing that a teaspoonful of cranberry sauce on the Thanksgiving Day turkey would be a serious risk in man. The Secretary based his action on the clause in the Federal Food, Drug, and Cosmetic Act which says that 'no additive shall be deemed safe if it is found to induce cancer when ingested by man or animal'.

At this stage the minds of some may run to the need for Government commissions—as respectable a method for postponing a decision as has been invented. There have been numerous commissions, national and international, on this subject. All have reached the same conclusions. We need no more. The latest commission, that of the Royal College of Physicians, was actually criticized for contributing nothing new,[108] which is hardly the duty of a commission, although the criticism emphasizes the sameness of their reports.

To those who suggest the need for more research, I would reply firmly there is no need for more research into the association between lung cancer and smoking. The association has been proved over the last 30 years and in as many separate independent investigations.*

I do not deny the need for research into particular aspects of this association or into the *mechanism* whereby cigarette smoking causes lung cancer; on the contrary, such research is essential. But let us have no further waste of time and argument about the existence of a causal relationship between smoking and lung cancer. In South African Whites the disease is responsible for more than 500 deaths a year, in the United Kingdom more than 25,000, and in the USA almost 40,000[110] deaths, of which 85%[31] to 90%[31] would not occur if smoking were abandoned. It accounts for about 20% of deaths from cancer among South African White males (and, as we have seen, 36% among White miners). Each year of delay allows lives to be lost which could have been saved by giving up smoking. The prospects of cure are distressingly low. These preventable deaths must be weighed against academic demands for absolute certainty.

Were someone to discover a technique for curing 20% of male cancers it would rightly be hailed as a tremendous advance and prompt availability would be demanded. We now have the power to prevent as many. The widespread failure to act calls to mind the episode[85] during World War II, on 11 February 1942, when the German battle cruisers *Scharnhorst* and *Gneisenau*, and the cruiser *Prinz Eugen* broke out of the blockade in the harbour of Brest and proceeded 560 miles up the English channel through the Straits of Dover to safety in Heligoland Bight. Admiral Sir Dudley Pound had the unenviable task of breaking the news to the British Prime Minister. Sir Winston Churchill's response to his unhappy Admiral of the Fleet was the single word: 'Why?' Future historians of medicine, looking at more than 30 years of inaction since this association was first demonstrated, will ask the same question.

*This is a favourite plea of tobacco manufacturers, whether British, American or South African. Viscount Hailsham, Lord President of the Council and Minister for Science, has answered this argument with a lucidity and sympathy that deserves close study.[116]

SUMMARY

Just as Koch's postulates have enabled bacteriologists to deduce a causal association from a statistical correlation between an organism and a disease, so also in cancer epidemiology there are postulates on which a causal relationship between an environmental factor and a cancer can be deduced. In the light of these, this article examines the evidence for the reality of the increase in deaths from lung cancer, its association with smoking, particularly cigarette smoking, and the experimental confirmation of the hypothesis that this association is causal. In addition to this review of the literature, some South African evidence is presented, which bears on the question.

1. In the period 1949 - 1958 the standardized lung cancer mortality for White males has almost doubled.

2. Since 1920 the relative frequency of lung cancer in necropsies on White miners has increased from 0·7 to 7·6% of all necropsies (and to 36% of all cancers). The percentages in miners are very similar to those in non-miners.

3. Proctor has provided some hitherto unpublished figures from Queen Square, London, relating to patients whose brain tumours were subsequently found to be of metastatic origin. With the passage of time, the lung has been found with increasing frequency to be the primary source of the metastasis. This indicates that clinically missed cases of lung cancer have undergone an increase: if the general increase in lung cancer could be explained away on improvement in diagnosis alone these clinically missed cases should have decreased in frequency.

4. From Dean's published material on lung cancer mortality in South Africa, the relative risk is shown to increase markedly (up to 12-fold) with heavy cigarette smoking.

5. In South Africa, White male lung cancer mortality is highest in Natal and lowest in the Orange Free State. In all provinces and in both sexes, the mortality is higher in the more heavily populated magisterial districts.

6. The standardized mortality rates for White males are 27·6 per 100,000 per year over the period 1949 - 1958, and 19·9 for Coloureds; for Asians the rate is 9·1% per 100,000 per year over the period 1950 - 1958. The male:female ratios of cancers of the oral cavity, oesophagus and lung are comparable (approximately 4:1), while that of the nose and sinuses is much lower (1·3:1). This is consistent with a carcinogen inhaled through the mouth rather than the nose.

7. The consumption of cigarettes in South Africa has risen markedly since 1930, and is still rising.

8. Cancer mortality figures from Durban show no evidence of an increased risk in White women in Durban. A low rate is also noted in South African males. The factor of atmospheric pollution would appear to be comparatively trivial, at any rate in non-smokers.

Alternative explanations and counter-arguments are shown to be inadequate. The only hypothesis that fits the facts is that inhalation into the bronchi of material derived from cigarette smoking is the major cause of lung cancer. This material contains carcinogens, promoting agents, free radicals and ciliostatics. The causal relationship is as well substantiated as any hypothesis in the aetiology of human cancer. Research into the mechanism whereby cigarette smoking causes lung cancer is still needed, although sufficient information is available to justify immediate steps.

We have in our possession sufficient knowledge to reduce one of the commonest cancers in men to a fraction of its present level. Lung cancer thus falls under the class of preventable diseases, and becomes the responsibility of the State Department of Health.

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