SECTION II

NEED FOR EPIDEMIOLOGICAL MONITORING OF INDUSTRIAL MORTALITY

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Epidemiological Perspective

This paper will discuss "risk assessment" from an epidemiological perspective, making reference to reviews published elsewhere to support its main arguments. This paper should be considered an introduction to the topic; for much more detailed information, the reader is referred to Doll & Peto (1), a review published after this paper was presented.

Information is still lacking on what proportion of human cancer in developed countries is due to occupational, environmental or consumer exposure to the type of chemicals to which "risk assessment" is usually applied. A large percentage (variously estimated as 70%, 80% or 90%) of cancer is avoidable, based chiefly on evidence that every cancer which is common in one country is rare in some other country. For example, lung cancer is common in the United Kingdom but much rarer (about 3% of the British rate) in Nigeria because the Nigerians have not smoked cigarettes for as long as have the British. Stomach cancer is common in Japan but much rarer (about 4% of the Japanese rate) in Uganda. Further evidence that these cancers are really preventable is provided by the changes with time in some of them. Stomach cancer is decreasing by about 50% every 20 years in most countries in the world, even though it is still almost incurable, while lung cancer is increasing rapidly in all countries where cigarette smoking increased substantially between 1920 and 1960.

Apart from the cancers associated with smoking, most of the cancers which are common today in North America, the United Kingdom and the rest of Europe have been common for at least half a century; the avoidable causes, therefore, must be sought in various aspects of our lifestyle and environment which were already present more than half a century ago. The most plausible factors appear to be dietary habits, including not only carcinogenic contaminants of diet but also trace elements, vitamins and other micro-nutrients and gross aspects of diet such as

frequency of feeding, and caloric, bulk or fat content. All of these elements can profoundly modify the incidence of either spontaneous or carcinogen-induced tumours in laboratory animals and may in principle do likewise in humans. These views are not substantiated by established scientific facts but may point to interesting lines of research. These views are mentioned merely to show that even though 90% of cancer may be avoidable, the percentage attributable to chemicals in the environment may be much smaller. The recent report from the United States Office of Technology Assessment (2) develops these views much more fully, especially with respect to the role of pollutants in air, water and food. A summary table from that report which gives a general epidemiological perspective on ways of avoiding cancer is reproduced in Table 1.

At present, no reliable data are available on which to base estimates of the percentage of cancer due to occupational factors. Reasonable estimates for the United Kingdom and the United States have ranged between 1% and 10%, and any figure from 2% to 5% may be plausible. The estimates of 20-40% (or 23-38%) that have appeared since 1978 all seem to derive from one wholly unreliable source: an unauthored, unpublished document circulated in 1978 in Washington. This document has been reproduced as Appendix F in a recent report by Peto & Schneider (3). Since that document would attribute to occupational factors alone about ten times as many mesotheliomas and nasal sinus cancers as actually occur in the entire population, its underlying assumptions are clearly erroneous, and it should not even be mentioned in reviews of the range of estimates of the percentage of cancers that have appeared in the published scientific literature. What the percentage may be in countries other than the United Kingdom and the United States is not known to the author, and the chief point of this present paper is to recommend research which would incidentally help to answer this question.

In most developed countries, epidemic increases in lung cancer have taken place, or are continuing to take place, due to the adoption of cigarette smoking. The old habit of pipe smoking had much less effect on lung cancer than does cigarette smoking. However, a switch from pipe to cigarette tobacco will not produce large changes in the onset rates of cancers caused by both habits, such as cancer of the mouth, pharynx, larynx and oesophagus.

Table I Proportion of cancer deaths attributable to different factors in the United States in 1977 (2)

Factor or class of factors	Percentage of all cancer deaths	
	Best estimate	Range of acceptable estimates
Tobacco (chiefly affects lung but also mouth, oesophagus, pharynx, larynx, bladder and possibly pancreas)	30	25 to 35
Alcohol (has little effect on nonsmokers, but enhances effects of smoking on mouth, oesophagus, pharynx and larynx)	3	2 to 4
Diet (chiefly gross aspects of diet, see text)	35	10 to 70
Food additives (possible effects of nitrites, possible protective effect for gastric cancer of sterilizants and anti-oxidants)	<1	−5 to 2
Reproductive and sexual behaviour (sexually-transmitted agents affect cervix, reproductive history affects breast and ovary. relevant only if protective effect can be simulated)	7	1 to 13
Occupation (asbestos, most important agent, lung and bladder, most important sites)	4	2 to 10
Pollution (nothing definite, but air pollution by combustion products probably more important than asbestos or other pollutants of air, water or food	1	<1 to 3
Industrial products (plastics, etc.)	<1	<1 to 2
Medicines and medical procedures (chiefly diagnostic X-rays and post-menopausal hormones, but also therapeutic X-rays and cytotoxic drugs)	1.5	1 to 3
Geophysical factors (ultraviolet sunlight, background radiation)	3	2 to 4
Infection (definite, sexual activity on cervix and hepatitis B on liver, possible, bronchial or intestinal flora, viral effects on immunocytes	5? 10?	1 to 7

Apart from the effects of tobacco on the trends in (chiefly lung) cancer, no evidence whatever appears in the mortality data from the United Kingdom or the United States of any generalized epidemic increases in cancer. A few cancers (e.g. melanoma) are increasing, a few (e.g. stomach and cervix uteri) are decreasing and many are not changing much in either direction except for the decreases in Hodgkin's disease and leukemia, attributable to recent improvements in treatment. In examining trends in mortality data, standardization for age is essential, and attention should be restricted to the age range 0-64 years or the age range 35-64 years recommended by the International Agency for Research on Cancer (4). Elderly people dying of cancer may not be correctly certified, and progressive rectification of such errors may cause artefactual upward trends in cancer death certification rates among the elderly. Examination of incidence rates of cancer, as recorded by special cancer registries which seek notification of all new cases, fatal or not, in a defined population, is subject to various other uncertainties. Some analyses of incidence data from the United States have suggested that large increases in incidence, over and above those attributable to tobacco, are in progress, but these increases may chiefly be artefacts of cancer registration (for a detailed review of the evidence, see reference 2).

Application of Laboratory Tests

This section turns from this brief review of epidemiology to an even briefer review of short-term and long-term laboratory animal tests to determine which compounds are important as potential human carcinogens. The first difficulty is that a large number of such tests exists, each of which will classify a fairly substantial number of chemicals as active, and the researcher is immediately faced with the practical problem of which test results to take most seriously. Good reasons can be cited for expecting that agents which are strongly active in many laboratory tests will cause substantial risks of cancer in humans who are heavily exposed to them, and many may also cause low risks of cancer even at low dose levels. However, much less reason exists for being confident that all the major ways of avoiding human cancer, occupational or other, will be picked out as important by laboratory tests. Table 2 summarizes some general reasons for this assertion.

Table 2. General reasons for the limited applicability of laboratory tests to humans

Both short-term tests and tests on small, short-lived animals may systematically miss whole classes of carcinogens that are particularly relevant to humans.

1. Humans are one thousand times larger and live thirty times longer than mice. By what mechanisms do our cells avoid the cancers which mouse cells would get - mutation avoidance, mutation repair or modification of the probability that a mutated cell will progress into the seed of a cancer?

2. In vitro, human cells can be mutated as easily as mouse cells by most animal carcinogens, but human cells are much harder to transform in vitro than rodent cells. Why?

3. Xeroderma pymentosum patients cannot repair the type of DNA damage inflicted by most Ames-type mutagens. Yet preliminary epidemiological studies suggest they have no marked excess of internal tumours. Why?

4. Many animals have mutagenic intestinal contents; have animals, including humans, adapted to this condition?

5. TCDD, the strongest known carcinogen, is inactive in the Ames test. What does TCDD do?

6. Most laboratory carcinogens cause liver cancer, yet human liver cancer is very rare in the developed world and is not increasing.

7. Roof workers and asphalt workers who ingested large amounts of polycyclic aromatic hydrocarbons and other combustion products via their mucus and saliva have been studied: yet they had no excess of internal cancers.

Although our present state of ignorance about the true causes of human cancer precludes our certainty, review of the known causes listed in Table 1 is not encouraging. For ten years, the inability of experimentalists to produce malignant cancers with inhaled cigarette smoke was used as evidence that the human data must be wrong, and for some time, animal experiments were held to show that radiation was carcinogenic only if given in doses sufficient to cause tissue damage (a claim which was conclusively refuted by later human experience). Asbestos, the most important occupational carcinogen, is not absorbed when fed to animals (and because most of the asbestos that humans inhale eventually goes down the gastrointestinal tract, feeding studies might have been envisaged), and alcohol, the cause of over 10 000 cancer deaths per year in the United States, is not carcinogenic in any other animal system yet studied.

Laboratory tests are of some value (Table 3), but they do not give a simple key to the truth. Hundreds of chemicals should be run through the Ames test (as is being done at present at the National Institute of Environmental Health Science, USA). In addition, some crude quantitative estimates made of the degree of human exposure to each chemical, including, where possible, both exogenous and endogenous exposure because some chemicals can be synthesized in our intestines, etc. The Ames test potency multiplied by the amount of human exposure then gives a product that could be called the "Ames test priority" for each chemical. If this procedure were done, the "Ames test priorities" for a few chemicals might vastly exceed those for all others. These high-ranking chemicals could then be considered for regulatory action, while low priority ones could be ignored (unless restriction could be imposed on them at negligible cost). The cost of restriction (or any other social factors) has deliberately not been multiplied into this priority formula, as such cost factors will inevitably be taken into account and are very poorly known. Definite action against the few high priority agents may, in the practical real world, produce a more rapid reduction in the total human exposure to Ames-type mutagens than might a more broadly based regulatory approach. Too general an approach risks paralysing either the regulators or the regulatees. No assumption exists in this approach that the quantitative human risks associated with Ames-type mutagens are known now or will be known five or ten years hence: maybe they matter and maybe they do not, but the restriction of total

Table 3. Selected laboratory methods for assessing chemicals carcinogenicity[a]

Long-term animal tests (usually rodent feeding)
Short-term tests
- Effects on DNA of isolated cells: Ames test, CHO V79, prophage, SCE, breaks, unscheduled synthesis, etc.
- Effects on DNA of living animals: alkaline elution, mouse spot, sperm, etc.
- Effects on cell behaviour: transformation, micro-nucleus, etc.

[a] For further information see the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.

human exposure to them is prudent. For obvious reasons, such an approach is best described as "priority setting" rather than "risk assessment". Indeed, much of what passes for risk assessment has no remotely reliable scientific basis and is of value only insofar as it aids in priority setting.

Likewise, similar use of the mass of data currently available from animal experiments could be made (preferably adopting as a measure of potency the TD_{50} defined as "that dose which halves the probability of animals remaining tumourless by the end of a conventional standard lifespan of two years"). The "animal priority" could be derived, and attention concentrated on the few agents with the highest priorities, as outlined above. Animal tests are fundamentally no more relevant than Ames tests; they just measure a different range of properties (relevance is determined by the unknown proportion in each system of false positives and false negatives, especially false negatives involving current or future major causes of human cancer).

Clearly from the foregoing discussion, no matter what tests are used or regulations enacted, some human carcinogens will escape notice, to be detected only by their effects after 10, 20 or more years. For chemicals and dusts (which are probably about as equally important as occupational carcinogens), some group of workers manufacturing, reprocessing or using the substance will likely then have a detectably elevated risk of cancer. Both to protect them and to protect the general public (from the effects of low levels of exposure on millions of people), the routine monitoring of cause-specific death rates for many defined groups of workers is important. Such surveillance must not be expensive or it will not be done in many countries. The outline of a scheme that might be inexpensive enough to be practicable in most countries is described in Table 4. More refined methods should probably not be devised for routine use until this basic minimum is reliably undertaken. Indeed, even the subdivision of factories by occupations that is suggested at the end of Table 4 will probably not be practicable as a routine exercise and may well be advisable only as a special project by particular epidemiologists, independent of the national plan to monitor industrial mortality.

An alternative approach to the monitoring of occupational mortality, which cannot be undertaken routinely and which certainly requires design and execution only by experienced epidemiologists, is described in Table 5. Exactly which combination of these several plans is appropriate will vary country to country, depending on the industrial pattern, the availability of death records and the availability of skilled epidemiologists. The minimum which I would urge is occupational mortality among the long-term workers still at, or moved or retired from, each medium or large factory should be monitored in a scheme which makes the cheapest use possible of already existing data. The continued failure to do this minimum in most countries is completely absurd in view of the much greater resources that are currently devoted to monitoring various chemicals and making laboratory studies of their possible effects.

Table 4. Outline of a possible strategy for routine surveillance of occupational mortality (Epidemiologic investigation and identification of occupations at high risk)

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1. Get personnel records back to 1950 (or the start of the factory if more recent) for all factories that operated for more than 10 years and had ever employed more than 1000 workers (include factories which have already closed).

2. Monitor cancer among workers who completed a total of 5 or more years of employment (when a worker completes 5 years, he enters your study, but if he dies or leaves before then, you ignore him).

3. Continued observation of all study subjects, even after they retire or move elsewhere, is essential.

4. Tabulate numbers of deaths from each specific cause by number of years since qualifying for the study (grouped as 0–4 years, 5–9 years, 10–14 years, etc.) irrespective of subsequent work history.

5. Contrast these observed numbers with the numbers that would have been expected if the age-specific death rates had been exactly equal to the national age-specific rates.

6. Deaths will almost always be fewer than expected in study years 0–4 because the men are still healthy enough to be working at the beginning of study year 0. In addition, years 0–4 are within the first 10 years of employment, and real risks may not yet be evident.

7. Interpret the findings cautiously: a $P < 0.001$ excess of deaths from a specific cause is much more convincing evidence for a real effect than a $P = 0.01$ excess would be (conversely, a $P = 0.01$ excess is not wholly convincing unless supported by independent evidence).

Table 4. cont'd.

8. Lack of a statistically significant excess (e.g. $P > 0.1$ does not prove safety, especially if few workers have been exposed for more than 15 years (simply because such results could have arisen by chance does not mean they did so).

9. If a moderately or highly significant excess appears, look up or start laboratory studies of the various agents known to be present, try to discover which subgroups of the workers at this factory seem most at risk and seek out or start mortality studies of similar workers elsewhere in the same country or abroad.

10. Analysis by occupation within each factory is the next stage; even the simple division between clerical workers and process workers may help. However, the difficulties of subdivision of the workers within one factory by their principal occupation may be large. Consequently, such a programme should not be undertaken, except in special cases, until all large factories have their mortality monitored.

11. Likewise, in a few special cases, analysis of a group of workers drawn from many different factories but with a common occupation would be desirable if it does not delay routine monitoring of whole factories (e.g. rayon workers exposed to carbon disulfide).

Table 5. Alternative, or parallel, epidemiology by case control studies

1. Define a group of cancers which is of special occupational interest (e.g. nose, pleura, scrotum, liver, larynx, trachea and bladder at ages 35-64 plus lung at ages 35-50; total = 4% of all).
2. Define a category of cancer or other disease of little occupational interest (e.g. intestinal cancer).
3. Take 5 years of data for all cancers of special occupational interest and find out the major job histories (e.g. those lasting more than 10 years) for each case.
4. Proceed likewise for a sample of controls with the disease(s) which are of little interest, selected to match approximately the predicted sex/age distribution of the cases.
5. Compare the two series to see which jobs stand out.

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