Interpretations of Epidemiologic Data*

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SUMMARY

Epidemiological observations have a special part to play in cancer research because of the limited possibilities for human experiment. Such observations cannot prove that an agent is the cause of disease in man—not even when coupled with the results of animal experiments—and decisions with regard to etiology usually have to be made on the basis of evidence that is logically incomplete. In these circumstances it may be desirable to attempt to prevent the disease in the manner suggested by the evidence and to see whether the results of the action support the conclusions on which it was based. This policy has paid well in regard to occupational cancers, and examples are given illustrating how similar epidemiological observations can be used to test the validity of current opinions concerning the etiology of other cancers.

For most cancers epidemiological evidence is limited to showing that the incidence varies from place to place or from time to time, and it has so far failed to link these differences with differences in the prevalence of any specific agent. The discovery of such links is the greatest contribution that epidemiology can hope to make, but it may also be able to contribute in another field that has been regarded as the province of the laboratory worker—that is, in the study of the mechanism of carcinogenesis.

Examples include the observation that, after a single exposure to radiation, the incidence of leukemia rapidly rises to a maximum and then slowly falls; it is possible therefore, that those cancers that normally show a similar type of distribution with age are also due to brief periods of exposure to the agent concerned. Prolonged exposure, as occurs with cigarette smoke, gives rise to a continuous increase in incidence which is similar to that seen with most of the common epithelial cancers. In these cancers the incidence increases approximately in proportion to the sixth power of the age; but other mathematical relationships can be adduced, and it is dangerous to build theories on this relationship alone. Data have been obtained for the relationship between the intensity of exposure and the resulting incidence, and for the effect of ceasing exposure and of starting exposure at different ages. All these results must be taken into account in constructing an adequate model. If they sometimes appear to conflict with laboratory experiments it may be because the conditions of life for laboratory animals do not reflect the complexity of the human environment.

In studying the etiology of disease we can seek information in three ways: We may devise experiments in the laboratory, using animals as our basic material; we may experiment directly on man; or we may observe and record what is happening to man in the course of his ordinary life. Each method has its strengths and its weaknesses,
and each has its special contribution to make to the advancement of knowledge. In the study of cancer, however, we are severely limited in the extent to which we can make use of human experiment—both for ethical reasons and because of the time scale of the disease. Opportunities may occasionally present themselves—particularly for what may be called experimental epidemiology, when there is suggestive but incomplete evidence of how to prevent the disease—but, in the main, we have to rely on the other two methods.

Of these, animal experimentation offers the most obvious advantages. The range of possibilities is enormous, and the imagination of the investigator can be given free rein; moreover, by good design and sufficient repetition it is possible to be virtually certain of the relationship between cause and effect. It has, however, the disadvantages that it may not be possible to reproduce in sufficient detail the relevant human conditions, limitation of numbers makes it difficult to study low dose effects, and an element of uncertainty is necessarily introduced by generalizing from one species to another.

The advantages and disadvantages of studying the results of Nature's experiments on man—some of which, it must be admitted, are apparently very ill planned—are almost exactly the reverse. Relationships may be suggested which would never otherwise be thought of, the results are certainly relevant to the problem of human disease, and the large numbers and the intensity of the medical care to which men are subjected may make it possible to recognize quite small effects. The range of possible observations is, however, strictly limited, and it may be difficult to distinguish cause and effect from an unimportant and secondary relationship.

Despite this last difficulty, the observation of Nature's experiments has contributed a great deal to knowledge about cancer. It is axiomatic that observation alone cannot prove, in the strict sense of the word, that any particular agent is the cause of disease in man—nor, it may be added, can observation coupled with the results of experiments on animals. We must, therefore, recognize that, in studying the etiology of cancer in man we shall usually have to take decisions on the basis of evidence that is short of proof. In these circumstances it is understandable that some should take the view of the Oriental historian who was asked at a recent international conference what he thought were the principal effects of the French Revolution, and is alleged to have replied that it was too early yet to say. A more constructive attitude, however, is to try to prevent the disease in the ways suggested by the evidence and to see whether the results of the action taken will themselves elucidate the correctness of the conclusions.

THE TEST OF PREVENTION

This policy has paid well with regard to occupational cancers, and there is no reason why it should not also pay in other fields—though it may be more difficult to apply. For example, recent work (21, 27), added to the original observations of Duffy and Fitzgerald (16) and Simpson and Hempelmann (29), leaves no reasonable doubt that doses of x-rays of the order of 300 rads or more to the neck of infants can produce carcinoma of the thyroid. Such doses used to be given for the treatment of a supposedly enlarged thymus, and abandonment of the treatment ought to lead to a reduction in the number of cases of thyroid cancer. The reduction will be small, but the total number of cases is also small, so that the proportional change may be large. An opportunity for demonstrating it may be provided by comparing the mortality from thyroid cancer in Britain and the U.S.A. During the decade 1950–1959 the rates per million persons were almost identical at ages over 30 years (10). At younger ages the mortality was about double in the U.S.A.—which accords with the fact that thymus irradiation in infancy was used extensively in the U.S.A. but seldom, if ever, in Britain. If, therefore, the observed association between irradiation and thyroid cancer denotes cause and effect and is not due, e.g., to an independent association between enlargement of the thymus and the susceptibility to thyroid cancer, we may hope to see abandonment of the treatment reflected by disappearance of the difference between the mortality rates in the two countries.

Similar evidence may also be obtained relating to cigarette smoking and lung cancer. The fact that the mortality from lung cancer is lower among ex-cigarette smokers than among men who continue to smoke (15, 15, 20) is one of the reasons for believing that cigarette smoking causes the disease. Data obtained from a 10-year follow-up of doctors are illustrated in Chart 1. In this study smoking histories were recorded at the beginning of the period of observation and again 7 years later. It was, therefore, possible for the last 5 years of the study to take into account the considerable changes that had taken place during the first 7 years. The rates have been calculated from the numbers of years at risk of developing the disease in each ex-smoking category and are standardized for age and amount smoked. To some extent the reduction in the first 5 years may be an artifact,

1 Doll and Hill, data to be published.
since doctors who know they have lung cancer may be disinclined to change their habits; but when we allow for this it is still clear that there must have been a very substantial reduction within 10 years and that the reduction becomes greater the greater the length of time smoking has been stopped—at least up to 15 years. It can be shown that these results do not arise because of differences in the age at starting to smoke; but it is possible to argue that the men who gave up are, in other respects, more like nonsmokers than continuing cigarette smokers, so that the observations could be explained if nonsmokers and ex-smokers were not susceptible to lung cancer for other reasons—for example, because of their genetic constitution. The same argument can also be extended, even though in so doing it may become so tenuous as to be almost transparent, to explain why the disease is so rare among Seventh Day Adventists, who are forbidden by their religion to smoke (38). Ideally, one would like to observe a group of cigarette smokers and be able to persuade a random sample of them to stop. If, however, this experiment is impracticable—as I suspect it is—we may have to be satisfied by observing the trend in lung cancer mortality that follows a reduction in cigarette consumption in a whole community. Unfortunately, such data may also be open to several interpretations, since the prevalence of other environmental factors—e.g., atmospheric pollution—may be reduced at the same time as cigarette consumption. Better evidence would, therefore, be obtained if a section of the community whose mortality was known to be similar to that of the community as a whole made a radical alteration in its smoking habits while the remaining sections of the community maintained theirs unaltered. Evidence of this sort may perhaps be obtained by studying the mortality of doctors. In recent years large proportions of British doctors have stopped smoking cigarettes, and it will be interesting to compare the trend in mortality among them with that observed in the country as a whole.

The numbers of cancer for which we may seek evidence of this type is still small. Apart from the two that have been mentioned, the most outstanding is, perhaps, cancer of the mouth which, throughout India and many other parts of Asia, is closely related to chewing various combinations of betel, tobacco, and lime. Another example is cancer of the penis, which probably never occurs if circumcision is performed within a few weeks of birth. The religious aspect of the operation would, however, make it very difficult to introduce it on a large scale in some areas, although if it were carried out in infancy it would probably bring about a major reduction in the incidence of cancer throughout large parts of Africa and Asia. In Uganda, for example, cancer of the penis accounts for 10 per cent of all male cancers and is the commonest type of cancer in man (19). In Europe and North America the incidence is so low that a preventive experiment of this type would not be justifiable. The position might be different if it were shown that circumcision in the male could prevent cancer of the cervix uteri in the female. The evidence for this is, however, conflicting, and, in my opinion, it is insufficient to justify the experiment.

For the great majority of cancers the epidemiological evidence is limited to demonstrating that the incidence varies from place to place or from time to time, and it has so far failed to link these differences with differences in the prevalence of some specific etiological agent. That such links exist is virtually certain, and their discovery is the greatest contribution that epidemiology can hope to make to the study of cancer. I would, however, like to suggest that it may also be able to assist in another field that has been largely regarded as the province of the laboratory worker. I have in mind the possibility that studies of the time relations between exposure to a carcinogen and the development of the disease and quantitative studies of the effect of modifying the duration and intensity of exposure may help in formulating and testing hypotheses about the mechanisms by which cancer is produced. In the last few years a substantial amount of data of this type has been collected, and the results permit a few tentative conclusions.
MECHANISMS OF CARCINOGENESIS

Induction period after a single exposure.—Information about the length of the induction period following a single exposure is available only for radiation-induced cancers. Data on the incidence of leukemia among persons exposed to the atomic bomb explosions in Hiroshima and Nagasaki within 1500 meters of the hypocenter have been reported by Brill, Tomonaga, and Heyssel (5). Estimates of the incidence among patients given radiotherapy for ankylosing spondylitis are illustrated in Chart 2. In each population the incidence rose to a peak a few years after exposure, fell, and subsequently remained fairly steady at a level that is substantially above that in the general population. Whether the incidence will eventually decrease to the usual level remains to be seen, but it is already clear that the data are unlikely to fit the simple hypothesis that induction periods are distributed normally about a mean. They would more easily fit the sort of model described by Neyman and Scott in which the production of the disease requires a second stimulus that occurs with a constant probability and the upswing is largely due to the time required for the tumor to grow sufficiently to produce a clinical effect.

It should be noted, however, that, although the general pattern of the distribution of induction periods is similar in the two series, they are not identical—the peak incidence being, for example, in the 4th or 5th year after irradiation in the spondylitic series and about 2 years later in Japan. Whether this pattern is limited to leukemia or whether it also appears with other cancers should be evident soon, since data have accumulated on the incidence of thyroid cancer in Hiroshima and following radiotherapy in infancy and on the incidence of various types of childhood cancer following irradiation in utero (23, 31). If the pattern is confirmed it would seem reasonable to suggest that those tumors that normally show a rising incidence followed by a fall—e.g., acute lymphatic leukemia, sarcoma of the long bones, and teratoma of the testis—are also primarily the result of a single exposure.

Usual relationship between incidence and age.—However, if this is the pattern to be expected with a single exposure, how are we to explain the rapid and continuous rise in incidence with age that occurs in most of the common cancers? This rise, which begins at about age 20 years and continues until age 80 years and possibly beyond, is one of the most striking characteristics of human cancer—and one of the most difficult to explain. It occurs characteristically in cancer of the skin, in most of the epithelial cancers of the respiratory, digestive, and urinary tracts, and in chronic lymphatic leukemia and myelomatosis—which, according to Burnet (9), may also be epithelial in origin. For these cancers a rough working rule is that the incidence increases approximately in proportion to the fifth or the sixth power of the age—i.e., when age is doubled the incidence is increased ca. 32–64 times.

Representative data for mortality rates from cancer of the stomach in Japan and in England and Wales are illustrated in Chart 3. Since the fatality of this disease is so high and its course so short the mortality rates have been taken to provide reasonable estimates of incidence: the age has, however, been reduced by 21/2 years to make some allowance for the duration of the clinical course. Mortality and age are both shown on a logarithmic scale, so that a linear relationship indicates that the mortality is proportional to a power of the age. Both sets of data lie approximately on a line with a slope of 5.1:1, indicating that the incidence increases slightly more rapidly than the fifth power of the age.

This type of relationship has been reported several times in the last 10 years and has been made the basis for several different models of the mechanisms of carcinogenesis. Nordling (34) and Stocks (32) accounted for it by postulating that the production of cancer required between five and seven independent events or mutations. Fisher and Holloman (18) suggested that it might mean that seven contiguous cells had to be altered before the altered cells could break loose from control and appear as a cancer. Later Armitage and Doll (2) and Fisher (17) postulated that only two or three changes were needed, but that each change gave the daughters of the affected cell an advantage over normal cells in that they multiplied more.

Chart 2.—Per cent of cases of leukemia among patients with ankylosing spondylitis at different periods after treatment by irradiation, after Wise (34).

\[ \text{\% of cases} \]
\[ \begin{array}{|c|c|c|}
\hline
\text{Years after irradiation} & \text{1} & \text{2} & \text{4} & \text{6} & \text{8} & \text{10} & \text{12} & \text{14} \\
\hline
\text{Cases} & \text{25} & \text{15} & \text{10} & \text{5} & \text{2.5} & \text{1} & \text{0.5} & \text{0.125} \\
\hline
\end{array} \]
rapidly; and this last hypothesis has been developed systematically by Burch (6-8).

In my opinion, however, these data provide unsafe grounds for the construction of a detailed hypothesis. First, the data themselves are insufficiently refined. Incidence rates have generally been equated with mortality rates, and these fail to distinguish between the various histological types. Moreover, the relationship between mortality and incidence is not necessarily the same at all ages; when fatality and duration of survival vary with age (as they do in carcinoma of the thyroid), this can again distort the pattern. Second, age at diagnosis and, still more, age at death are separated by several years from age of first pathological appearance of the disease. The interval may be as short as 15 months in acute leukemia, but it may be much longer; and the average duration is unknown within wide limits. Third, accuracy of diagnosis varies with age; diagnosis is less complete at old ages, and at these ages the incidence of some cancers may be seriously underestimated. Finally, few major cancers in any country show a constant incidence from year to year—cancer of the stomach in Japan is, perhaps, the most important exception—and the relationship with age will be affected by variation in the extent of exposure of men born at different periods.

Another difficulty is that the range of observations is insufficient to discriminate with confidence between several different mathematical relationships. For example, Chart 4 shows the estimated cumulative mortality from gastric cancer in the absence of other causes of death, plotted on a probability scale against the logarithm of the age (reduced, as previously, by 2½ years). When plotted in this manner a linear relationship is comparable to that commonly found in pharmacological experiments in which the proportion of affected animals is plotted against the logarithm of the dose, and this is interpreted to mean that the susceptibility of the animals to the drug is log. normally distributed. Between the ages of 30 and 80 years—the range over which the log. log. relationship has been reported—the relationship could also be interpreted to mean that dose accumulated with age and that the rapid increase in incidence with age was a reflection of the variation in susceptibility—a mechanism similar to that proposed by Sacher (26). At younger ages, however, the log. log. relationship fits the data much better.

The use of lung cancer as a model.—Clearly we cannot be dogmatic about the exact nature of the relationship, and conclusions based on it can only be tentative. That is not to say that we shouldn’t attempt to draw conclusions, but we ought to base them on a great deal of other evidence as well and not on these data alone. At the present time other quantitative data are largely limited to radiation-induced cancers and to lung cancer among cigarette smokers, and there is some doubt whether this latter type of cancer can be regarded as a representative model. In many countries the death rate from lung cancer has not increased progressively with age, but has reached a maximum between 55 and 75 years of age and then decreased. Korteweg (22), however, pointed out that this pattern could be expected when the prevalence of an environmental cause was increasing. In these circumstances the mortality among men, e.g., 75-79 years of age, might be low in comparison with the mortality of men born 10 years later and yet still be high in comparison with the mortality among younger men born at the same period.

That this is the probable explanation for the anomaly has been confirmed by subsequent expe-
rience. In England and Wales, for example, the mortality among men has now become stabilized at all ages under 60 years. At older ages the mortality continues to increase rapidly, and the shape of the curve relating age and mortality, illustrated in Chart 5, is beginning to assume the characteristic pattern. Further evidence can now be obtained by examining the mortality among men with known smoking habits. Data obtained from the follow-up of British doctors show that their mortality varies with age in a manner similar to that recorded for the country as a whole. The smoking habits of the doctors, however, are known to vary among the different age groups, the young containing many nonsmokers and moderate cigarette smokers, the middle-aged containing many moderate and heavy cigarette smokers, and the old containing many pipe smokers and ex-smokers (Table 1). These differences must be expected to have a substantial effect on mortality at different

![Chart 5](chart5.png)

**Chart 5.**—Change in the death rate from lung cancer in England and Wales at different ages between 1945–46 and 1960–61.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMOKING HABITS OF BRITISH DOCTORS OF DIFFERENT AGES (1951)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Non-smokers</th>
<th>Ex-smokers</th>
<th>Current smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pipe or cigar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Light</td>
</tr>
<tr>
<td>Under 35</td>
<td>27</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>50-59</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>75 or over</td>
<td>14</td>
<td>31</td>
<td>23</td>
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</tbody>
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ages. When, however, the age distribution is examined among continuing cigarette smokers and standardized for the amount smoked, the results are different. The mortality is then found to increase progressively until 85 years of age (Chart 6). Moreover, the rate of increase is similar to that found with the majority of other epithelial cancers—i.e., the incidence is proportional to approximately the sixth power of the age.

It seems probable, therefore, that lung cancer among cigarette smokers can be taken as a representative epithelial cancer and that the rapid increase in mortality with age, characteristic of so many cancers, may be interpreted as the result of repeated exposure to carcinogenic stimuli of approximately equal strength. It follows that we can tentatively use the quantitative data obtained in studies on lung cancer to clarify the nature of the mechanisms involved.

Dose-response relationship.—One interesting set of data relates the incidence of the disease to the number of cigarettes smoked daily—i.e., presumably, to the dose of the agent. The most accurate data are obtained by excluding (a) men who have also smoked pipes or cigars, since it is uncertain what weight should be given to this type of smoking, and (b) men who have already stopped smoking. This reduces the number of cases available for study, but the reduction in numbers is more than compensated for by the purity of the material. Follow-up has so far revealed 141 deaths from lung cancer among British doctors who are known to have been pure cigarette smokers and who were smoking regularly at the start of the study. Mortality rates, standardized for age, are shown for six levels of smoking (Chart 7), in comparison with the rate for life-long nonsmokers. The relationship with quantity appears to be linear throughout the whole range from under ten a day (average, five) to 35 or more a day (average, 41).

This finding accords with the tentative conclusions reached from the studies of leukemia incidence following large doses of radiation in Hiroshima and Nagasaki (5) and among patients with ankylosing spondylitis (11), and, if it is confirmed, it will have several important implications. First, it follows that if cancer is the end-result of a series of mutations each genetic change must be produced by a different agent—for if cigarette smoke were responsible for more than one change the incidence of the disease would be expected to vary at least with the square of the dose. For the same reason these findings are incompatible with the postulate that several contiguous cells have to be altered before the potential cancer can grow. They are also, I think, incompatible with the belief that dose accumulates with age and that susceptibility is normally distributed in relation to the logarithm of the dose. This is illustrated in Chart 8, which shows the cumulative mortality from lung cancer in the absence of other causes of death plotted on a probability scale against the logarithm of the duration of smoking—taken to be approximately 20 years less than the age. Three sets of data have been plotted corresponding to men smoking less than fifteen cigarettes a day, fifteen to 24 a day, and 25 or more a day. The points lie on three ap-

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*Pike and Doll, data to be published.*
proximately parallel lines—as they should according to the hypothesis. The lines should, however, be much farther apart, the distance between them being the difference between the logarithms of the dose rates.

Effect of ceasing exposure.—Other data, already referred to, show the effect of ceasing exposure. Compared with the mortality among men who continue to smoke, the mortality from lung cancer falls rapidly, and 10–14 years later the rate is about fifteen per cent of what it would otherwise have been. It should be noted, however, that these results do not necessarily mean that the mortality actually falls. No data are yet available to test this, and it is possible that the rate remains stationary instead of continuing to rise.

![Chart 8. Per cent of men estimated to develop lung cancer after different durations of smoking and in the absence of other causes of death, at different levels of cigarette consumption, shown on a probability scale. (Pike and Doll, unpublished data.)](chart8)

The rapid decrease in the relative mortality is not, I think, what was expected before these observations were made. Such a decrease may not, however, be atypical. For example, the rapid decrease in mortality from cancer of the stomach that is taking place in the U.S.A.—approximately 20 per cent in men between 1952–1953 and 1958–1959—is occurring to approximately the same extent at all ages, and this is easier to understand if the effect of reducing exposure is rapid than if it occurs only after a long delay. Human evidence for the belief that the risk is unaltered for many years is, in fact, not strong. There is no doubt that occupational cancers can occur many years after the cessation of industrial exposure—carcinoma of the scrotum has occurred 40 years after ceasing exposure to shale oil and carcinoma of the ethmoids 50 years after stopping work in a nickel refinery—but we have no factual knowledge of the incidence of such cancers relative to the incidence that would have occurred if exposure had been allowed to continue. The most striking evidence of an effect that cannot be modified for many years is provided by circumcision and cancer of the penis (1, 28). Circumcision within a week or two of birth protects completely; in childhood it diminishes the risk; but after about 17 years of age it is apparently without effect. Here, however, we may be dealing with a different type of phenomenon. The changes that take place in the mucosa covering the glans when circumcision is performed in infancy may be qualitatively different from those that take place when circumcision is delayed, and the former changes may diminish the susceptibility to cancer induction later in life.

The finding of a change in the pattern of mortality after stopping smoking may be linked with the observations of Auerbach and his colleagues on the pathology of the bronchial mucosa (4). Their results show that the proportion of sections containing cells with atypical nuclei and the proportion containing lesions composed wholly of such cells (which may be equated with carcinoma in situ) increases with age and with the amount smoked, but disappears almost to zero 5 or more years after smoking has been stopped. Moreover, among ex-smokers the lesions appeared to be replaced by the occasional finding of a degenerate cell of a type that was hardly ever found among nonsmokers or subjects who continued to smoke. Their results are particularly impressive because of the meticulous way in which the study was designed; all the pathological reports were made blindly without knowledge of the subject's history, and comparisons were made between sets of subjects matched for age and place of residence. Presumably, therefore, we must conclude that one effect of cigarette smoking is to maintain the lesions and allow them to develop.

Promoting agent or initiator.—Does this mean that we should regard cigarette smoke as a promoting agent—comparable, perhaps, to croton oil—and that we should seek for some other factor to initiate the process? According to Passey (25) cigarette smoke should not be classified as a true carcinogen, because the average age at which men die of lung cancer is the same, irrespective of the amount smoked. Under experimental conditions an increase in the dose of a carcinogen usually leads to a reduction in the average length of the induction period, and Passey argues that a higher dose of a true carcinogen should lead, in men, to an earlier average age at death. The average age at death is, however, a most unsatisfactory statistic with which to work. In the absence of detailed information about the age distribution and general
mortality rates of the various groups studied, it is impossible to give it any precise meaning and certainly impossible to compare it with experimental data that have been obtained in quite a different way. The data that compare best with those obtained from animal experiments are the proportions of men affected, in the absence of death from other causes, at different ages. Data obtained from the follow-up of doctors with known smoking habits have been examined by Pike and Doll, and the results are illustrated in Chart 9. These results are distinguished from most animal experiments by the relatively small proportion of individuals affected, even with the highest dose. Under these conditions, an increase in dose cannot be expected to reduce the length of the induction period, and, that multiple tar warts occurred more frequently among men who were first exposed to tar in the coal-gas industry when 25 years or over than among men who were first exposed at younger ages (Table 2). Table 3 shows that the incidence of bladder cancer and lung cancer has also been greater, the greater the age at first exposure—irrespective of whether the carcinogenic agent was coal-tar, β-naphthylamine, or asbestos. The data on tar-warts and bladder cancer are particularly

<table>
<thead>
<tr>
<th>No. warts</th>
<th>Men with 10–34 years exposure to tar, first exposed at age:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Under 25 yr.</td>
</tr>
<tr>
<td>Under 10</td>
<td>56</td>
</tr>
<tr>
<td>10 or more</td>
<td>1</td>
</tr>
<tr>
<td>Average duration of exposure (yr.)</td>
<td>21.7</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Age at first exposure (yr.)</th>
<th>Bladder tumors in chemical workers</th>
<th>Lung tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asbestos-workers</td>
<td>Coal-gas workers</td>
</tr>
<tr>
<td>Under 20</td>
<td>59</td>
<td>26</td>
</tr>
<tr>
<td>20–39</td>
<td>88</td>
<td>165</td>
</tr>
<tr>
<td>30–39</td>
<td>101</td>
<td>195</td>
</tr>
<tr>
<td>40 or more</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>No. developing tumors</td>
<td>288</td>
<td>19</td>
</tr>
</tbody>
</table>

striking, because the incidence due to industrial exposure is relatively so high that any error introduced by assuming that all the tumors are due to the specific exposure is very small. This is not so in the case of lung tumors among coal-gas and asbestos workers, and in these groups the number of lung tumors normally expected has had to be estimated and subtracted. Data on the incidence of chronic myeloid and acute leukemia among spondylitic patients treated by radiotherapy give a similar result (14). The older the patient at the
time of irradiation, the greater the effect. Here again the normal incidence of these diseases is relatively small and can be ignored. The effect of dose can also be ignored, because the older patients are known to have had the smaller doses; moreover, a higher proportion of the older patients will have died, so that the opportunity for them to have developed leukemia will have been less. Both these factors will, therefore, have tended to reduce the real differences.

Two sets of data give different results. An incidence of thyroid cancer of nearly 1 per cent has

been produced following irradiation of the thymus in infancy, and, although there are no firm figures for the incidence of thyroid cancer following irradiation in adult life, it has generally been thought to be appreciably less. Second, the experience at Hiroshima and Nagasaki showed that leukemia was induced most easily among young children, whereas at older ages the incidence appears to have been unrelated to age (5, 14). Japanese data for cancer other than leukemia are still too uncertain to justify any definite conclusion.

How can these apparently conflicting results be reconciled? It is, I think, reasonable to suppose that the activity of the tissue is one factor. This is demonstrated by many animal experiments and is presumably the explanation of the greater susceptibility of the thyroid in infancy and of the marrow in childhood. But why should the Japanese show no difference in susceptibility to radiation-induced leukemia throughout adolescence and adult life, whereas in Britain susceptibility increases with age—not only for irradiation-induced leukemia but also for several industrial cancers?

First it must be remembered that the Japanese survivors are a highly selected population. A large proportion of heavily exposed persons were killed, and possibly there was a higher mortality for a given dose among older persons. The apparent discrepancy may, therefore, be an artifact. If it isn’t, I can suggest only that the explanation may be found in the fact that the normal relationship between leukemia mortality and age appears to be different in the two countries. Mortality rates are shown in Chart 10. The mortality from chronic lymphatic leukemia has been subtracted from the British rates, since this disease occurs very seldom in Japan and does not appear, in either country, to be readily induced by irradiation. In Britain the mortality increases steadily with age; but in Japan the increase is relatively slight. All the human data could therefore be explained on the hypothesis that susceptibility to cancer induction is determined by the extent of the past exposure to all those other factors that contribute to the normal incidence of cancer. In these circumstances, susceptibility to a single stimulus would not be expected to alter with age, unless there was evidence that the normal incidence also altered; but when it increased rapidly the susceptibility to cancer induction would be expected to increase also.

CONCLUSION

These data have, I realize, been presented in a one-sided way, and for that I apologize. Each set of observations should have been assessed in the light of the great mass of experimental data that are relevant to them. That I have not attempted to do so is partly because of lack of time, but more because of lack of knowledge. Considered in the light of other findings it may appear that some of the observations are so anomalous as to be unacceptable, and further experience may indeed show that they are artifacts or have been incorrectly interpreted. Nevertheless, if the observations do at times conflict with laboratory experience, it does not necessarily mean that they are wrong; it is possible that laboratory experiments have not adequately reproduced the situation to which man is exposed. If, for example, cancer is not more readily induced in a 1-year-old mouse than in a mouse of 3 months, it is possible that the mouse’s environment has protected him from factors com-
parable to those which, in the case of man, increase his susceptibility with advancing age.

If some of the data appear to confuse the picture more than they elucidate it, that is a reason not so much for ignoring them as for more intensive study. I do not wish to suggest that epidemiologic data such as these will ever, by themselves, enable the whole picture of the mechanism of carcinogenesis to be constructed. They are, however, the product of the mechanism that occurs in the animal whose cancer we are trying to prevent, and no theory is likely to be of value for this purpose unless it is able to account for them.

Meanwhile, in the absence of such a theory, epidemiologic observations will continue to provide links between the incidence of cancer and the prevalence of various environmental agents. Whether such knowledge will enable us to prevent the disease can be shown only by the test of practice. In this respect it is encouraging to realize that, though the sort of weak carcinogen to which man appears to be most commonly exposed may provide links between the incidence of cancer and the product of the mechanism that occurs in the animal whose cancer we are trying to prevent, and no theory is likely to be of value for this purpose unless it is able to account for them.

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Interpretations of Epidemiologic Data

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