FEATURES

Distorting the epidemiology of cancer: the need for a more balanced overview

The politics of cancer are becoming increasingly polarised with environmentalists taking one extreme view and industrialists the other. Richard Peto argues that a more dispassionate and disinterested approach is required for a realistic assessment both of the risks from environmental carcinogens and of the preventative regulations needed

THERE exist, both in the general environment and in certain occupations, chemical or physical agents which increase the likelihood of human cancer. Our political response to this would, in an ideal world where sufficient knowledge was available, depend on the direct and indirect costs of the various possible measures of control and on how many cancers each such measure would prevent. In the real world, estimates of the direct financial costs of the control of particular agents can easily differ by one or two orders of magnitude, the indirect costs may be grossly exaggerated, or some major indirect costs may be completely overlooked. Worst of all, we have in general no remotely reliable estimates of the numbers of cancers which particular legislative controls would prevent. Consequently, there is wide scope for pressure groups to have considerable influence on public policy.

Historically, the most powerful pressure groups in US society have been the large financial interests, which have almost always put financial advantage before human health. Over the past few years the major tobacco companies have launched massive sales drives in the Third World, which if successful will kill millions of people. (About one in four regular cigarette smokers is killed prematurely by smoking.) In the US, where cigarettes cause well over 100,000 deaths every year from lung cancer or chronic obstructive lung disease, the tobacco industry refuses to accept in public that cigarettes cause either disease, let alone to collaborate in serious public information, and no epithet can suitably describe the collective efforts of their advertisers.

No other industry kills people on anything like the scale that the tobacco industry does, but where other industries have been found to cause cancer (or dust-induced lung disease) in their workers or in the consumers of their products, their immediate response has usually been to delay acceptance of the findings, to minimise their relevance to current practice, and in general to delay or obstruct any hygienic measures which will cost money. Even when human danger has been unequivocally demonstrated, industrial consortia may actively lobby for controls so weak that (as with the new UK government regulations limiting inhaled asbestos to 1 fibre/ml from 1981) they leave no reasonable safety margin. Large amounts of money are available to mount press or TV publicity campaigns about the homely apple-pie virtues of asbestos, journals financed by the tobacco industry run populist articles which misrepresent research results to lay readers, and some US television journalists are explicitly told always to ce or all refer ce to the dangers of smoking.

Even the scientific literature is not immune from distortion by financial interests. The decades-long argument that "threshold" dose levels of carcinogens must exist below which the general population is absolutely safe has not been entirely motivated by the scientific plausibility of the hypothesis. With increasing understanding of the derivation of tumours from single cells acted on by mutagenic carcinogens, industry is slowly abandoning "threshold" arguments in favour of arguments[1,2] (where the biological fallacies[3,4] are somewhat better concealed by the mathematics) that thousandfold reductions in dose can conveniently be "statistically guaranteed" to produce a million-fold or some other enormous reduction in risk.

Even if the scientists who propound such models are disinterested, industrial endorsement of them is not. Much excellent toxicology may be done by industry, and many industrial scientists and managers may be directly and honestly concerned with the prevention of hazards. But so many examples of financially-motivated bias exist that the motives and work of industrial scientists and consultants are inevitably distrusted.

Over the past quarter century, the "environmentalist" camp in North American society has pressed for (and achieved) stricter control of particular carcinogens in the work-place, the general environment, and the diet. Usually, their efforts have been directly resisted by the relevant financial interests. Inevitably, in view of the scantiness of reliable quantitative knowledge about the cancer risks to man of nearly all carcinogens, the argument has polarised. In the politics of cancer, each side takes a very extreme position. Industry usually argues for the irrelevance to man of animal or *in vitro* cancer tests, or minimises the quantitative hazards and exaggerates the costs of control. The environmentalists usually exaggerate the likely hazards and are largely indifferent to the costs of control.

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The vacuum of reliable scientific knowledge is such that each side can find scientists who will maintain in courts, in public hearings or in the scientific literature whatever is politically convenient, and it is important to recognise that scientists on both sides of this debate now have career interests at stake in it.

A particularly good example of the biased writings of politically active environmentalists is Samuel Epstein's *The Politics of Cancer* (Sierra Club Books, 1978, revised in Anchor Press, 1979). Epstein outlines, for university-educated but not necessarily science-educated readers, his view of our present state of knowledge about prevention of death from cancer. He concludes that the cure rates for the major cancers have not been improving much over recent years, but that we do know enough now about the causes of cancer for the testing and regulation of environmental contaminants to prevent the majority of US cancer deaths, and that the main obstacles to our doing so are political rather than scientific. He therefore reviews the scientific and political circumstances surrounding a

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dozen or so disputed consumer products or occupational hazards, providing much fascinating political detail, and then describes at length the internal politics of the various agencies which research, regulate and litigate in Washington.

Epstein's book has been written to inflame political passions against environmental carcinogens, and parts of it are well worth reading. However, the political punch is often achieved at the expense of scientific accuracy and balance. Despite this, the book has already gained wide and apparently uncritical acceptance even among scientists. For that reason, it is worth considering some of the misrepresentations of scientific evidence which it contains, and some of the more general defects in the environmentalist perspective on cancer.

First, a few details. Epstein's book is very useful as a source of reference to original papers, but it is not in itself a reliable secondary reference because the material presented is so often distorted. Sometimes this distortion is due to the effects of Epstein's vigorous campaigning style on his scientific judgement and is, perhaps, forgivable; at other times it appears to be deliberate, which cannot so easily be forgiven.

For example, consider the (by now generally agreed) finding that incorporation of about 5% by weight of saccharin into rat diets gives a few rats bladder cancer, but has no generally accepted effects on any other type of cancer. By human standards, 5% represents a vast saccharin intake (and so, of course, the industrial "Calorie Control Council" have tried to shrug off these findings). To refute the common reaction that "anything given in large enough doses will cause cancer in animals", Epstein's chief argument is to report that 0.01% saccharin has also been shown to be carcinogenic. In support of this extraordinary claim, he presents in tabular form the control and 0.01% data for selected cancers from certain multi-group feeding experiments, leaving out the observations from those same experiments which would have refuted it (see table). This appears to be a deliberate attempt to deceive the reader. It is not a casual slip in a 600-page book, as Epstein devotes twenty pages and two full-page tables to saccharin. His entire table 6.4, entitled "Tumours other than the bladder in rodents fed saccharin", appears to be so subject to artefacts of selection that it provides no evidence that saccharin does cause any rodent tumours other than in the rat bladder.

Saccharin is not an isolated example of bias; indeed, I found that in many places where he discussed data with which I was familiar inaccuracies were present, almost always in the direction of accentuating the need for battle with the devils of industry.

Turning to more important matters, Epstein asserts that any benefits from the "less dangerous" cigarettes which the tobacco industry has developed will be outweighed by people increasing their consumption to get more nicotine, and he is therefore in many places particularly scathing about (or even downright opposed to) research into changed cigarette composition. This is a distorted prerspective on one of the more promising immediate means of preventing fatal cancers, a quarter of which in America are currently due to smoking.

Smokers of "less dangerous" cigarettes have already been found in various epidemiological studies to have disease rates which are materially lower than smokers of other cigarettes[6,7]; at autopsy they have far fewer "pre-malignant" histological changes in their bronchi[8] and, perhaps due to the changes in cigarette composition 10 or 20 years ago male lung cancer death rates in early middle age are now decreasing in North America, in Britain and in Finland.

After lung, the next commonest fatal cancers in the US are those of the breast and the large intestine, for which the most striking epidemiological finding to date is a 90% correlation between fat consumption in different countries and their breast or colon cancer rates (see figure; similar correlations exist for colon cancer[10]). Epstein suggests that dietary fat may merely be acting as a vehicle for fat-soluble pesticides and industrial chemicals, which predictably emerge as his villains yet again. However, his suggestion is implausible: countries with high levels of contamination do not stand out from the general cancer/fat relationship, colorectal and breast cancer were common long before the widespread use of pesticides, and in experimental animals high-fat or low-fat diets can greatly enhance or reduce the risk of cancer[11]. Something more interesting is waiting to be discovered in our diet than simple contamination by carcinogens.

'Scientists on both sides of the environmentalist debate now have career interests at stake'

The fat-associated and smoking-derived cancers collectively account for more than half of all cancer deaths, and people concerned with cancer politics should try to understand them considerably more accurately than Epstein appears to. One can list many other instances where Epstein's content or style are misleading or unbalanced. For example:

- The discussion of alcoholism and cancer is entirely erroneous because of failure to standardise properly for age.
- One of Epstein's chapters ends: "Eisenhower warned against the growing national threat of the military-industrial complex. The medical-industrial complex now appears to be as serious a threat".
- There is idealisation of the value of long-term animal tests with concomitant denigration of the value of the Ames test and other short-term tests. This is one of Epstein's most inexplicable errors of scientific judgement, unless he wants cancer tests to be difficult and expensive for industry.
- He is irritatingly puritanical, sneering at "the plastic age which symbolises how the value of our lifestyle has been degraded".
- He seeks by stylistic tricks to attribute to oral contraceptives some of the established hazards of hormone replacement therapy and of diethylstilboestrol.
- He claims that cancer costs the US economy over $25 billion per year. (In fact, cancer must be prevented for humane, not for economic reasons; without cancer, there would be three or four million more retired North Americans to support, costing over $25 billion per year).

And so on. He seems so certain about everything — how can anybody be justified in being so certain about so many details? Sometimes I know he's wrong, but more often (especially in the many places where inconclusive scientific results are presented as established fact) I know that nobody knows for sure. Lewis Thomas once wrote, in another context: "The sceptics in medicine have a hard time of it. It is much more difficult to be convincing about ignorance concerning disease mechanisms

Table: Data from OTA report[5] on the tumour sites selected for presentation in Epstein's book to substantiate the claim that 0.01% saccharin is carcinogenic. Groups selectively omitted in Epstein's book are marked with an asterisk. These omissions substantially alter the implications of the original data.

Saccharin dose (% in rat diet; these doses have no material effect on longevity)	Male or female lymphosarcomas (FDA, 1948)	Female breast (FDA, 1973)	Male breast (FDA, 1973)
0 (control)	0/20* (0%)	6/26 (23%)	6/29 (21%)
0.01	8/14 (57%)	14/30 (47%)	14/25 (56%)
0.1	5/16 (31%)*	13/34 (38%)*	9/27 (33%)*
0.5	2/15 (13%)*	—	—
1	1/18 (6%)*	12/30 (40%)*	8/27 (30%)*
5	10/17 (59%)	12/27 (44%)*	7/25 (28%)*

*Omitted in Epstein's book.

*In addition to these 20, since some other sweeteners were being tested concurrently, 34 other control animals were studied in the same experiment, and the 1977 OTA review of these data, considering all the control animals to be equivalent, cited 9/54 control lymphosarcomas. (0/10 saccharin controls of each sex were studied, not 0/20 as Epstein inadvertently indicated.)

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than it is to make claims for full comprehension, especially when the comprehension leads, logically or not, to some sort of action. When it comes to serious illness, the public tends, understandably, to be more sceptical about the sceptics, more willing to believe the true believers."

Epstein (like many others) is unjustifiably definite about three major issues. He seems certain that even after the effects of cigarettes have been allowed for, Americans live in an era of rapidly increasing cancer rates. But trends in recorded cancer death rates (and, perhaps more so, recorded incidence rates) over the past quarter century are biased upwards (since the cure rates for the major cancers have not materially improved) by improvements in medical care and cancer counting. These improvements have

'The NCI-NIEHS report shows how a group of reasonable men can collectively generate an unreasonable report'

affected all sectors of US society, but most particularly old people and previously poor people, especially blacks. Epstein, along with most other US commentators, does not allow for these biases even to the limited extent of restricting his attention to trends in age-specific mortality rates among middle-aged whites, where they might be expected to be least prominent.

Among middle-aged whites during the past quarter century, cancer cure rates have not materially improved, but some US cancer mortality trends seem to be genuinely down (stomach, cervix) while some seem to be genuinely up (pancreas, melanoma, and certain lymphomas). I can discern no net pattern other than that due to the massive effects of smoking on lung cancer, although no extension to 1978 yet exists of the excellent 1950-67 trend analyses in NCI monograph 33. In Britain, the same is true[12] as long as we examine mortality in middle age. (Interestingly, although Epstein emphasises that bladder cancer death rates among whites in the industrial north-eastern US are high, this may not be chiefly due to any current industrial hazard, for they have been decreasing both relatively and absolutely for a quarter of a century[13].)

Epstein also seems certain that the majority of human cancer is caused by chemical and physical agents in the environment and could be prevented by their testing and regulation. There is no sound scientific basis for this certainty. Since the cancers (lung, breast, large intestine) which are commonest in the US are rare in certain other countries, and *vice versa*, they probably really are preventable, but (see figure) not necessarily by regulation of any environmental pollutants or food additives. Indeed, one of the most intriguing animal findings is the effect in many studies of gross aspects of diet on cancer; for example, mice randomised between 5g of food once daily and *ad lib* consumption averaging 6g/day of the same food, had respectively 8% and [illegible]% spontaneous mammary tumours, and the role of dietary fat[11] has already been discussed.

Thirdly, Epstein seems certain that at least a quarter of all cancer deaths are attributable to occupational exposure to carcinogens. There is as yet no good evidence for hazards of anything like this magnitude, and there is clear evidence that many of his particular claims are exaggerated. For example, he says that asbestos has led to approximately 50,000 deaths per year in the US from cancer and related disease (referencing a paper by Selikoff[13] which actually neither makes nor implies any such claim). This is sheer nonsense; of 50,000 asbestos deaths, several thousand should be certified as being due to pleural mesothelioma, yet only several hundred per year are thus certified.

Likewise, Epstein cites with approval (indeed, he describes it as being of "epochal significance") Health, Education and Welfare Secretary Califano's absurd 1978 estimate, in a speech to labour union leaders, that as many as half of the 8-11 million workers who have been exposed to asbestos could develop serious diseases such as cancer or asbestosis. In his second edition, Epstein draws extensively on Califano's source, a curious but extremely influential document which has been circulating privately for the past year or more. This unpublished typescript, with no listed authors, was prepared by a working group of nine well-known scientists including Arthur Upton and David Rall, the National Cancer Institute and National Institute of Environmental Health Sciences directors,

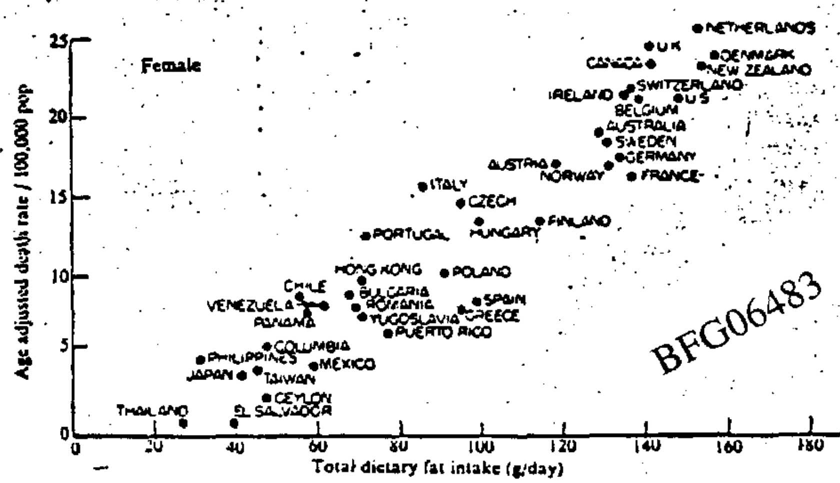
'Present day cancer rates and trends are probably not dominated by occupational carcinogens or environmental pollutants'

both of whom still seem more ready to defend than to repudiate it.

Entitled "Estimates of the fraction of cancer in the US related to occupational factors", it shows how a group of reasonable men can collectively generate an unreasonable report. The group multiplied the 12 million workers exposed in any way in 1972-4 to any of asbestos, As, Ni, Cr, benzene or petrochemicals by the very large risk factors (e.g. fivefold lung cancer excesses) typical of much more extensively exposed industrial populations, finally multiplying again by "4-5" to allow for the additional cancers that will be caused by these six agents among workers exposed to them at times other than 1972-4. (In casual disregard of dosimetry, this whole process is very like predicting 100,000 occupational lung cancer deaths per year among non-smokers due to their exposure to other people's cigarette smoke at work, "since 20% of heavy smokers get lung cancer").

These assumptions "predict" over 200,000 extra respiratory tract cancers per year in the near future due to the above six agents alone (and are the sole source of the currently widespread prediction of "20-38%" of cancers being due to occupation). But, in reality, fewer than 90,000 males/year get respiratory tract cancer in the US (and most of these are due to cigarettes and not to occupation at all), and moreover the US male rates in the first 25 years of working life are currently decreasing! A prediction of 100-200,000 extras due to the above six agents is clearly

Figure: data[9] plotting for 39 countries age-versus total dietary fat (animal or standardised breast cancer death rate vegetable).



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very unrealistic.

The unreality of the whole method is further highlighted by the fact that the assumptions "predict" 7,300 × 4.5 nickel-oxide induced occupational lung cancers/year. Since nickel refining causes a lot of nasal as well as lung cancer, we would presumably then also soon "expect" something like 13,000 nasal cancer death certificates per year among nickel workers. Nickel has already been widely used for decades, so many thousands of these should presumably already be evident. In reality, each year in the US population there are only 300-odd male and 200-odd female nasal cancer death certificates. The majority of these are not ex-nickel workers and no marked trends are evident. This demonstrates the unsoundness of the NCI-NIEHS methodology.

Unfortunately, such exaggerated estimates are so much what many people want to believe of modern society that they have now achieved a life of their own, and although they are utterly without foundation they are quoted widely, repeatedly and reputably both in the lay and scientific press. In Geneva the International Labour Organisation reportedly endorsed them, as did the Toxic Substances Strategy Committee in their recent draft report to the US president[16], and they have been used in OSHA to emphasise the need for stricter laws. Most recently, the UK trade union the Association of Scientific, Technical & Managerial Staffs (ASTMS) released a policy document which appears to have been strongly influenced by Epstein's book, and which is notable for its prominent but erroneous assertion, derived solely from the foregoing unpublished US typescript, that 20-40% of current UK cancer deaths are caused by occupational carcinogens.

Epstein now claims that these exaggerated estimates seriously underestimate the impact of industrial carcinogens. There is obviously a valid political need to exaggerate the importance of the preventive measures we can already implement, but in the long run we do also still need to discover the main preventable causes of cancer other than smoking. Bearing both these needs in mind, there are limits beyond which it is not even politically wise to distort the science of cancer, and some of today's exaggerations may well transgress those limits. Reliable reviews of the known and suspected causes[17,18,19] of human cancer and of trends in British death rates[12] should be more widely known.

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My criticisms of Epstein's science, however, must be viewed in the light of the continued resistance of many industries to reasonable controls. One has only to read some of his descriptions of industrial behaviour to see where his passion comes from, and a suitably sceptical reader could derive much important information from the dozen or so detailed case-histories of particular carcinogens that make up the bulk of this book. But, although I cannot prove it, I suspect that environmentalists as a whole (including Epstein and those US and British trade unions which have already modelled their public statements closely on his book) would be better respected and could therefore press more effectively for controls in particular instances if their overview of cancer was more balanced in the following ways:

'The politics of cancer is dominated on both sides by exaggeration'

- if they accepted that present-day cancer rates and trends are probably not dominated by occupational carcinogens or environmental pollutants (especially since they could still warn that future rates might perhaps be so dominated unless present-day exposures are regulated[20]);
- if their chief concern was with the identification and control of the few major determinants of human cancer (or, in an industrial context, the few major industrial carcinogens) rather than the large multitude of sins which Epstein denounces;
- if they discussed the costs and benefits of research into the control of toxic substances in the context of other possible ways of improving longevity (bad diet and tobacco in rich countries, malnutrition and infective and parasitic diseases elsewhere);
- if they took the costs of imposing restrictions on society more seriously. Epstein's general assertion is that the total direct and indirect costs of failing to regulate usually exceed the real costs of the testing and regulation, but I suspect that this is a slogan to avoid political embarrassment rather than a carefully researched conclusion;
- if they accepted that for most toxic chemicals we have both qualitative and vast quantitative uncertainty about the health benefits of restriction.

Particularly, even if the sort of grossly biased interpretation which Epstein applied to the animal saccharin data is avoided, the results of animal experiments simply are not an uncomplicated key to human hazard identification. First, moderate alteration of gross aspects of the diet of animals greatly modifies their spontaneous tumour onset rates[11] (so, for example, increasing the sugar content of rat diets may increase their cancer rates more than the equivalent amount of dietary saccharin would have done[11]). Also, any chemical which causes proliferation or necrosis in any organ that is subject to spontaneous cancers is likely to modify the onset rate of tumours in that organ, and since the aim of most animal experiments is to study a dose which is nearly, but not quite, sufficient to cause significant weight loss or mortality within three months, it is not surprising that so many chemicals at such doses can cause cancer in animals.

However, it may be that where adversary politics operate one needs views at both extremes in order to get a balanced outcome. And there is a possibility that over-emphasis on the avoidance of scientific error would emasculate the environmentalist passions and merely lead to my own rather inactive conservatism. (After all, no scruples about scientific certainty of safety usually precede the widespread introduction of new chemicals, so should the imposition of prudent restrictions require absolute proof?)

Environmentalists with biased judgements and a quasireligious certainty of right will fight more battles than any reasonable sceptic would do, and even if their victories confer 10 or 100 times less benefit on humanity than they imagine, they will in the long run probably do more good than harm — unless they materially reduce food production, distort research priorities, or direct attention away from the smoking problem in the process. Epstein justly quotes, from the 1st century AD, the Plutarch chronicles: "He who in time of faction takes neither side shall be disenfrachised". So, I feel, should both environmentalists and industrialists who suppress or deliberately misinterpret data, but they probably won't be. For the moment, the 'politics of cancer' is dominated on both sides by exaggeration. □

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