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Control of Industrially Induced Cancers

by Richard Peto*

Nowadays, government agencies limit the permitted levels of some carcinogens in industrial environments. Such regulatory agencies should also routinely consider whether to limit the number of years that individuals may work in certain such industrial environments. Although such restrictions would be inconvenient to administer (just as further restrictions on permitted levels would be), the proportion of industrial cancers thus prevented might be substantial.

In order to transform a normal tissue cell into a cancer cell, heritable changes must be made to the genetic material of that cell. In animal carcinogenesis studies, "initiators" and "promoters" have been identified; if to the skin of mice we apply first an initiator and then, either soon afterwards or much later, a promoter, many small tumors will result, but if these agents are given in the wrong order there will be little or no effect. The tumors thus produced are not usually malignant, but a few may later progress into being so, especially in the presence of suitable stimuli. Presumably, similar phenomena exist in humans; different agents are required to accelerate different stages of alteration of a normal human cell into a cancer cell, these stages can only occur in certain orders, and "initiated" human cells can remain dormant, but dangerous, for most of the human lifespan.

Any particular cell in a human tissue, even after is has been "initiated," must have a very low probability of going through all the remaining changes needed in order to be malignant; if, as might be the case, three further changes are needed, each moderately improbable, the chance of all three happening to this particular cell is the product of three separate small probabilities. Now, consider two cells, one initiated 10 years ago and one 20 years ago. Each of the three separate subsequent changes has twice as long to happen, and hence about twice the chance of occurring, in the cell initiated 20 years ago, and thus the overall risk of malignancy might be about eight ($2 \times 2 \times 2$) times as big. (In a cell initiated 50 years ago, the overall risk of malignancy might be more than a hundredfold bigger than in a 10-year cell.) Initiating agents might thus be less dangerous for older people, since natural death will come sooner and will cut short the time each initiated cell has to suffer the subsequent stages of malignant alteration. These considerations could obviously have practical implications for regulating the ages of workers allowed into carcinogenic industrial environments.

Unfortunately, if a "promoting" agent affects only the last cellular alteration in the series of changes, the opposite is true: the old are likely to be more vulnerable than the young since, compared with young adults, people in late middle age may have many more cells which have suffered all but the final state and are at risk of promotion to full malignancy. Although, perhaps, the death of an older worker is less to be mourned than the death of a young one, a larger number of cancers in older workers must be worse than a small risk in the young. There is thus no one simple safety rule for carcinogenic environments such as "employ old workers" or "employ young workers," and available epidemiological evidence is, unfortunately, unlikely to be sufficient to tell regulatory agencies whether the old or the young should be excluded from a particular industry.†

An easier restriction for regulatory agencies to impose, since the problem of which way round to

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†Since many initiators are also mutagens, another advantage of preventing younger workers (who might subsequently have children) from working in such environments might be that subsequent generations are thereby protected from germ line mutations.

impose it does not need scientific study in each particular case, is the prevention of all who have worked in a particular carcinogenic environment for more than (say) five years, or perhaps 10 years, from continuing to do so. The rationale of this restriction is that if the industrial environment has to affect a particular cell twice or more to cause cancer, then it is better to employ two people for five years each than one person for 10 years, since the risk to a five-year employee is less, perhaps much less, than half the risk of a 10-year employee. This is because the probability of two industrially determined alterations to a particular cell is only a quarter as likely, if each separate change is only half as likely in five years as in 10. (If more than two changes are industrially induced, or if two industrially induced changes which have to be separated by a "spontaneous" change are involved, the benefits of restricting exposure duration might be greater still.) If, in most cancers caused by a particular industrial environment, only one of the necessary cellular alterations was industrially induced, there will, unless the age structure of the work force is thereby changed favorably or unfavorably, be no net effect from restricting the maximum permissible duration of employment to a fixed number of years.

Our suggestion would be particularly relevant when the evidence of carcinogenic risk is not yet definite (which is usually the case at first), or when the actual causative agent is not known and cannot therefore be legally controlled. For example, at the first reasonable suggestion of a carcinogenic risk in a particular industrial environment, it would be sensible to move everybody who has worked there for more than 10 years out of it, and then try to replace most of those who started there over five years ago by fresh staff fairly soon afterwards, while scientific investigations proceed. Depending on the alternative jobs available in the industry concerned, this rotation of staff may sometimes be so easy that medical adviser to industry could recommend it as a safety precaution long before formal controls can be imposed.

Finally, we note one restriction which medical advisers to industry could recommend but which cannot be imposed by law: the exclusion of all cigarette smokers. Because different carcinogens can enhance each others' effects, the large majority of lung cancer induced by industrial environments such as the asbestos industry could probably be avoided by this curious regulation, and if in addition it persuaded many cigarette smokers to stop, then that particular industrial hazard might, in the long run, save lives!