

An Epidemiological Perspective of the Biology of Cancer¹

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Introduction

The epidemiologist studying cancer concerns himself with the frequency with which the various types occur in different groups of people. Since cancer is commonly fatal, the only human experiments directly concerned with its cause that are ethical are experiments in prevention. These are seldom practicable for social reasons, quite apart from the difficulty of dealing with the large numbers that are needed when the annual incidence of a disease is low. The epidemiologist is, therefore, usually limited to the analysis and interpretation of experiments that Nature has carried out (if we can subsume the bizarre range of human activity under this head), and it cannot be supposed that he will make any material contribution to our understanding of the mechanism by which the disease is produced comparable to that which can be made in the laboratory. Nevertheless, he does study disease in the animal whose health we are seeking to preserve, and any theory that is going to lead to practical results should be able to account for the observations that are made on humans. It may, therefore, be of interest to review some of the epidemiological data to see whether they can contribute to our knowledge of the origin of cancer by, for example, elucidating the genetic component of susceptibility, the roles of infection and immunodeficiency, or the nature of the relationship between the risk of cancer and the intensity and duration of exposure to chemical carcinogens.

Genetic Variation

Consider first the extreme hypothesis that the proportion of people who are susceptible to cancer is limited, so that differences in the prevalence of environmental factors determine only the site in which the tumors originate. This idea, which was suggested by Cramer in 1934 (11), is resurrected periodically, as, for example, when it was found that in Britain the reduction in mortality from some types of cancer is almost exactly canceled out by the increase in mortality from others, so that the total age-specific rates have remained much the same over 50 years. The hypothesis is disproved, however, by the experience of industrial workers who are exposed to agents that cause cancer in one organ and who, despite this, continue to suffer the normal hazard of cancer in other organs. Typical data from six occupational studies are summarized in Table 1. Similar data for cigarette smokers and nonsmokers derived from a study of British doctors (13, 15) are illustrated in Chart 1. Despite the greatly increased mortality from cancers of the bronchus, upper respiratory and digestive tracts, bladder,

and pancreas, the cigarette smokers have at each age essentially the same mortality from other cancers as do men who have never smoked at all.

The relative constancy of cancer incidence from time to time and from place to place is in all probability an artifact of chance, due to the independent variation of a large number of different causes. That this is an adequate explanation has been demonstrated by Julian Peto,² who chose incidence rates for cancers of each site at random from the records of 78 registries (44). The resultant rates for all cancers, obtained by summing the individual site-specific rates, had a S.D. that corresponded closely to that actually observed for the whole set of registries.

There remains, of course, the possibility of differences in susceptibility to individual types of cancer, and there is much evidence to suggest that such differences do exist. Most of the common cancers show some degree of familial clustering, and there is conclusive evidence for a variety of rare mutations that give rise to gross hazards of specific types of the disease. For the common cancers the risk among siblings of cancer patients is seldom more than twice that in the general population, and we cannot exclude the possibility that an excess of this degree is due to a common environment. Even childhood cancers, which might be expected to have a large genetic component, show only a minimal tendency for familial clustering. This is illustrated by the experience of some 15,000 families in which one or more child developed cancer under 15 years of age, *i.e.*, the majority of affected families in Britain during a 20-year period (18). If we exclude data for twins and for children with cancers with a known genetic basis, such as retinoblastoma and xeroderma pigmentosum, the risk among siblings of affected children was about 2/1000, *i.e.*, about twice normal; the relative risk was not much greater even when the individual types were considered separately, as is shown in Table 2.

Such relatively small differences are, however, consistent with large differences in susceptibility (30). Consider, for example, a recessive gene that increases the risk of a particular cancer 50-fold in homozygotes. The relative risk in the siblings of probands would be just over 4-fold if the population frequency of the gene was approximately 10%.² With either greater or lesser frequencies, the relative risk would be less and possibly much less. Even in identical twins it could be relatively small, as is shown in Table 3, depending on the population frequency of the gene.

The progressive increase in cancer incidence with age that is observed with many common cancers is also compatible with a mixture of susceptibilities ranging up to 100-fold.² It is not compatible, however, with a small proportion of the population being highly susceptible while the rest are

¹ Based on the Seventh Alexander D. Langmuir Lecture given at the Center for Disease Control, Atlanta, Ga., April 6, 1978.

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² J. Peto, personal communication.

not susceptible at all. In that case the age-specific incidence rate would have to cease increasing with age once a substantial proportion of those at risk had already developed the disease, and with the common cancers this does not happen (9).

Infection

The epidemiologist has been hardly more decisive in defining the role of infection in the cause of cancer, apart from the demonstration that cancer as such is not infectious in the ordinary sense of the word. Statistical techniques to help decide whether small clusters of rare diseases constitute a genuine epidemic or merely reflect chance occurrence have been greatly improved since Knox (27) suggested a method by which the distances between the location of members of all possible pairs of cases in a defined population are compared with the times between

the dates of occurrence of the disease in the members of the same pairs; unfortunately, the results have been disappointing. In sum, there is strong evidence of clustering of Burkitt's lymphoma in a few parts of Africa but only for a few years at a time, and there is the faintest possible suggestion of a tendency for clustering of acute lymphatic leukemia in children in New Zealand and the United Kingdom.

The failure to find stronger evidence of clustering does not, however, weigh heavily against positive evidence for the existence of infective agents obtained in the laboratory or the ward. Statistical techniques to allow for different durations of infectivity and different lengths of induction time (36) are clumsy in the absence of any clinical indications of what the periods are likely to be. More importantly, the possibility that clinical infection may occur without the appearance of overt disease makes the techniques inefficient, so that they may fail to detect evidence of clustering of diseases that are known to be infectious, such as infectious mononucleosis (31) and, if familial cases are ignored, cerebrospinal fever (20).

The evidence of Vianna and his colleagues (42, 43) of contact between 31 people with Hodgkin's disease in Albany, sometimes directly and sometimes indirectly through an intermediary, is even more difficult to evaluate. In principle, it can be assessed only by using objective criteria to define a contact and then comparing the contacts with those in a control series that is investigated equally intensively. When Smith *et al.* (41) used this method in Oxford, they failed to find any greater number of contacts between patients developing Hodgkin's disease under 40 years of age than between a random sample of patients of the same ages and same social classes, treated in the same hospitals during the same period. Nor is there any evidence of a greater hazard for doctors or nurses, who might be thought

Table 1
Cancer in hazardous occupations

Ref.	Occupation	Occupational cancers		Other cancers	
		No. of deaths	Excess over expected	No. of deaths	Excess over expected
38	Asbestos insulation	74	58.0	21	0.5
32	Asbestos textile manufacture	60	36.2	34	-6.5
7	Chromate manufacture	12	8.7	9	1.1
16	Coal gas manufacture	112	52.1	70	3.9
8	Hematite mining	36	15.4	65	9.0
14	Nickel refining	193	170.8	64	-0.4
4	Uranium mining	144	114.2	62	-2.1

Chart 1. Incidence of cancers related to smoking and of all other cancers in regular cigarette smokers and in life-long nonsmokers: by age.

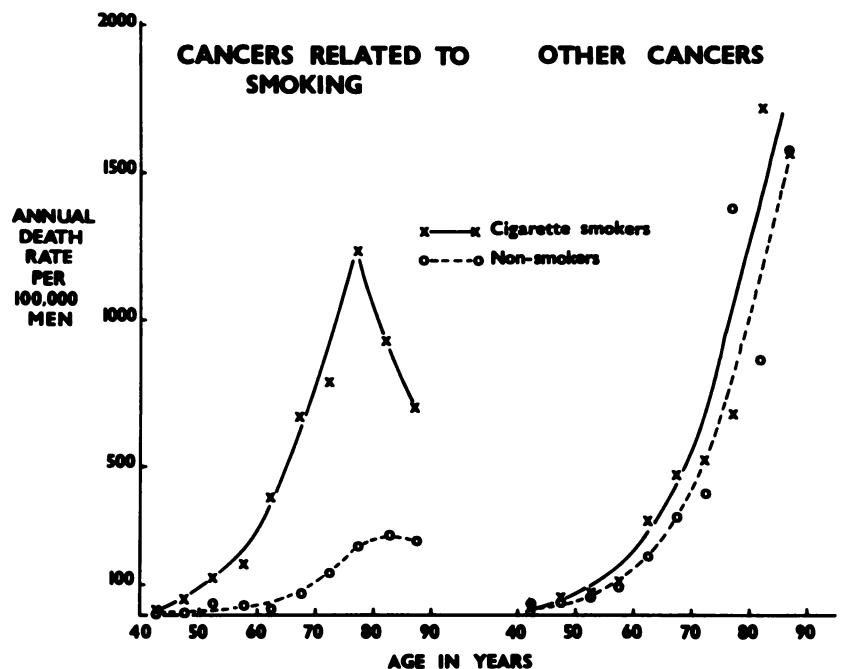


Table 2
Pairs of siblings developing cancer in childhood [after Draper et al. (18)]

Type of cancer	Ratio of numbers observed and expected with these types of cancer:						
	Leukemia	Lymphoma	Central nervous system	Neuroblastoma	Wilm's	Bone	Other
Leukemia	2.3				1.2		
Lymphoma		5.4			0.6		
Central nervous system			2.9	2.5	1.2	5.0	3.1
Neuroblastoma				7.5	—	—	5.4
Wilm's					—	—	—
Bone						—	—
Other							3.6

Table 3
Risk of cancer in relatives of probands relative to unit risk in general population: susceptibility determined by recessive gene

Incidence in homozygotes relative to unit incidence in others	0.01 gene frequency		0.10 gene frequency		0.50 gene frequency	
	Identical twin	Sibling	Identical twin	Sibling	Identical twin	Sibling
2	1.00	1.00	1.01	1.00	1.12	1.05
10	1.01	1.00	1.67	1.20	2.44	1.60
50	1.24	1.06	11.7	4.16	3.56	2.07
100	1.96	1.24	25.5	8.24	3.77	2.15
∞	10 ⁴	2550	100	30.3	4.00	2.25

to be at special risk of infection because of the nature of their work (21).

Reasons for believing that the EB³ virus plays some part in the production of Burkitt's lymphoma have recently been strengthened by the findings of a field survey of 20,000 children in the West Nile District of Uganda (3). Fourteen cases of Burkitt's lymphoma were diagnosed, and the antibody titers in the patients' sera before and after diagnosis were compared with titers in a control group of children, four of whom were selected to match each of the affected children for age, sex, and place of residence. The results show that in nearly all cases the antibody titers against the viral capsid antigen (but not those against other viral antigens) were materially higher than in the control children 7 to 54 months prior to the appearance of the tumor. The only exceptions were two cases that were atypical because the viral genome was not detected in the nuclei of the tumor cells.

Epidemiological evidence of a viral role is also accumulating for several other types of cancer. That the EB virus plays some part in the production of Hodgkin's disease was suggested by the clinical observation that the onset of the disease tended to follow an attack of infectious mononucleosis. This has now been confirmed by the observation that the incidence of the disease in Denmark was increased nearly 8-fold between 1 and 6 years after infectious mononucleosis had been diagnosed on the basis of a positive Paul-Bunnell reaction (16 observed cases against 2.05 expected); similar observations have been made in smaller

series in Sweden and Scotland (2, 37). No part of the EB genome can be detected in Hodgkin's cells, and the infection presumably exerts its effect by stimulating the mitotic activity of the relevant stem cells. A similar synergistic effect may, perhaps, account for the close but imperfect association between hepatoma and the hepatitis B virus that has been reported in four continents (J. Higginson, personal communication).

A cancer that is epidemiologically a good candidate for having a viral origin is cancer of the cervix. That it is venereal in origin is almost certain. We know that the disease spares nuns and is most common in prostitutes and that the risk of developing it increases with the number of marriages and inversely with the age at which coitus first occurs; the risk does not increase independently with the number of pregnancies nor with the frequency of intercourse within marriage. Also, more of the husbands of affected women have had extramarital intercourse than have the husbands of control women. To these facts we can add the observation of Kessler (26) that the second wives of men whose first wives had cervical cancer are particularly at risk, the observation of Beral (6) that the mortality from cervical cancer in cohorts of women of different ages varies with the incidence of gonorrhoea at the time that they were 20 years old, and the accumulating evidence that obstructive methods of contraception are protective.

Lastly, there is the striking increase in the incidence of lymphomas, particularly reticulosarcomas, within 1 year of the start of medical treatment aimed at suppressing immune

³ The abbreviation used is: EB, Epstein-Barr.

Table 4
Cancer following the use of immunosuppressive drugs

Source	Type of patient	Type of tumor	Ratio of numbers observed and expected at following time after start of treatment		
			Under 2 yr	2 to 4 yr ^a	5 or more yr ^a
International Transplant Register	Transplant	Lymphoma	19.2 (32) ^b	16.1 (15)	24.0 (6)
Anglo-Australasian Register	Transplant Medical	Lymphoma	63.3 (19)	34.5 (10)	60.0 (3)
International Transplant Register	Transplant	Other cancer ^c	1.1 (32)	2.5 (39)	5.7 (24)
Anglo-Australasian Register	Transplant Medical	Other cancer ^c	1.6 (10)	1.9 (12)	3.1 (4)
		Other cancer ^c	1.3 (9)	1.6 (14)	0.5 (1)

^a Two to 5 years and 6 years or more for the Anglo-Australasian Register.

^b Numbers in parentheses, number of cases.

^c Excluding cancer of the skin.

reactions. The principal evidence has been obtained from the records of the International Transplant Register (23), but Kinlen *et al.*⁴ have obtained similar, although numerically less impressive, results by following patients given immunosuppressive drugs for medical conditions who were investigated in a collaborative study between physicians and surgeons in Australia, New Zealand, and the United Kingdom (Table 4). The rapid occurrence of this particular type of tumor after starting treatment is reminiscent of the effect of immunosuppression in experimental animals infected with the polyoma virus and suggests that at least one form of reticulosarcoma is virus induced.

With the possible exception of hepatoma, for which the existing incidence data are inadequate, all of these cancers, together with nasopharyngeal cancer (for which there is strong laboratory evidence of a viral involvement), have incidence rates that vary with age unlike the common epithelial cancers. In some there is a peak incidence in childhood, while in others the incidence increases and then levels off. Only reticulosarcoma increases materially with age after a brief plateau in young adult life, but the increase is much less rapid than that, for example, that occurs with cancer of the stomach.

Immunodeficiency

Immunosuppressive Drugs. Observations on the effects of immunosuppressive drugs also provide evidence about the role of immune reactions in preventing the onset of cancer in general. The available data⁴ (23), which are summarized in Table 4, suggest that the incidence of several different types of cancer may begin to increase after 2 years treatment. Not all types of cancer, however, appear to be equally affected. Data from the International Register suggest that the excess may be limited to a few types, such as soft-tissue sarcomas, adenocarcinomas of the lung, primary tumors of the liver and bile ducts, and cancers of the lower urinary tract, thyroid, and perhaps the uterine cervix. There is not, as yet, any evidence of an excess of the common cancers of the stomach, large bowel, breast, and bronchus (other than adenocarcinoma), although there is

certainly an excess of skin cancers in the Australasian transplant series, more than 100 having been reported in 1600 patients.⁴ Several explanations for these findings are possible, and more data are required before we can distinguish between them. We may, however, conclude with Hoover (23) that they do not support the general theory of the prevention of cancer by immunological surveillance.

Immunodeficiency Syndromes. Other relevant evidence is provided by (a) the incidence of cancer in groups of people suffering from various types of immunodeficiency and (b) the way in which susceptibility to cancer induction varies with age. Clinical experience has shown that leukemia and lymphoreticular tumors occur unusually often in association with Bruton's agammaglobulinemia, ataxia-telangiectasia, and the Wiskott-Aldrich syndrome; this is now supported by the records of 196 cases reported to the Immunodeficiency Cancer Registry (25). Family studies and surveys of small populations (19) confirm that the incidence of leukemia and lymphoreticular tumors is many times greater in patients with these conditions than in normal children, but it is not clear whether the cancers are the result of the immunodeficiency or are associated with it because of some common cause (for example, the chromosomal instability in ataxia telangiectasia). The data for older patients are dominated by the frequency of gastric cancer in patients with common variable immunodeficiency, and this is confirmed by the experience of nearly 400 patients with agammaglobulinemia whom Kinlen (personal communication) is following in England. Nine of the 302 patients with common variable immunodeficiency have developed cancer more than 1 year after the immunodeficiency was diagnosed, 5 of whom developed it in the stomach. The relative excess of this type of cancer is probably due to the gross atrophic gastritis that occurs in about half the patients with this immunological defect.

Age Differences in Susceptibility to Irradiation. The most important evidence, however, should be obtained from observations on the ease with which cancer is induced at different ages. Unfortunately, these are far fewer than they could be. Industrial data are seldom available in sufficient detail and, in the case of lung cancer, are practically never accompanied by the necessary information on smoking habits.

⁴ L. Kinlen, J. Peto, R. Shiell, and R. Doll, personal communication.

The most precise evidence comes from observations on men and women who have been exposed to ionizing radiations either in Hiroshima and Nagasaki or as a result of medical treatment. In one large study cancer mortality was determined in over 14,000 patients who were irradiated for the treatment of ankylosing spondylitis at British clinics between 1935 and 1954 (10, 17). All but 208 (1.5%) were successfully followed until the beginning of 1970, or for 1 year after they had been given a second course of treatment, or until they had emigrated or died, whichever was the earliest. The findings provide an estimate of the distribution of induction periods for different cancers following a brief period of irradiation and also of the relationship between the extra risk of cancer and the age at which the patient was exposed.

Normal death rates from unrelated diseases increase rapidly with age (and so with time after irradiation), so that the younger patients at the time of irradiation contribute an increasing proportion of the years at risk as time passes. It is necessary, therefore, to take account of each factor when examining the influence of the other. Chart 2 shows the attributable mortality for patients irradiated at different ages, standardized for period after exposure. The observations show that the biological effect is approximately proportional to the second power of age at the time of irradiation for leukemia and to the third power of age at the time of irradiation for other cancers of heavily irradiated sites.

These data, which are compatible with observations on the survivors of Hiroshima and Nagasaki (5) and the sparse data on women given a radiation-induced menopause (40), accord with the concept that susceptibility increases because of a systemic effect of age, such as a progressive breakdown in the efficiency of immunosurveillance. They are, however, also compatible with another mechanism that will be referred to later.

Tobacco Carcinogenesis

British Doctors. Consider now the data relating the appearance of cancer to exposure to a chemical carcinogen (in particular, tobacco smoke). In one study observations were made on 34,440 male British doctors who answered questions about their smoking habits in 1951 and again, if they had survived, in 1957, 1966, and 1972 (Ref. 15; R. Doll and R. Peto, unpublished data). In 1972, 99.7% were successfully traced, and we have, as a result, information about the date of onset and the reliability of diagnosis for 483 cases of lung cancer in a total population of 34,440 men whose smoking habits were defined periodically during a 20-year period. Among these men the incidence rate standardized for age was 14 times higher in those who continued to smoke cigarettes than in the lifelong nonsmokers, and the excess risk may be attributed to exposure to the smoke.

Duration of Exposure. With the data obtained in this study, we can examine the relationship between the incidence of the disease and the age of the subject, the duration of exposure, the dose of smoke received per day, and the length of time since exposure was stopped. Chart 3 shows the incidence rate standardized for amount smoked plotted against age for men who started to smoke when aged 16 to 25 years, smoked only cigarettes, and continued to smoke while under observation. Only 7 cases of lung cancer occurred in nonsmokers, and the relationship has, therefore, been compared with that obtained for 127 cases in 150,000 male nonsmokers in two large prospective studies in the U. S. A., reported by Kahn (24) and by Hammond (22). We are justified in using these studies for comparison because the mortality rates in nonsmokers in the two countries are almost identical (11.8 and 11.4, respectively, per 100,000 men aged 35 to 84 years standardized on the

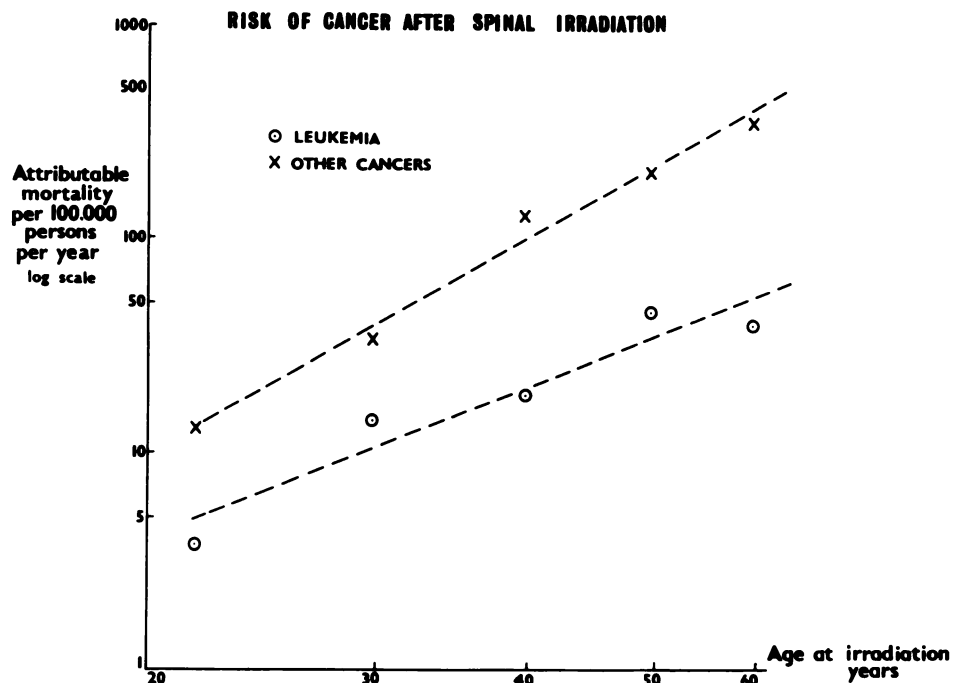


Chart 2. Incidence of leukemia and of other cancers of heavily irradiated sites attributable to irradiation, standardized for duration of time since irradiation: by age at irradiation (double logarithmic scale).

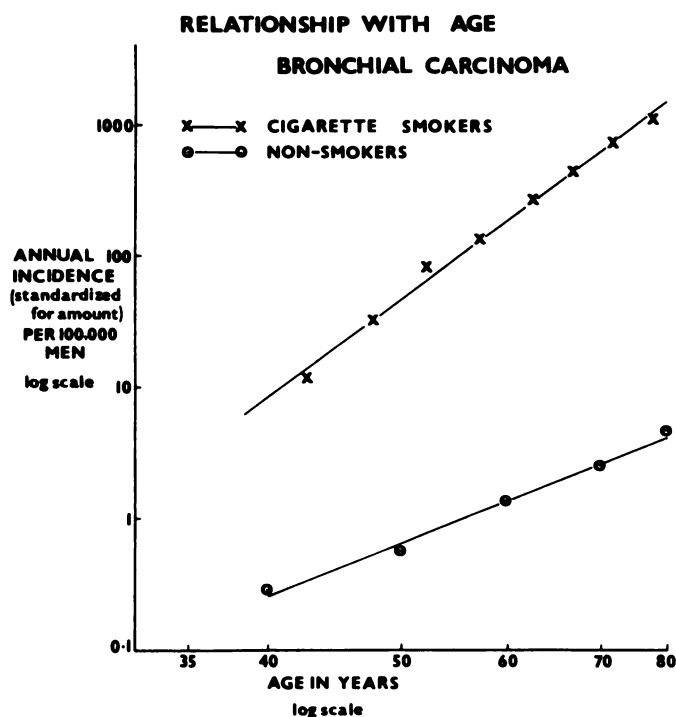


Chart 3. Incidence of lung cancer in regular cigarette smokers, standardized for the amount smoked per day, and in lifelong nonsmokers: by age (double logarithmic scale).

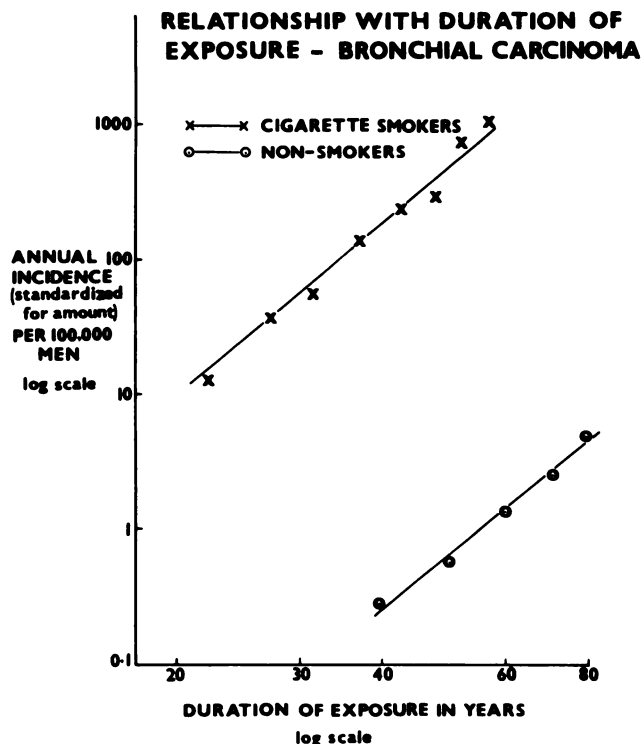


Chart 4. Incidence of lung cancer in regular cigarette smokers, standardized for the amount smoked per day, and in lifelong nonsmokers: by duration of exposure to relevant carcinogens (double logarithmic scale).

male population of England and Wales at the 1961 census). The data were plotted on a double logarithmic scale so that a straight line indicates a power relationship. From the chart it is evident that the incidence in continuing cigarette smokers increases approximately in proportion to the seventh power of age, at least up to 80 years of age, while in nonsmokers it increases approximately in proportion to the fourth power. If, however, the incidence in cigarette smokers is plotted against duration of smoking, the position is changed. The data continue to show an approximate power relationship, but the slope of the regression line is now the same as for nonsmokers (Chart 4). If, therefore, nonsmokers are exposed from birth to the agents that cause lung cancer in the absence of smoking, it would appear that the character of the relationship is determined more importantly by the duration of exposure than by the age of the subject.

Unfortunately, it is not possible to use our data to test directly whether men who have smoked similarly for the same number of years suffer the same incidence of the disease irrespective of their age at starting, as nearly 90% of the continuing smokers started to smoke between 16 and 25 years of age. Very few started later, and those who started earlier are not comparable with the others in the extent to which they inhaled or in the amount they smoked during the early years of their smoking history.

However, these results indicating the overriding importance of the duration of exposure are paralleled almost exactly by skin painting experiments in mice, despite the fact that experimental animals are genetically homogeneous while humans are genetically diverse.⁵ The most compara-

ble experiments have been reported by (a) Lee and O'Neill (28), who applied benzopyrene regularly to the skin of 1200 mice and recorded the relationship between dose rate, duration of application, and tumor incidence; (b) Peto *et al.* (35), who applied benzopyrene regularly to the skin of 950 mice in four groups, starting at 10, 25, 40, or 55 weeks of age and continuing for the rest of the animals' lives; and (c) Lee *et al.* (29), who applied various cigarette smoke fractions regularly to the skin of over 7000 mice throughout their lives.

In all three studies the tumor incidence increased with a power of duration of exposure, the best-fitting power being about 4 in the study with fractions of cigarette smoke and somewhat less in each of the studies with benzopyrene. Unfortunately, it is difficult to be sure of the exact value of the power as it depends crucially on the estimated time taken for the tumor to grow from a single cell until it is large enough to be detected macroscopically. If this growth time is moderately large in comparison to the life span of the animal, failure to allow for it adequately will result in overestimation of the value of the exponent, while variation in the length of the growth time and heterogeneity of susceptibility in different animals will have the opposite effect (33).

In the one study designed specifically to determine whether age exerted any effect *per se* independently of duration, the results were unequivocal (35). In each age group tumors appeared after the same length of exposure, and the rate of appearance of the tumors was unaffected by

⁵ of the curve relating incidence to duration of exposure at incidence rates normally observed in humans, unless the heterogeneity was extreme, as was discussed earlier.

the age at which exposure began.

Intensity of Exposure. As a measure of intensity of dose, we have information on the number of cigarettes smoked per day. At its best this can be only a crude measure of the dose received by the bronchial mucosa, which may be influenced by (a) the number of puffs taken per cigarette; (b) the length of butt discarded; (c) the depth of inhaling, which may not be deep enough for much of the smoke to reach the bronchi at all or may be so deep that the smoke droplets are carried past the bronchi and are deposited in the alveoli; and (d) pathological changes in the bronchial mucosa produced by smoking, including both excess mucous secretion and the destruction of the mucosal cilia. Moreover, no one smoker will have exposed himself to exactly the same dose throughout his life; some heavy smokers will have smoked less in the past, while some light smokers will have cut down.

With so many sources of variation, it is remarkable that the many case-control studies that have been carried out have provided such uniform evidence that the risk increases approximately in linear proportion to the amount smoked. Peto (33), however, has pointed out that random errors in the estimate of the dose will tend to flatten the curve, and, if the error is of the same order of magnitude as the number of cigarettes smoked per day, an apparent linear relationship could mask a truly quadratic one.

In our study (34) we attempted to eliminate as many sources of variation as possible by standardizing for age in 5-year age groups and limiting the observations to men who started to smoke when aged 16 to 25 years, smoked only cigarettes, continued to smoke while under observation, and stated (in response to each questionnaire) that they were smoking the same amount within ± 5 cigarettes/day. The results are shown in Chart 5. If we exclude the point for the estimated highest dose, the risk appears to increase more rapidly than does the dose, a crude estimate being that it increases approximately in proportion to the dose to the power of 1.7. If we include the last point (which may be unreliable due partly to exaggeration and partly to a failure to distinguish between the number bought and the number actually smoked), we might have some evidence of saturation, but it would still be difficult to postulate a linear relationship at low doses.

The result is similar to that observed in skin painting experiments in mice. In the experiment with benzo(a)pyrene of Lee and O'Neill (28), the age-specific incidence rate varied approximately with the daily dose squared, while in the experiment of Lee *et al.* (29) with various cigarette smoke fractions it varied with dose to the power of 1.8.

Effect of Stopping. Data for the effect of stopping smoking are shown in Chart 6. The numbers of cases in exsmokers are too few to enable comparisons to be made for men who gave up at a specific age. The rates at different periods after stopping are, therefore, presented as proportions of the rates in cigarette smokers at the ages at which the exsmokers gave up, standardized for the amount smoked at the time of stopping. In this analysis it is unnecessary to take account of age at starting, as it was practically the same (about 19 years on the average) in all groups. Data for men aged 80 years and over have, however, been excluded to reduce the risk of diagnostic bias in the group of

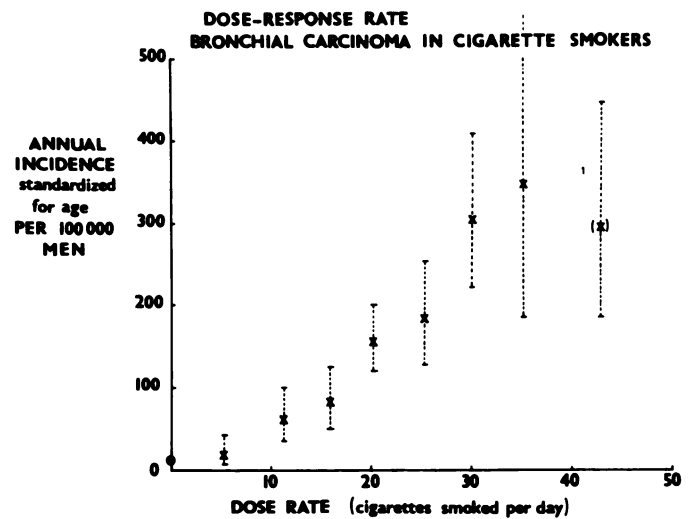


Chart 5. Incidence of lung cancer in regular cigarette smokers, standardized for age: by number of cigarettes smoked per day.

INCIDENCE IN EX-CIGARETTE SMOKERS BRONCHIAL CARCINOMA

● EX-CIGARETTE SMOKERS
 X CIGARETTE SMOKERS OF SAME AGE
 ○ NON-SMOKERS OF SAME AGE

Risk relative to that expected at rates for cigarette smokers at age ex-smokers stopped

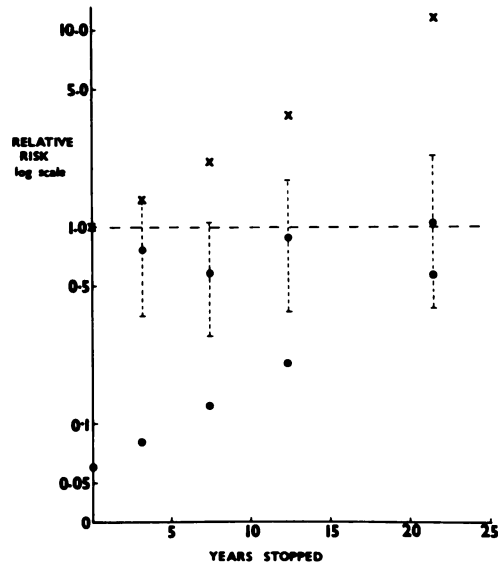


Chart 6. Numbers of cases of lung cancer in exsmokers, expressed as proportions of the numbers expected on the assumption that the rate remained the same as in regular cigarette smokers at the ages at which smoking was stopped: by time since smoking was stopped (double logarithmic scale). For comparison, similar proportions are shown estimated on the assumption that exsmokers would have continued to show the same incidence as (a) regular cigarette smokers of the same age and (b) lifelong nonsmokers of the same age.

exsmokers of longest duration. The chart also shows the corresponding proportions for men who continued to smoke cigarettes and for nonsmokers of the same ages. In all cases the proportions are shown on a logarithmic scale.

The effect of stopping smoking is evident within 5 years. On stopping the rate ceases to increase as it would have if smoking had continued, but whether it actually falls is uncertain because the numbers are small (9 and 11 cases in each of the first two groups of exsmokers). The trend,

however, suggests a fall followed by an increase, which keeps the rate ahead of that in lifelong nonsmokers.

Interaction. Cigarette smoking is so common that it is sometimes associated with exposure to other carcinogens, so that tobacco-induced cancers in humans can also provide evidence of the interaction of two agents. Such evidence has been obtained for the production of esophageal cancer by smoking and alcohol and of lung cancer by smoking and either asbestos or ionizing radiations.

The most clear evidence on smoking and alcohol consumption in relation to esophageal cancer has been obtained by the International Agency for Research on Cancer in Normandy and Brittany (1). Neither factor alone produces much disease, but the man who each day drinks 81 g or more of alcohol (equivalent to 7 whiskies) and smokes 20 or more cigarettes has about 45 times the risk of developing esophageal cancer as the continent man who drinks less than 40 g and smokes less than 10 cigarettes. This evidence of interaction is extremely important from the point of view of prevention, but it tells us little about the mechanism by which the disease is produced. The carcinogenic effect of alcohol may be produced by simply bringing the agent in cigarette smoke more effectively into contact with the esophageal stem cell or by inducing the production of enzymes that activate precarcinogens.

Asbestos fibers, which grossly increase the effect of cigarette smoke in the production of lung cancer (Table 5), may do so by the physical adsorption of cigarette tar. The fibers can, however, produce cancer when injected into the pleural cavity of laboratory animals, even when freed of polycyclic hydrocarbons, and it seems more probable that the two factors are producing a multiplicative effect as a result of separate biological actions on the cells at risk. In the case of ionizing radiations and smoking, the most recent evidence for a multiplicative effect (4) is not conclusive, but if there is such an effect from chronic exposure to both agents, as is suggested by the data for uranium miners, two independent biological actions must be involved.

Other Cancers

That lung cancer can be taken as an example of a typical epithelial cancer would not have been obvious 30 years ago, when the age-specific mortality rates showed a peak at 60 to 64 years of age. The peak was, however, a social artifact due to the fact that in 1950 old men had not smoked cigarettes for the whole of their adult lives. With the evolution of the epidemic, the peak has moved progressively to older ages, and it is now clear that the peculiar relationship with age observed in the 1950's reflected differences in the smoking habits of different birth cohorts. As male smoking habits have stabilized, the age distribution has come to resemble that of other common cancers, most of which show a continuous increase in incidence proportional to about the fourth, fifth, or sixth power of age. Data for 12 types of cancer recorded in 11 populations are summarized in Table 6. The data were obtained from the records of cancer registries that are believed to secure registrations of virtually all the cases in the areas that they cover (9); even so we cannot attach much significance to the individual values of the exponents beyond the general conclusion that they are probably in the same broad category. The data already reviewed for bronchial carcinoma showed that the relationship with age was less steep for nonsmokers than for cigarette smokers and that the value of the exponent for cigarette smokers is materially reduced if incidence is related to the duration of exposure rather than to the age of the individual. Some of the higher values for other cancers might also be reduced if we knew the age at which exposure to the relevant carcinogen began.

Further complications are introduced by the variation in incidence with time and by the way the population is affected by changes in the prevalence of the external agent. The whole population may be affected at the same time, as with a change in general atmospheric pollution, or individual cohorts may be affected selectively, as with changes in social habits.

The cancers listed in Table 6, which share the common

Table 5
Mortality of U. S. and Canadian asbestos insulation workers [after Selikoff and Hammond (39)]

Smoking history of men	Lung cancer deaths				
	Observed	All men	Expected from:		
			Men with relevant smoking history ^a	Interaction of smoking and asbestos	
			Additive	Multiplicative	
Smoked cigarettes	179	31.6	35.8	153.9	176.0
Smoked pipes or cigars only	1	3.1	0.7	8.2	3.6
Never smoked	1	4.4	0.6	18.6	2.9
Not known	94	16.8	18.8 ^b	94.4	92.5
All histories	275	55.9	55.9	275.1	275.0

^a Estimated from mortality ratios for U. S. men with different smoking habits observed by Hammond (22).

^b Smoking habits estimated from risk relative to that in all men.

Table 6
Relationship between incidence of cancer and age in 11
populations

Site of cancer	Mean value of exponent of age ^a
Esophagus	6.2
Stomach	6.0
Bladder	5.8
Pancreas	5.7
Rectum	5.6
Colon	5.4
Pharynx	5.1
Mouth	5.0
Tongue	4.4
Kidney	4.4
Skin	4.3
Lip	4.0

^a Exponent (k) in equation $I_t \propto t^k$, where I_t is incidence at age t .

characteristic of a rapidly increasing incidence with increasing age, are all epithelial in origin. The only common cancers that share this characteristic and are not epithelial are chronic lymphatic leukemia and myeloma, which are both tumors of B lymphocytes. Many of the other epithelial cancers probably also share it, but the pattern is less certain because the numbers of cases are relatively few. Others definitely do not. These are mostly cancers of the sex organs, which may share the characteristic over a limited range of ages but then either increase more slowly, cease to increase at all, or decline in incidence, depending presumably on the effect of changes in the secretion of hormones that affect the activity of the tissue or, perhaps, in some cases the activity of the individual. One only, cancer of the prostate, increases in incidence with age more rapidly than do the cancers listed in Table 6, but it could be brought into line with the generality of epithelial cancers if exposure to the relevant carcinogen did not begin until after about 30 years of age and then continued throughout life.

The few remaining epithelial cancers, together with all other cancers of other tissues, are related to age in a bewildering variety of ways. Some have been described previously in relation to cancers for which there is evidence of a possible viral origin, but there are many others, varying from a progressive but slow increase with age to virtual constancy throughout adult life, as occurs with sarcoma of bone unassociated with Paget's disease.

Mechanisms of Carcinogenesis

What then do these observations imply for the mechanism of carcinogenesis?

First, there is no such thing as genetic susceptibility to cancer as a whole, but there is plenty of scope for variation in susceptibility to individual types of cancer in particular organs.

Secondly, the variations in age distribution of the different types of cancer suggest that most of them fall into two distinctive groups: (a) one that consists of cancers that are nearly all epithelial in origin, are extremely rare until 30 years of age, and then increase in incidence approximately in proportion to the fourth, fifth, or sixth power of the age;

and (b) another that consists of cancers of the reticuloendothelial system, the central nervous system, and connective tissues, which occur throughout life, including childhood and adolescence, and increase in incidence with age only slowly, if at all. The first category includes 70% of all human cancers, and the second category includes less than 10%. None of the human cancers for which there is any suggestion of a viral origin falls into the first category, while the great majority of tumors that are produced experimentally by infection of animals with viruses are analogous with tumors in the second category. It would, therefore, seem reasonable to postulate at least two main mechanisms.

Thirdly, the category of tumors that have the greatest impact on human health and are the most important to prevent is the first category, typified by the bronchial carcinomas that develop in cigarette smokers. All cancers in this category vary grossly in incidence from place to place and probably also from time to time (12). The evidence of migrants, whose experience of cancer rapidly adjusts to that of the country to which they migrate, and of changes in incidence with time shows that this variation is not, for the most part, genetic in origin. If, therefore, the analogy with bronchial carcinoma is correct, all of these tumors are probably produced by prolonged and continuing exposure to environmental carcinogens.

Fourthly, the weight of evidence suggests that age *per se* does not affect the rate at which tumors occur independently of the effect of prolonging exposure. Three pieces of evidence point to this conclusion. First, the percentage rate of increase in the incidence of lung cancer with the passage of time is greater in cigarette smokers than in nonsmokers, if time is measured from birth, but the two rates of increase are equal if time is measured from the start of smoking in smokers and from the start of life in nonsmokers. Secondly, the incidence in exsmokers remains approximately constant after smoking is stopped. Thirdly, an experiment designed specifically to distinguish between the separate effects of age and duration of exposure on the incidence of chemically induced skin cancer in mice showed unequivocally that the latter was paramount (35).

If this is indeed so, the simplest explanation for the observed age distribution is that the production of cancer is a multistage process and that the various stages of the process represent a series of discrete changes in the cell that cumulatively result in the production of a malignant clone, as is implied by the common pathological observation of progression to cancer through a papilloma and the laboratory evidence of separate roles for initiators and promoters. The finding that the age-specific incidence rates increase in proportion to a power of the duration of exposure could be explained if the number of stages was one more than the exponent of the duration of exposure, which, in the case of lung cancer, would be 5. This, however, is not the only model that satisfies the equation. The same result would be obtained if the number of stages was one less than the exponent of the duration (which in the case of lung cancer would imply three stages) and the cells that were altered but not yet malignant had a slight selective advantage over their normal neighbors. With such an advantage the altered clones would need to grow approximately in proportion to the square of the time since they

first appeared, which might be biologically plausible, as they would normally be expanding in the two-dimensional basal layer.

Other epidemiological evidence that supports the concept of a multistage process is the effect of dual exposure to cigarette smoke and other carcinogenic agents. The fact that the effect of such exposure is multiplicative is easily explained if the agents affect different stages in a multistage process. On this basis the observation that a brief exposure to ionizing radiations in adult life increases the subsequent risk of cancer approximately in proportion to the third power of age at the time of irradiation suggests that these radiations affect one, and possibly several, of the later stages of the process.

That smoking affects a late stage in the sequence is demonstrated conclusively by the rapidity of the effect of stopping smoking. If there is, then, actually a fall in incidence below the rate in continuing smokers, the stage affected could be the last. The incidence does not, however, resume the rate in nonsmokers, and it must be concluded that an irreversible effect has been produced by an effect on an earlier stage as well. That smoking affects an early stage, and probably the first, is also suggested by the high-power relationship between the incidence of the disease and the duration of exposure. Cigarette smoke, therefore, seems likely to affect at least two stages.

If this is so the relationship between dose rate and incidence would be expected to be at least quadratic, as is consistent with the observations on British doctors and some animal experiments. The linear relationship with the number of cigarettes smoked per day that has often been reported in the past might then be an artifact due to the inadequacy of the history of the number of cigarettes smoked to indicate the average intensity of the dose received by the stem cells of the bronchial mucosa.

In a multistage process one or more of the series of discrete changes is probably a genetic mutation, but there is no reason why all the changes should be. Indeed, there are reasons for supposing that some are not. The experimental evidence that the rate of appearance of cancer in other animals is affected by wound healing, dietary restriction, and vitamin A deficiency, as well as by a variety of phorbol esters that have no initiating capacity, provides one reason. Another, as Peto (33) points out, is the mathematical evidence from experimental studies on animals and from observations on man that the exponent of the dose rate is always less than the exponent of time in the equation linking these two factors to the occurrence of the disease.

Possible mechanisms that may be envisaged include the conversion of a heterozygous state containing a recessive neoplastic lesion to an effectively homozygous state (by, for example, mitotic recombination), interference with the normal kinetics of stem cells, stimulation to proliferate of clones of cells that are already abnormal, and, doubtless, many more. No one would expect epidemiology to suggest new mechanisms, but by obtaining precise quantitative data it may help to separate productive hypotheses from sterile ones.

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REFERENCES

1. Annual Report, 1975, pp. 29-35. Lyon, France: International Agency for Research on Cancer, 1975.
2. Annual Report, 1975, pp. 85-86. Lyon, France: International Agency for Research on Cancer, 1975.
3. Annual Report, 1977, pp. 68-78. Lyon, France: International Agency for Research on Cancer, 1977.
4. Archer, V. E., Gillam, J. D., and Wagoner, J. K. Respiratory Disease Mortality among Uranium Miners. *Ann. N. Y. Acad. Sci.*, 271: 280-293, 1976.
5. Beebe, G. W., Kato, H., and Land, C. E. Studies of the Mortality of A-bomb Survivors. 8. Mortality Experience of A-bomb Survivors, 1950-74. In: RERF Technical Report, pp. 1-77. Hiroshima: Radiation Effects Research Foundation, 1977.
6. Beral, V. Cancer of the Cervix: A Sexually Transmitted Infection? *Lancet*, 1: 1037-1040, 1974.
7. Bidstrup, P. L., and Case, R. A. M. Carcinoma of the Lung in Workmen in the Bichromates-producing Industry in Great Britain. *Brit. J. Ind. Med.*, 13: 260-264, 1956.
8. Boyd, J. T., Doll, R., Faulds, J. S., and Leiper, J. Cancer of the Lung in Iron Ore (Haematite) Miners. *Brit. J. Ind. Med.*, 27: 97-105, 1970.
9. Cook, P., Doll, R., and Fellingham, S. A. A Mathematical Model for the Age Distribution of Cancer in Man. *Intern. J. Cancer*, 4: 93-112, 1969.
10. Court Brown, W. M., and Doll, R. Mortality from Cancer and Other Causes after Radiotherapy for Ankylosing Spondylitis. *Brit. Med. J.*, 2: 1327-1332, 1965.
11. Cramer, W. The Prevention of Cancer. *Lancet*, 1: 1-5, 1934.
12. Doll, R. Strategy for Detection of Cancer Hazards to Man. *Nature*, 265: 589-596, 1977.
13. Doll, R., and Hill, A. B. Mortality in Relation to Smoking: Ten Years' Observations of British Doctors. *Brit. Med. J.*, 1: 1399-1410 and 1460-1467, 1964.
14. Doll, R., Mathews, J. D., and Morgan, L. G. Cancers of the Lung and Nasal Sinuses in Nickel Workers: A Reassessment of the Period of Risk. *Brit. J. Ind. Med.*, 34: 102-105, 1977.
15. Doll, R., and Peto, R. Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors. *Brit. Med. J.*, 2: 1525-1536, 1976.
16. Doll, R., and Smith, P. G. Mortality from Cancer and Other Causes after Radiotherapy for Ankylosing Spondylitis: Further Observations. In press, 1978.
17. Doll, R., Vessey, M. P., Beasley, R. W. R., Buckley, A. R., Fear, E. C., Fisher, R. E. W., Gammon, E. J., Gunn, W., Hughes, G. O., Lee, K., and Norman-Smith, B. The Mortality of Gasworkers—Final Report of a Prospective Study. *Brit. J. Ind. Med.*, 29: 394-406, 1972.
18. Draper, G. J., Heaf, M. M., and Wilson, L. M. K. Occurrence of Childhood Cancers among Sibs and Estimation of Familial Risks. *J. Med. Genet.*, 14: 81-90, 1977.
19. Gatti, R. A., and Good, R. A. Occurrence of Malignancy in Immunodeficiency Diseases. *Cancer*, 28: 89-98, 1971.
20. Goldacre, M. J. Space-time and Family Characteristics of Meningococcal Disease and *Haemophilus Meningitis*. *Intern. J. Epidemiol.* 6: 101-105, 1977.
21. Grufferman, S., Duong, I., and Cole, P. Occupation and Hodgkin's Disease. *J. Natl. Cancer Inst.*, 57: 1193-1195, 1976.
22. Hammond, E. C. Smoking in Relation to the Death Rates of One Million Men and Women. *Natl. Cancer Inst. Monograph*, 29: 127-204, 1966.
23. Hoover, R. Effects of Drugs: Immunosuppression. *Cold Spring Harbor Conf. Cell Proliferation*, 4: 369-379, 1977.
24. Kahn, H. A. The Dorn Study of Smoking and Mortality among U. S. Veterans: Report on Eight and One Half Years of Observation. *Natl. Cancer Inst. Monograph*, 19: 1-125, 1966.
25. Kersey, J. H., and Spector, B. D. Immune Deficiency Diseases. In: J. F. Fraumeni, Jr. (ed.), *Persons at High Risk of Cancer*, pp. 55-66, 1975.
26. Kessler, I. I. Human Cervical Cancer as a Venereal Disease. *Cancer Res.*, 36: 783-791, 1976.
27. Knox, G. Epidemiology of Childhood Leukaemia in Northumberland and Durham. *Brit. J. Prevent. Soc. Med.*, 18: 17-24, 1964.
28. Lee, P. N., and O'Neill, J. A. The Effect Both of Time and Dose Applied on Tumour Incidence Rates in Benzpyrene Skin Painting Experiments. *Brit. J. Cancer*, 25: 759-770, 1971.
29. Lee, P. N., Rothwell, K., and Whitehead, J. K. Fractionation of Mouse Skin Carcinogens in Cigarette Smoke Condensate. *Brit. J. Cancer*, 35: 730-742, 1977.
30. Lilienfeld, A. M. Genetic Factors in the Aetiology of Cancer: An Epidemiologic View. *Cancer Res.*, 25: 1330-1335, 1965.
31. Nye, F. J., and Spicer, C. C. Space-time Clustering in Infectious Mononucleosis. *Brit. J. Prevent. Soc. Med.*, 26: 257-258, 1972.

32. Peto, J., Doll, R., Howard, S. V., Kinlen, L. J., and Lewinsohn, H. C. A Mortality Study among Workers in an English Asbestos Factory. *Brit. J. Ind. Med.*, 34: 169-173, 1977.
33. Peto, R. Epidemiology, Multistage Models, and Short-term Mutagenicity Tests. *Cold Spring Harbor Conf. Cell Proliferation*, 4: 1403-1428, 1977.
34. Peto, R., and Doll, R. Lung Cancer in Regular Cigarette Smokers: Dose and Time Relationships in British Doctors. *Brit. J. Prevent. Soc. Med.*, in press, 1978.
35. Peto, R., Roe, F. J. C., Lee, P. N., Levy, L., and Clack, J. Cancer and Ageing in Mice and Men. *Brit. J. Cancer*, 32: 411-426, 1975.
36. Pike, M. C., and Smith, P. G. Disease Clustering: A Generalisation of Knox's Approach to the Detection of Space-time Interactions. *Biometrics*, 24: 541-547, 1968.
37. Rosdahl, N., Larsen, S. D., and Clemmesen, J. Hodgkin's Disease in Patients with Previous Infectious Mononucleosis: 30 Years Experience. *Brit. Med. J.*, 2: 253-256, 1974.
38. Selikoff, I. J., Churg, J., and Hammond, E. C. Asbestos Exposure and Neoplasia. *J. Am. Med. Assoc.*, 188: 22-26, 1964.
39. Selikoff, I. J., and Hammond, E. C. Multiple Risk Factors in Environmental Cancer. In: J. F. Fraumeni, Jr. (ed.), *Persons at High Risk of Cancer*, pp. 467-483. New York: Academic Press, Inc., 1975.
40. Smith, P. G., and Doll, R. Late Effects of X Irradiation in Patients Treated for Metropathia Haemorrhagica. *Brit. J. Radiol.*, 49: 224-232, 1976.
41. Smith, P. G., Pike, M. C., Kinlen, L. J., Jones, A., and Harris, R. Contacts between Young Patients with Hodgkin's Disease. *Lancet*, 2: 59-62, 1977.
42. Vianna, N. J., Greenwald, P., Brady, J., Polan, A. K., Dwork, A., Mauro, J., and Davies, J. N. P. Hodgkin's Disease: Cases with Features of a Community Outbreak. *Ann. Intern. Med.*, 77: 169-180, 1972.
43. Vianna, N. J., Greenwald, P., and Davies, J. N. P. Extended Epidemic of Hodgkin's Disease in High School Students. *Lancet*, 1: 1209-1211, 1971.
44. Waterhouse, J., Muir, C., Correa, P., and Powell, J. (eds.). *Cancer Incidence in Five Continents*, Vol. 3. Lyon, France: International Agency for Research on Cancer, 1976.
45. Wright, N. H., Vessey, M. P., Jonson, B., McPherson, K., and Doll, R. Neoplasia and Dysplasia of the Cervix Uteri and Contraception: A Possible Protective Effect of the Diaphragm. In press, 1978.