Environmental Tobacco Smoke

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Francis Roe: In his contribution Dr. Layard has analyzed such facts as there are in a way that in my view is both informative and open-minded. Rather than go over the same ground again I propose in this short presentation to do no more than expand on a few of the matters that he raised. My basic proposition, with tongue only partially in cheek, is that "the model has no clothes."

Anyone who is mindful of the welter of really serious health and environmental problems with which mankind is faced must surely be amazed, if not disgusted, by the huge effort and resources that have been and are being devoted to trying to distinguish between "a very low cancer risk" and "no cancer risk" from ETS. Eminent statisticians such as Nathan Mantel (Mantel, N. (1987). Lung cancer and passive smoking. *Brit. Med. J.* 294:440) have repeatedly stated that epidemiology is too blunt a tool to make such a distinction where relative risks are less than 2. Obviously there has to be another attraction in continuing with such research. Can it be that nakedness is attracting the wrong sort of people to the fashion show?

For a subject to merit serious and continuing discussion as distinct from immediate but short-lived interest, it has to be dressed in good quality fabrics that have been expertly tailored. This has not been and cannot be done in the case of the ETS and cancer risk since the fabrics, in terms of accurate exposure data over adequately long periods and in terms of accuracy of diagnosis, are not available. Furthermore, because of the impossibility of controlling for all the important confounding variables and of collecting data about exposure to them in an unbiased way, there is no possibility of expert tailoring by epidemiologists. It is for these reasons that ETS and cancer risk is like a more or less naked model at a fashion show.

Most of the seemingly endless succession of inconclusive papers aimed at seeing if there is a relationship between spouses' smoking habits and lung cancer risk end with the investigators expressing the view that "more research will be needed before firm conclusions can be reached." A more sound conclusion would be that no further research of this kind is warranted because of the impossibility of collecting either accurate exposure data over an adequate time period or accurate diagnostic data based on 100% necropsy rates. Clearly our model is destined never to wear fine clothes. Hopefully, as the attractions of her nakedness diminish with age so will the frequencies of her appearance in the fashion show.

Sooner rather than later not only will preoccupation with things such as the greenhouse effect, gaps in the ozone layer, AIDS, societal hard drug problems, computer-based intrusion into privacy and computer fraud take over from the borderline issues such as ETS and cancer risk. Indeed, those who keep this pot boiling now may well be accused of having got their priorities wrong and having thereby delayed progress towards solving much more serious problems.

Even under conditions of very heavy exposure of humans to potent carcinogens (e.g., as has happened in the past in certain occupations), it is unusual to find examples of cause and effect relationships where the interval between the start of exposure and the diagnosis of cancer is less than ten years. Latent intervals are much more often on the order of 20–50 years. From animal studies it is clear that dose determines not only the incidence of cancer but also the length of the period between first exposure and onset (Druckrey, H. (1967). Quantitative aspects in chemical carcinogenesis. In Rene Truhaut (ed.) *Potential carcinogenic hazards from drugs.* UICC Monograph Series Vol. 7, pp 60–78). Common sense dictates that ETS, if it is carcinogenic at all, cannot be more than very weakly active in this respect. It follows that, for any epidemiological study to have a real chance of throwing useful light on the subject, exposure data will need to be collected for periods of up to 20–50 years prior to the point at which one compares cancer incidence in exposed and unexposed individuals. In this regard, none of the reported studies are adequate and even the prospective studies starting at the age of about 40 may lack information that is highly relevant to exposure earlier in life.

Forty years ago in Britain and in many other industrialized countries, outdoor air pollution was a major problem and a major cause of chronic bronchitis and emphysema. Many studies at that time revealed differences between urban and rural lung cancer death rates ranging upwards from about 1.5 (Curwen, M.P., E.L. Kennaway, and N.M. Kennaway (1954). The incidence of cancer of the lung and larynx in urban and rural districts. *Brit. J. Cancer* 8:181–198. Royal College of Physicians (1970). *Air pollution and health.* pp 1–80). We ourselves quite readily produced skin tumours in mice by applying acetone-soluble extracts of airborne particulates collected over St. Bartholomew's Hospital in London (Roe, F.J.C. and F. Kearns (1967). Comparison of carcinogenicity of tobacco smoke condensate and particulate air pollutants and a demonstration that their effects may be additive. *Alkylierend wirkende Verbindungen*, Second Conference on Tobacco Research, Freiburg, pp 110–111.). Hopefully this problem has receded, although possible lung cancer risk from diesel exhaust fumes is presently a matter for considerable concern (Albert, R.E. and C. Chen (1986). U.S. EPA diesel studies on inhalation hazards. In: N Ishinishi, A. Koizumi, R.O. McClellan and W. Stober (eds.) *Carcinogenic and mutagenic effects of diesel engine exhaust.* pp 411–419).

The point I wish to make is that laboratory studies involving the exposure of animals to carcinogens indicate quite clearly that damage done to the lungs by carcinogenic industrial air pollutants during childhood is likely to have an indelible influence on the risk of developing lung cancer during later life. The same is, of course, true for exposure to other inhalable carcinogens (e.g., radon).

The importance of exposures during the first 10–30 years of life in relation to subsequent lung cancer risk is powerfully illustrated by observations on migrants from Britain to countries that lack substantial industrial air pollution. Such migrants have been found to have a higher risk of developing

lung cancer than comparable members of the indigenous population after standardization for personal smoking habits (Roe, F.J.C. and M.A. Walters (1965). Some unsolved problems in lung cancer etiology. *Progr. Exp. Tumor Res* 6:126–227). Obviously, characterization of exposure to ETS based mainly on questionnaire data concerning personal and spouse's smoking habits during adult life falls ridiculously short of what is needed. Further, none of the prospective studies of Hirayama (1981, 1984), Garfinkel (1981) and Gillis et al. (1984) were prospective in respect of potentially important exposures during childhood and early adult life.

It also is apparent that some epidemiologists have little idea of the frailty of medical diagnostic data. Indeed some go so far as to say that inaccuracy of diagnosis only gives rise to false positive associations if bias is involved. As a pathologist I doubt whether this argument really holds good under conditions of extreme variability of diagnostic criteria and of high levels of inaccuracy. Or to put the point in a different way, I doubt whether one could expect to identify all the sources of bias under actual field conditions.

Adenocarcinomas of similar microscopic appearance may arise in many different sites in the body. In women, the breast, ovary, uterus and colon are common sites. All these tumours commonly metastasize to the lungs. The pathologist presented with a biopsy sample of adenocarcinomatous tissue obtained during bronchoscopy is wholly unable to tell the physician/surgeon whether the neoplasm arose primarily in the lung or whether it metastasized from another body site.

None of the epidemiological studies aimed at seeing if exposure to ETS increases lung cancer risk is based 100% on diagnoses made in surgical resection or necropsy specimens. As a consequence, the scope for inaccuracy of diagnosis of lung cancer in many of the studies is enormous. Of particular concern in this regard is the study of Hirayama (1981; 1984). Hirayama relied on death certificate data for the diagnosis of lung cancer while in only 21 of his 200 lung cancer subjects was a necropsy carried out.

A glance at necropsy rates in different countries as reported in the 1988 WHO World Health Statistics Annual shows, first, that necropsy rates are especially low in Japan and secondly that in no country are they high enough for one to be able to base a large epidemiological study on diagnostic data for primary lung cancer established by necropsy.

However, even these rates are misleading insofar as many of the necropsies shown were undertaken merely to establish accidental death or lack of foul play. In other respects such necropsies are often rather superficial in nature so that distinctions between primary and secondary adenocarcinoma of the lung would not necessarily come to light. Generally speaking, persons who are known to have advanced cancer before they die are not subjected to necropsy since the precise site of the primary cancer is considered to be of little more than academic interest in such cases.

In addition to the factors discussed by Dr. Layard, two others need to be

considered. First, with the relevant experts agreed that exposure to radon or its daughters in the home is likely to be responsible for thousands of deaths from lung cancer in the USA (National Research Council Committee on the Biological Effects of Ionizing Radiations. *Health risks of radon and other internally deposited alpha emitters. Nat. Acad. Press,* Washington DC, 1988) and Britain (Clarke, R.H. and T.R.E. Southwood (1989). Risks from ionizing radiation. *Nature* 338:197–198), it would be irresponsible to embark on yet further epidemiological studies aimed at assessing lung cancer risk from ETS without attempting to control for exposure to radon. Second, the recent publication by Holst et al. (Holst, P.A. (1988). For debate: Pet birds as an independent risk factor for lung cancer. *Brit. Med. J.* 297:1319–1321) of data suggesting a 6–7-fold increased lung cancer risk associated with the keeping of pet birds in the home after standardizing for smoking habits points to another variable which in future will need to be taken into account. In the case of radon, there is already enough background information to be sure that there really is a lung cancer risk. In the case of the study by Holst et al., the data seem to be sound. However, confirmation in a further larger scale study is needed.

I would offer the following observations, then, in conclusion:

1. Epidemiology is too blunt a tool to distinguish between 'very low risk' and 'no risk' of lung cancer from ETS.
2. One would need to have reliable data for exposure to ETS, mainstream tobacco smoke and numerous other factors (asbestos, radon, urban air pollution, diesel fumes, pet birds, etc.) *from childhood onwards* before one could make epidemiology into a sharper tool.
3. Also one would need to have far more reliable cancer diagnostic data than are presently available.
4. Since there is no prospect of achieving either of these conditions, it is probably morally wrong to devote further resources to research in this area while much more serious threats to human health, society and the environment from other causes are looming larger by the day.
5. Epidemiological studies of the possible association between ETS and lung cancer are like a model for whom there is no prospect of ever being dressed in fine clothes. Her nakedness is bound to pall sooner or later.