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Spontaneous cancer and its possible relationship to oxygen metabolism

(oxidizing radicals/DNA defects/oncogenesis)

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ABSTRACT **Mortality statistics for cancer in various countries and periods of time indicate that there has been little effect of industrialization on the inherent or spontaneous rate of occurrence of cancer. From U.S. cancer statistics and the BEIR values [Report of the Advisory Committee on the Biological Effects of Ionizing Radiation (1979)] for radiation dose response, the ionizing radiation exposure required to produce a number of cancers equal to this spontaneous incidence was estimated to lie between 450 and 2100 rads (1 rad = 0.01 J/kg). From these "cancer equivalent" doses the number of single-strand DNA breaks required to produce the spontaneous cancers is estimated to be 0.26–1.3 per cell DNA per day. It is suggested that the univalent reduction of oxygen in normal metabolism to O_2^- and subsequent production of more harmful radicals is the source of the DNA defects that, in cases where the defense mechanisms fail, lead to spontaneous cancer in the individual.**

In this paper I review the relationship between cancer mortality rates and energy consumption in order to ascertain whether a small or large proportion of the rate may be attributable to injury from intake of carcinogens because of industrialization. My conclusion is in accord with that of others—that only a small proportion of cancer deaths can arise from general pollution (1). If we assume the initiating event in cancer is a DNA injury, we can calculate the rate of internal (i.e., endogenous) injury that must be steadily sustained by individuals to account for the observed spontaneous cancer mortality. I suggest that this endogenous injury is caused by the small, but probably steady, rate of univalent oxygen reduction and subsequent production of harmful radicals.

Advances in molecular biology in the last three decades have provided strong support for the idea that the mechanisms leading to mutation are similar or identical to those which, when applied to somatic cells, may produce cancers. Mutation (in genetic material) at a low but finite rate provides the flexibility to adapt. One can speculate that the price paid by the species for its ability to adapt is the necessity to deal with somatic mutations that may lead to cancer when the organism's defense mechanisms fail, in short, that cancer is the price the individual pays for the evolutionary survival of the species.

Spontaneous cancer

In order to estimate the spontaneous cancer mortality, I compared the crude and "corrected" mortality rates for 32 countries (identified later) and the energy consumption per unit area of each country. To anticipate the findings, because there was little correlation between corrected cancer rates and industrialization, I conclude that most cancer is spontaneous rather than being the result of man-made environmental agents. The choice of energy consumption per unit area as a crude "pollution" index was used because it is (*i*) correlated positively with the per capita energy consumption, (*ii*) directly related to the pollution per unit volume of air where people live, (*iii*) reasonably closely related to the pollution per unit volume of run-off water which may enter domestic water supply systems, and (*iv*) directly related to the opportunity for industrial exposure. Other indices might be used, but it is obvious from the narrow range of corrected cancer lifetime risks (2-fold) that the choice of index is largely irrelevant.

It would be desirable for this study to be able to estimate net cancer mortality rates from tabulated values of crude rates. This cannot be done directly because where the "other and unknown causes of death" category is large, the net cancer mortality rate [the cancer mortality rate that should exist if there were no competing causes of death, independence assumed (see ref. 2)] is seriously underestimated. This is crucial because it is in the undeveloped countries where "other and unknown causes of death" represent a very large correction to the crude cancer death rate. Comparison between industrialized and nonindustrialized countries is therefore possible only if the crude cancer rate is corrected for "other and unknown causes."

The correction for "other and unknown causes" is based on a remarkable constancy of the ratio of the probability of cancer deaths (P_c) to the probability of cardiovascular deaths (P_{cv}) with time up to 1964 as all other causes of death (P_o) diminish in 12 different countries. This is apparent from Figs. 1 and 2, in which P_c and P_{cv} are plotted against P_o for the United States (males) from 1900 to 1964 (during which time P_o went from 0.77 to 0.27) and for England and Wales (males) from 1861 to 1964 (P_o went from 0.86 to 0.30). The data in these figures, taken from ref. 2, are closely fitted by

$$P_c = A(1 - P_o) \quad [1]$$

$$P_{cv} = (1 - A)(1 - P_o), \quad [2]$$

with $A = 0.275$ for England and Wales and 0.20 for the United States. Values for the other 10 countries for which time series are available are listed in Table 1. Eq. 2 follows from Eq. 1 because

$$P_c + P_{cv} + P_o = 1.$$

However, Eq. 1 is an empirical observation, not an identity. That $P_c/P_{cv} = A/(1 - A)$ is constant over time (i.e., as P_o changes), with the value of A being characteristic of the country, is plausible if the two major diseases of old age—cancer and cardiovascular—reflect underlying genetic predispositions.

Time series are not available for most of the undeveloped countries. However, if we assume that in every country a relationship like Eq. 1 holds, then from a single pair of values P_c and P_o (or P_c and P_{cv}) at a given time we can compute the value of A for that country. Knowing A, we can calculate from Eq. 1 what P_c is for any other value of P_o. In particular, we can compare P_c in all countries at the same value of P_o.

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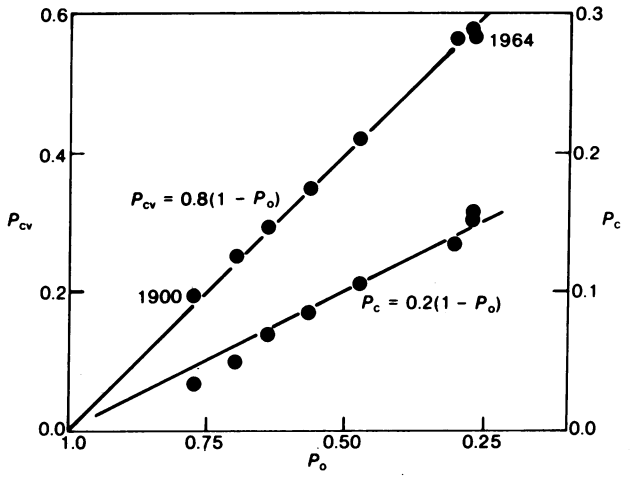

FIG. 1. Relationship between cancer (P_c) and cardiovascular (P_{cv}) mortality of men and "age-unrelated" causes of death [$P_0 = 1 - (P_c + P_{cv})$] in the United States, 1900–1964. (Data are from ref. 2.)

The results are given in Fig. 3, where I plot for 32 countries (identified by their initial letters) the logarithms of the uncorrected probability of cancer death in 1964 and of the corrected probability when all P_o values have been taken to be 0.25 (the value characteristic of advanced Western countries).

The uncorrected crude risks show a significant ($P < 0.01$) positive correlation (slope = 0.10) with the measure of industrialization, whereas the slope of 0.029 of the least squares line through the corrected cancer mortality risks is not significantly different from zero. If per capita energy consumption is used as an index, the correlation is slightly negative (−0.11).

It is clear from Figs. 1 and 2 that as causes of death that are not strongly age dependent diminish, they are replaced by those, chiefly cardiovascular and cancer deaths, that do depend strongly on age. The data support the view that up to 1964 (the significance of changes in the ratio after 1964 are briefly discussed below) there has been no differential effect of industrial effluents on these two causes. This interpretation is further supported by the behavior of the median life spans of men dying with cancer in the 32 countries. The median for all 32 countries was found to be 69.26 years, with a standard deviation of 1.78 years. There was no significant correlation between these median life spans and the industrial index described above ($r = 0.07$). It seems highly improbable that a differential effect on cancer deaths as compared with cardiovascular deaths would not be found on the life spans of those dying of cancer if industrialization were contributing heavily to cancer deaths in some countries and not in others. It was concluded from these two mutually supporting lines of evidence that the 1964 crude cancer death rates corrected to a uniform fraction of deaths from causes other than cancer or cardiovascular diseases provided a good measure of the spontaneous cancer mortality rate accurate perhaps to within 5% or 10% of its true value. Devesa and Silverman (3) have studied changes in the cancer mortality statistics of the United States between 1935 and 1975. Their results are not in conflict with the conclusion drawn above. It is suggested that the spontaneous rate for total cancers remains nearly the same for each country regardless of differences in the distribution of cancers of specific types except when very serious and long continued exposures to carcinogenic insults occur.

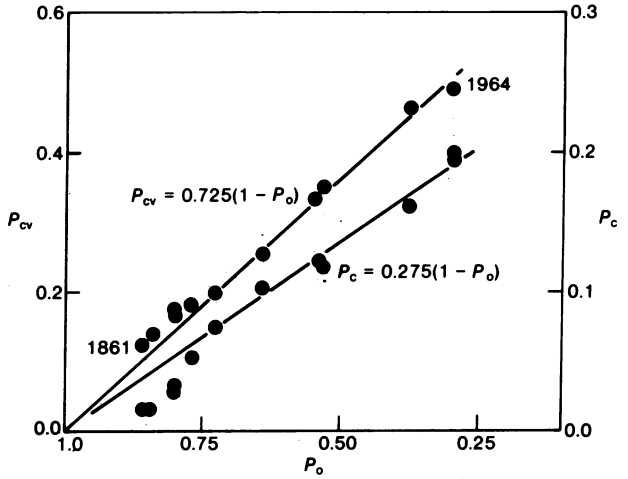

FIG. 2. Relationship between cancer (P_c) and cardiovascular (P_{cv}) mortality of men and "age-unrelated" causes of death [$P_0 = 1 - (P_c + P_{cv})$] in England and Wales, 1861–1964. (Data are from ref. 2.)

DNA defects equivalence

By comparing the spontaneous (or for that matter the crude) cancer mortality rate to the increase of cancer mortality after whole-body expousre to x-rays or γ-rays, we can estimate the number of DNA defects that must occur to give rise to the spontaneous (or the crude) rate. Estimates of the increase in rate ("excess cancer deaths") brought about from low linear-energy-transfer ionizing radiation vary from about 100 deaths per 10^6 persons per rad (1 rad = 0.01 J/kg) exposure acutely delivered (4) to about 160–820 deaths per 10^6 persons per rad (5).

In the BEIR report (5) are figures that permit a calculation of the results of a continuous exposure of 1 rad per year for a life time. The extreme values are 3.1–15.7% increase in cancer mortality per rad per year.

The dose required to equal the cancer mortality is therefore 32.3–6.37 rads per year during the life time. The lower value is apparently estimated from acute exposures without much allowance for an effect of protraction. The dose is delivered at a very low rate and therefore may be underestimated by 2- or

Table 1. Values of the ratio of P_c to $(P_c + P_{cv})$ in men calculated from data over periods of time for 10 countries compared with the same ratio calculated from 1964 data alone

Country	Period	$P_c/(P_c + P_{cv})$*	r	$P_c/(P_c + P_{cv})$†
Australia	1911–1964	0.193	−0.964	0.212
Canada	1921–1964	0.219	−0.985	0.238
Chile	1909–1964	0.337	−0.946	0.321
Denmark	1921–1964	0.272	−0.969	0.293
France	1926–1964	0.381	−0.979	0.375
Italy	1881–1964	0.291	−0.980	0.275
Japan	1899–1964	0.290	−0.990	0.272
New Zealand	1881–1964	0.229	−0.971	0.230
Portugal	1920–1964	0.251	−0.962	0.244
Taiwan	1920–1964	0.235	−0.999	0.238
Mean		0.270	−0.975	0.270
SD		0.057	0.015	0.049

P_c, crude cancer mortality risk; P_{cv}, crude cardiovascular mortality risk; r, correlation coefficient of P_c; and $1 - (P_c + P_{cv}) = P_o$.

* Values calculated by regression of P_c against P_o by the method of least squares and the assumed point (1, 0) in addition to the observed data points.

† Values calculated from the 1964 data. All data are from ref. 2.

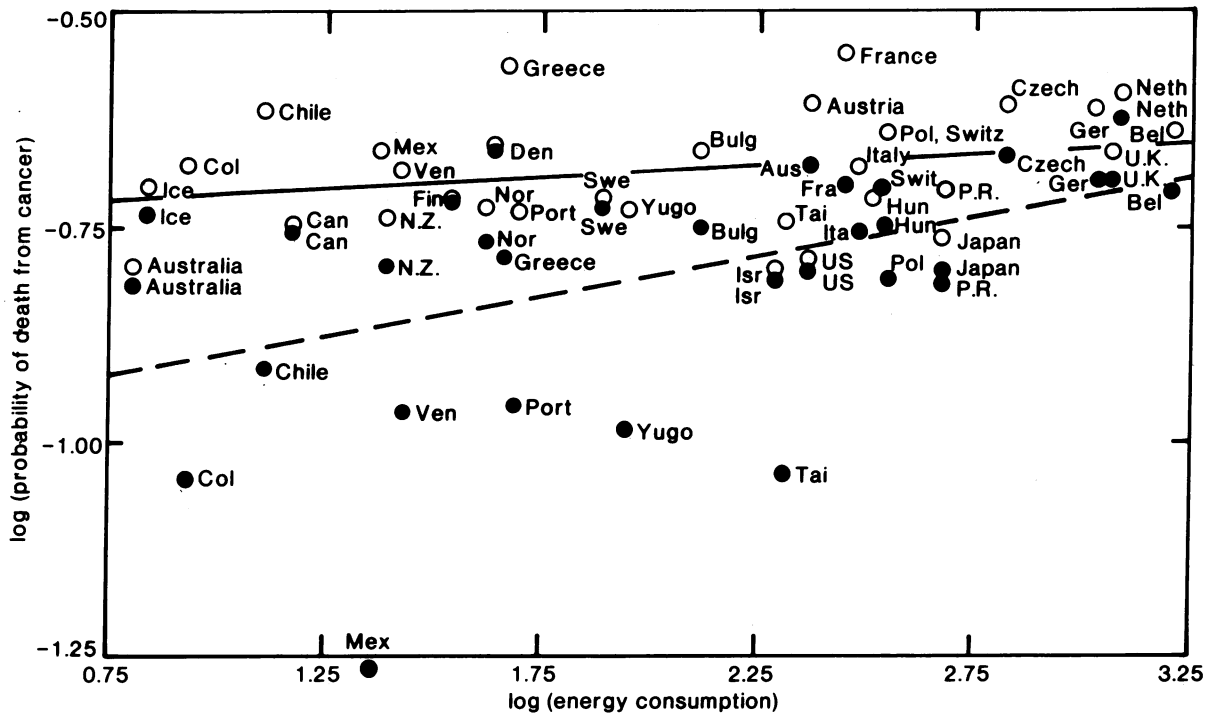

FIG. 3. Relationship between cancer mortality in men in 1964 and the energy consumption in metric tons of coal per unit area in km^2 per year of 32 countries in 1964. Cancer data are from ref. 2. ●, Data uncorrected for competing risks; ○, data partially corrected for competing risks as described in the text.

3-fold (6). The upper range given may be sufficient to include this effect, however.

The number of DNA single-strand breaks produced by an exposure to high-energy low linear-energy-transfer ionizing radiation may be estimated from the known G value for electron products. If this is taken as 3.2 (7, 8), we have $3.2\ e^- \cdot (100\ eV)^{-1} \cdot 6.25 \times 10^{11}\ eV\ erg^{-1} \cdot 100\ erg\ rad^{-1}\ g^{-1} \cdot 6 \times 10^{-12}$ g of DNA per cell = 12 e^- per cell DNA per rad.

One ·OH radical and one H atom is derived from a single absorption event. The H atoms rapidly react with O_2, if present, to give $O_2^{\cdot-}$ and $HO_2^{\cdot}$. The $O_2^{\cdot-}$ or $HO_2^{\cdot}$ from the H atom may react in the following way (9):

$$HO_2^{\cdot} + O_2^{\cdot-} + H^+ \rightarrow H_2O_2 + O_2$$

$$O_2^{\cdot-} + M^{3+} \rightarrow M^{2+} + O_2$$

$$M^{2+} + H_2O_2 \rightarrow M^{3+} + OH^- + {}^{\cdot}OH$$

where M represents a metal with an appropriate redox potential. Thus, there is a potential, indirect production of one-third as much ·OH as is produced initially by direct means. The ·OH radicals give rise to single-strand breaks in DNA.

These calculations agree closely with the result of 15–18 breaks per rad from measurements after exposure to ionizing radiation as reviewed by Hartwig (10).

At 15 single-strand breaks per rad, there may be, therefore, the equivalent of between 0.26 and 1.3 breaks in the DNA of each of the $\approx 10^{13}$ cells of the body every day. For each fatal cancer (median age at death ≈69 years, 19% fatal cancers) there are associated $\approx 3.4 \times 10^{17}$ to 17×10^{17} single-strand breaks or their equivalent in DNA defects. The repair of essentially all of these breaks and the smaller number of associated more complex defects must represent a considerable burden to the organism. The body must maintain a variety of effective repair enzymes that are continually active and must supply the necessary high-energy phosphate bonds required for the repair work. The known repair mechanisms have been reviewed by Williams (11).

As shown by the (usual) lack of discernible histological distinctions between spontaneous cancers and those that are radiogenic, the basic mechanisms for introduction of the primary DNA defects in the two cases are plausibly similar, if not identical. The fact that the spectrum of radiogenic cancers may differ somewhat from that of spontaneous cancers is not a strong argument against the hypothesis that the origins of all or nearly all cancer are caused by the action of the same types of primary radicals. The spectrum from whole-body radiation is not yet fully known, but evidence is accumulating that in humans some leukemias and many solid tumors can be radiogenic (see ref. 12). An acute dose of ionizing radiation would not be expected to result in exactly the same time course of tumor appearance or to mimic precisely the slow steady production of the same number of radicals over many years in different organs and tissues.

Role of oxygen

Numerous observations of the effects of oxygen on chromosome breaks and on mutations have been accumulating since the observations of Conger and Fairchild (13). These authors attributed the effects of increased oxygen pressure on *Tradescantia* chromosomes to oxygen radicals.

Their observations were quickly confirmed and extended to other organisms (14–16). The mutation rate in *Escherichia coli* was shown by Fenn *et al.* (17) to be elevated by hyperbaric oxygen. More recently, Burns (18) found increased mutation rates in three strains of *Salmonella typhimurium* subjected to high-pressure oxygen exposure. Bruyninckx *et al.* (19) have shown similar changes with variation of the partial pressures of oxygen without elevating the total pressures. Plaine (20) observed tumor induction in *Drosophila melanogaster* when the embryos were subjected to 60 min of oxygen under pressure.

There is in the body a ready source of oxidizing radicals from the univalent reduction of oxygen. Several enzymes produce

O_2^- during the oxidation of their substrates—for example, xanthine oxidase (21–23) and peroxidase (24). Numerous substances, upon auto-oxidation, also produce O_2^-; reduced flavins and vitamin C are among these. That the O_2^- actually appears in metabolism is attested to by the ubiquitous occurrence of superoxide dismutases in all aerobic cells. A review of the function of this group of enzymes has been published (25). See also ref. 26 for earlier speculations concerning oxygen radicals and DNA.

The rate of O_2^- production is not known, but it would require only a very small fraction of the total oxygen metabolism to provide a copious amount. A day's amount of food equaling 2500 calories of energy requires about 23 mol of O_2 for combustion; that is, about 3.3×10^{-4} mol or 2×10^{20} molecules per g of tissue per day. As given above, 3 molecules of O_2^- can potentially produce one ·OH radical.

A little over 2×10^{12} ·OH radicals are produced by exposure of 1 g of water to 1 rad of ionizing radiation. Only $(6 \times 10^{12})/(2 \times 10^{20})$ (3 parts per 100,000,000) of the daily oxygen used is required to escape the initial lines of defense against oxygen toxicity to provide ·OH radicals equivalent to a 1 rad exposure to ionizing radiation. The cost to the organism of complete protection against the radicals produced is probably much higher than can be borne and, of course, might abolish another required function such as the oxidation of substrates to which the organism has not been adapted.

Discussion

The mean life span in developing countries has increased over the past century or so owing to the elimination of most fatal infections by public health measures and sanitation. This resulted in a change from a relatively random pattern of mortality approaching a death rate proportional to the number of people alive to one that appears to be largely genetically determined. The major "natural" causes of death are now age related. It has been assumed above that genetically determined death rates are fixed by the results of natural selection and that the ratios of the various age-related causes will not change over a small number of generations if they are undisturbed by external conditions that change the apparent rate of aging.

That cancer is a "natural" cause of death is shown by its well-known age dependence. The net cancer death risk plotted against age is in no significant way distinguishable from the net cardiovascular risk, which is almost universally believed to be age related or age determined. Both of these relationships are shown in Fig. 4. The values were averages calculated from male death rates (1964) for 11 developed countries from tables of Preston *et al.* (2). The results were plotted on probit paper, which gives straight lines for normally distributed values. There is a sharp inflection dividing straight-line segments in both curves at about the end of the age of reproduction. This behavior strongly supports the idea that death rates for age-determined causes are the result of successful natural selection for longevity. There is little reason to believe that the total cancer mortality risk has been significantly altered as a consequence of the industrial revolution. Mortality risk for some individual cancer sites (lung and stomach cancers particularly) have, however, changed sharply in recent years. Where increases have occurred, they cannot really be called "extra" cancers unless they have been subtracted from the other age-related causes of death. They are for the most part replacements for other cancers and, as such, would only alter general longevity in very small degree. This is not necessarily in conflict with the observation that *age-specific* risks from other cancers may not change (27, 28) when the mortality from one site increases or decreases over a period of time. By contrast the *lifetime risks*,

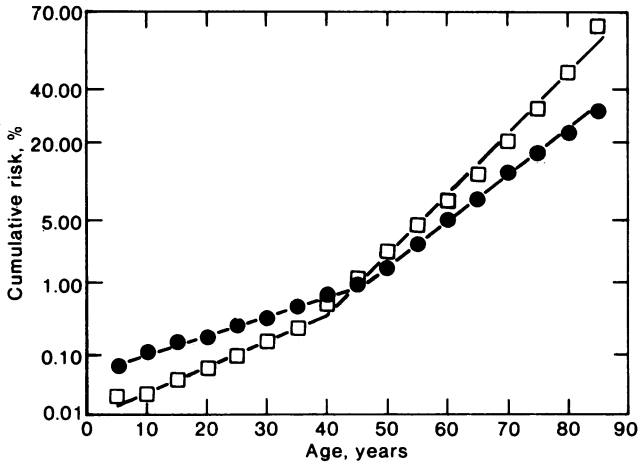

FIG. 4. Cumulative net risk of death in men from cardiovascular disease and cancer (1964) with increasing age in 11 developed nations. Data are from ref. 2. □, Cardiovascular mortality risk; ●, cancer mortality risk.

however, must adjust or there would be a change in slope of the lines relating P_c (and therefore P_{cv}) to $1 - P_o$ if the increase in one cancer were not balanced by decreases in others.

Prolongation of life by successful treatment of cardiovascular diseases is probably changing this picture; this may explain the diminution in P_{cv} relative to P_c after 1964. Treatment should result in an increase in the mean life span, which will bring about an increased cancer risk, and consequently a larger fraction of the population will die of cancer but at an older mean age.

Few cancers arise in tissues whose metabolism is largely governed by physical activity. Thus, if there is truly a relationship between oxygen metabolism and cancer incidence as is proposed here, then it should be more clearly linked to the basal metabolic rate than to total oxygen consumption. If this is correct, it will conveniently explain why small short-lived mammals (because their metabolic rate per g of tissue is high) can get fatal cancers in short periods of time, even though the life history of individual cells in large and small mammals does not seem to differ with respect to time in nearly so great a degree. In humans, women appear to have a somewhat lower cancer mortality rate than men. They also have a roughly 10% lower metabolic rate.

From an evolutionary point of view, selection for longevity probably occurs in all populations that have a death rate proportional to the number alive (random). The selection may result in changes in size (basal metabolic rate), in defense mechanisms (superoxide dismutase, catalase, DNA repair enzymes, and immune mechanisms), and in reproductive strategy.

In conclusion, evidence has been presented that suggests that most cancer mortality is independent of external conditions. What is here termed "spontaneous" cancer was calculated to arise from DNA damage equivalent to a radiation dose of between 6.37 and 32.3 rads per year for a life time. This suggests that there are at least 0.26–1.3 single-strand breaks on the average in the DNA of each cell of the body each day. It was suggested that these cancer-producing defects arise from univalent oxygen reduction and conversion of a small fraction of the O_2^- produced to ·OH radicals by operation of a Fenton-like series of reactions (9). The rate of production of these damaging radicals is probably closely linked to the basal metabolic rate. Defense mechanisms are likely to have been strengthened by natural selection.

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