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CANCER: A RESULT OF INCIDENTAL EXPOSURES OR OF SENESCENCE, OR OF BOTH?

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Discussions of cancer epidemiology usually start from a foundation of assumptions that are rarely explicit enough to provide a base from which a firm argument can be built. In this discourse I will attempt to state as clearly as possible the assumptions, usually only implied, that are necessary to arrive at the conclusions one sees or hears about almost daily in the media.

The current most popular hypothesis on the origin of cancer was epitomized most succinctly by Dr. Robert Hoover in his oral presentation at the New York Academy of Science Symposium in March 1975. He stated that "...every cancer has a cause...." Although one can hardly take exception to a simple restatement of the principle of cause and effect, in the context of his other words, it was clear he meant that we could find the cause, eliminate it, and therefore be free of that type of cancer, thus reducing the total cancer burden of the population by that much. For this to be a reasonable conclusion to draw, one must make a rather complex set of assumptions and find support for them. Most simply, one might assume that humans are potentially immortal, all causes of death are "accidental" in the sense that they are not inevitable, and then it would follow that Dr. Hoover was presenting a conclusion that is a necessary consequence of these premises. But, where is the scientific support for the hypothesis that our bodies are immortal?

DISEASES OF SENESCENCE

Some causes of death are clearly accidental and these include traumatic injury as well as most of the infections and parasitic diseases we die of, because, at least the exposure is not inevitable. If we are not immortal then some of the mortal diseases must be diseases of senescence. The categorization of the causes of death we use is all inclusive and there is no category that is labeled "old age," or "senescence" in this country. Therefore, an operational definition of the classes of diseases that are to be labeled "diseases of senescence" must be made.

One way to do this is to examine mortality tables and discover which diseases tend to be very infrequent in early life but highly prevalent in old age and associated with death. If the relationship is such that it can be expressed as a smooth mathematical function, its frequency rising steadily with age then that disease is a candidate for designation as a disease of senescence. If all, or at least all of the quantitatively important causes of death, are treated in this fashion and the results expressed by some parameter such as median age at death, they can be compared as in Tables 1 and 2, which list causes of death of women in England and Wales for 1861 and 1964 respectively. The data are from the compilaton "Causes of Death" (Preston, Keyfitz, and Schoen, 1972). The last three categories listed in both tables are the only causes of death that fullfil the two criteria listed above for "senescent" causes of death. Death from influenza, pneumonia, and bronchitis fit the two criteria in the 1964 Table but not in the 1861 Table. In most other countries examined, only the last

three causes of death listed in Tables 1 and 2 appear to be suitable as candidates. Preston (1976) has earlier shown the special relationship of the "other and unknown" category to cardiovascular disease and cancer.

The acceptance of these three groups of causes of death as the main contributors to "senescent" deaths is not in qualitative conflict with current views on cancer. With the exception of a few vocal extremists, many epidemiologists accept the view that there are some "spontaneous" cancers. The problem then becomes one of differentiating the fraction of the mortality from cancer that is "spontaneous" (chiefly owing to senescence) and for the remainder determining the causes (presumably from detectable external environmental conditions or from "life styles" that can be altered or removed entirely). If this part of the problem can be solved, there still remains a less obvious problem: Why, assuming that we find a large fraction of cancer mortality to be in fact the result of senescence, does cancer mortality appear to be "independent" of cardiovascular mortality? In other words, if most or all of the diseases classified as belonging to the category of cardiovascular disease are the result of senescence, shouldn't all of the diseases classified as cancer behave in the same statistical manner if they are also found to be chiefly the result of senescence? The answer to this question is very complex and involves yet another subject--the cause(s) of aging itself.

CURRENT VIEWS ON CANCER CAUSATION

Before proceeding further with the relationship of cancer to aging, additional information about the origin of the current popular view of cancer causation will be briefly reviewed. Most problems of the type posed by cancer occurrences are attacked in the laboratory by reductionist means. The first clues pointing to possible laboratory study arose from observations of cancers associated with certain occupations that involved exposure to chemicals. The most striking of these, but by no means the only one, was the association of scrotal cancer with chimney sweeping pointed out by Sir Percival Pott (1775). Chemicals implicated as specific causes of human cancer were certain nickel carbonyls (Doll, Morgan, and Speizer, 1970) and 2-naphthylamine (Friedell, 1969; Hueper, 1969). These discoveries led to successful searches for other cancerogenic agents. The findings gradually gave rise to a general belief that all or almost all cancers may indeed arise from exposures to chemicals. If exposure to cancerogenic chemicals could be prevented or avoided, then perhaps, it was thought, most cancers could be eliminated.

Another and quite unrelated series of studies provide additional reasons to consider seriously that cancers are entirely "accidental" in the sense that their causes might be avoided. These studies arose from interest in geographical differences in the occurrence of different types of cancer. For some years there was a section of the National Cancer Institute under the leadership of H.L. Stewart that gathered data on incidence and mortality from cancer on a world-wide basis and evaluated the completeness of the data

(see Dunham and Bailar, 1968 for an example). The chief (but not the only) early proponents of the idea that the differences in incidence or mortality from specific cancers in different locatilites must be, at least in part, attributable to differences in exposure to external agents, were John Higginson (1976), and Richard Doll (1977). Doll (1977), in his review lists several cancers which show ratios of about 5 to 1 to more than 200 to 1 between high and low incidence areas.

Both of these investigators now prefer to attribute most cancers (at least 60-70 percent) to "life-styles," perhaps because they recognize that it is difficult to identify sufficient concentrations of known carcinogens in the environment to account for more than a few percent of the observed total cancer burden. It is clear, however, that both Higginson and Doll still support the idea that cancers are independent of each other and of cardiovascular disease. This assumption is a vital part of their arguments.

THE PROBLEM OF INDEPENDENCE OF CAUSES OF DEATH

It is difficult to explain to people unfamiliar with statistical procedures or with epidemiology, the effect that the assumption of independence has on both calculations and conclusions concerning the effects of environment on life spans. Perhaps the following story will help introduce the problems to the reader who may be unfamiliar with the importance of the assumption to epidemiology:

"A Martian biologist was given a grant to spend one year in the U.S.A. to determine the secret of human longevity. Being asexual itself (as all

Martians are) and never having encountered sexual reproduction in populations it had studied, it was somewhat perplexed by the noticeable differences in the two major classes of humans it saw. It was far too busy gathering data to study the matter closely but did manage to mark down whether the subjects habitually wore dresses or trousers, and insured that the otherwise random sample had equal numbers of the two classes even though it was evident that many more wore trousers than dresses.

"Recognizing that the quickest way to study the problem of longevity was to prepare a life table, it proceeded to gather data from a suitable sample of the U.S. population for 1964. There wasn't time to do a complete study but it did manage to get death rates from all causes, and separately for cancer and cardiovascular disease for all ages. The median age at death for the Martian's sample was determined to be 75.59 earth years. There was just enough time to prepare Table 3.

TABLE 3. SUMMARY OF STATISTICS AT THE MEDIAN AGE OF DEATH

Subject Class	Median Age at Death	Cause of Death		
		Cancer	Cardiovascular Disease	All Causes
	yrs.	Fraction of the Population		
Trousers	73.8	.053	.141	.284
Dresses	77.99	.050	.104	.216

"By the time this table was finished, the Martian embassy notified the investigator that, owing to the large national budgetary deficits, its support would be terminated immediately and it must return to Mars. The report was written in great haste with the conclusion that the wearing of

trousers imposed a serious environmental hazard, the effects being shown mainly by a 6 percent increase in the cancer risk and a greatly elevated cardiovascular death rate. The average life shortening, owing to trousers, that was observed was estimated to be 4.19 years.

"The Chief of Environmental Health at Interplanetary University, who received a copy of the report and knew all about sex, observed that the Martian's results would agree with his own records if 33 percent of the Martian's "trousers" group were women."

This story illustrates many of the problems that confront the epidemiologist especially when he attempts to assign causes for the differences that he sees in his samples. In the story the epidemiologist did not know that genetic difference might be the underlying cause of the difference in longevity as well as some of the difference in wearing apparel. The Martian assumed that it was seeing differences that were independent of constitution. Even people who have access to knowledge of the differences that arise from differing genetic constitutions sometimes prefer to ignore them. For example, Miller and Gerstein (1983) prefer to attribute the male-female difference in longevity entirely to differences in smoking habits, a conclusion that demands complete independence of causes of death. Many epidemiologists take a less extreme stand and attribute one-half or somewhat less to cigarette smoking prevalence among males. However, is it possible that they (for that matter most of us) are as blind as the Martian toward some constitutional difference in those who can and usually do become addicted to cigarettes and those who do not? Following R.A. Fisher (1958, 1959) and others, P.R.J. Burch (1975, 1978, 1984) has repeatedly tried with-

out much success to convince skeptical epidemiologists that they have no sound logical foundation upon which to base their contention that smoking cigarettes shortens the life-span by several years. In a recent letter to the editor of Chemical and Engineering News, Richard J. Hickey (1986) has also reiterated his dissatisfaction with the basis of the U.S. Surgeon General's attack on tobacco use.

The conclusions that are usually drawn about cigarettes causing life shortening are squarely based on three assumptions: Firstly, that lung cancers are caused by cigarette smoking; secondly, that deaths from the smoking-associated lung cancers and cardiovascular diseases occur at younger ages than the smokers would otherwise have succumbed; thirdly, and most importantly, that cigarette smokers consitute a valid random sample of the (male) population.

If the third point made above were to be resolved, the other two would also be quickly resolvable. To illustrate, let us look again at data from the U.S. male 1964 life table (Preston, Keyfitz and Schoen, 1971). From this data it can be calculated that the median age at death of the shorter-lived one-half of the male population is 59.28 years while for the longer-lived one-half it is 79.93 years (these are the life table ages at which 25 percent and 75 percent respectively of the population have succumbed) for a difference of 20.65 years. Combining these two linearly in different proportions allows us to estimate, rather crudely, the divergence from randomness that would give any desired shortening (spurious) of life span that might occur if the cigarette smoking cohort were to be unevenly divided between the two halves. If it is evenly divided the median age at death

becomes 69.61 years. (The actual median age is 70.81. This difference is small compared with the 20.65 years and attributable to the error involved in assuming a straight line survival curve.) If the division is 65:35, that is, 15 percent more of the total smokers are in the short-lived group, the calculated median age is given by:

$$0.65 \times 59.28\text{yr} + 0.35 \times 79.93\ \text{yr} = 66.51\ \text{yr}$$

or 3.1 years shorter than the 69.61 years given for the 1:1 ratio. Of course, in a real well-designed epidemiological study there would be many refinements built in to try to minimize the errors but this crude estimate shows how close the distribution of smokers into the two halves of population, long-lived and short-lived, must be in order to calculate a reasonably accurate median age at death for the smokers.

There is no direct way to resolve this difficulty. We cannot bring the dead smokers back to live their lives over again without smoking to see what their life-spans would then be. Many indirect methods have been tried but they are, without exception, plagued by the same difficulty detailed above or by an analogous one.

Is there is any reason to believe that smokers are not a valid random sample of all of the genetic constitutions that occur? It may be speculated that most people do not adopt a costly habit unless they derive some benefit from it. Could it be that the benefit is the relief of some perceptible stress that is strongly associated with a genetic constitution that is in part the cause of a short life?

The problem of independence can be understood better if we compare the epidemiologists' needs with those of the insurance actuary. Both have

available the same information and both use many of the same statistical techniques to organize the data. The question that should be uppermost in the epidemiologists' mind if he is comparing the longevity and causes of death of two individuals living in two separate but not distant communities, is, if these two people were to be exchanged, would they have the same or different longevities; the same or different causes of death? If it were possible to have the two live their lives over from birth but each in the others' enviroment, we would be able to say something about how much the environment affected their longevity and causes of death and how much stemmed from their different genetic constitutions.

On the other hand, the actuary has much less interest in whether the genetic constitution largely determines longevity. He deals with large numbers of individuals and he knows that the mortality curve is unlikely to change rapidly. He can therefore deal with his insurance problem with little worry that his calculations can be rapidly outmoded. Whether the environment or heredity determines the shape of the curve is not important for his calculations. He can use the assumption of independence of causes of death to estimate the number of deaths from other causes when one or two causes are removed, without making a significant error in the estimate, even if the assumption is not biologically correct. He has no responsibility for attempting to define the mechanism of aging.

It is when we wish to attack the problem of cause or to promote means to eliminate a cause of death that the assumption of independence begins to assert an overriding importance. With the possible exception of sufficiently large studies on identical twins reared in different environments,

epidemiological studies cannot offer definitive proof of independence or dependence of different causes of death, because the direct experiment of bringing deceased people back after death to relive their lives in a different environment, cannot be accomplished. The inability to provide a scientifically acceptable resolution to the problem of independence, places most of the current hypotheses attributing causal relationship to factors that correlate well with cancer incidences and mortalities, into an intellectual limbo. This opens the way for promotional fervor to overcome natural scientific skepticism and for some dedicated believers to misuse their power as reviewers of manuscripts to suppress scientific dissent and degrade the system of self correction of science through peer review. This aspect of the problem was noted by Efron in her review "The Apocalyptics" (1972). Many grave consequences follow from this distortion of the scientific effort. In particular "campaigns" planned to eliminate this or that cause of death may result in much ill-aimed and costly effort detracting attention from the routes that must eventually be followed to achieve the real and usually worthwhile goals of the campaigns. It would be ironic if someone who almost was within grasp of a solution of a key problem in aging, was frustrated from doing so by failing to benefit from the soothing effect of a good smoke at a crucial moment because his workplace was off-limits for smokers.

SENESCENCE AS A CAUSE OF CANCER

The alternative to the hypothesis of "complete" independence is "complete" dependence. That is, all causes of death attributable to senescence are strictly determined genetically. Of course, genetic causes exert themselves differently in different environments. The problem is to determine to what degree, and in what manner, does the environment have to change in order to change, by a given amount, the age at death of a person dying from a genetically determined cause of death. It is pointless to ignore the environment with whichever hypothesis one is concerned.

It should be evident that the choice between hypotheses concerning the relative importance of heredity and environment in determining the life-span of individuals and populations, cannot be made on a basis of solid proof. That is not available and the choice we make will have to depend first on the degree to which a hypothesis can explain, without stress, findings that can be accepted as factual. Second, it must fit comfortably within broader aspects of biology, not conflicting with generalizations that are basic to our understanding of biology.

With these thoughts in mind some comparisons will now be made between the currently popular hypothesis placing emphasis on "environmental" (or "life-style") causes of cancer and a hypothesis placing a much larger dependence upon constitutional (genetic) causes. It should be clear that what is being striven for is a reasonable compromise that accounts for the facts, with the outcome expected to be somewhere between the extremes of

100 percent "accidental" (as defined above) and 100 percent "natural" causes leading to mortality from cancer.

The first question to be considered concerns the form of the mortality curve for cancer as compared with other causes of death tentatively placed in the "senescent" group, as indicated above. It can be noted that if we accept the idea of the deaths being mostly "accidental" i.e., not due to senescence, we have to explain the mathematically regular increase in death rate with age. This requires an additional ad hoc hypothesis, that of a series of latent periods with just the right length to make the curve ascend smoothly.

Alternatively, if we accept the constitutional hypothesis, the cancer mortality curve should resemble that obtained from the other "senescent" causes which, in fact, it does, although it is not identical with them. In particular, the median age at death is lower and the variance differs from that for cardiovascular diseas. Because individual components of the cardiovascular group also differ among themselves, this does not seem to present a difficult problem. The shape of the curves are near enough to the normal curve to qualify as showing the usual type of variability that is expected to result from genetic heterogeneity.

The lower median age of death from cancer allows us to examine this difference for variability inasmuch as time series data is available for several countries. Some of these available from Causes of Death (Preston, Keyfitz, and Schoen, 1972) are shown in Table 4. The high correlation of the differences in median ages at death, for both men and women between "all" senescent causes and cancer, provides good evidence that the

differences are not accidental but rather must be constitutional. Also, the fairly close concordance between median ages at death for cancer in men and women suggest that only a small difference could result from the rather large differences in environment (including smoking) encountered by men and women over the course of the years represented in Table 4. This argument, of course, may not hold for other components of "life-style."

The secular changes in median age at death seen in Table 4 may be in small part arithmetical but a close examination reveals that spurious effects, if any, must be small. The changes are largely owing to real changes in life-span under the environmental conditions extant during the lifetimes of the populations. If they are largely owed to the current environment, there is little support for any argument that conditions have deteriorated during the 50-100 years preceding 1964.

On the contrary, it appears much more likely that genetic changes have occurred rapidly during the last few hundred years and these have become manifested (i.e., phenotpyes have more closely approximated genotypes) since the industrial revolution began increasing the general prosperity of the various populations.

THE RELATIONSHIP OF QUANTITATIVE NUTRITION TO SENESCENCE

Charles Dickens has written of a persons' fiscal balance: "Annual income twenty pounds, annual expenditure nineteen, nineteen and six; result happiness. Annual income twenty pounds, annual expenditure twenty pounds ought six; result misery."

Nature accounts for an animals' energy balance just as rigidly. If we have a smaller energy income than outgo she will demand her pound of flesh. If it is the other way and what may be even worse she will add the pound of flesh. These are temporary expedients, however, and there are more subtle adjustments that go on over the long-term. We can see why there must be other ways to adjust by estimating weight that would have to be added if we consumed each day a 10 percent excess in calories. A pound of flesh represents about 600-1500 calories depending on how much is fat. This is one-third to about two-thirds of a days' caloric requirement for a sedentary adult male. If another 500-1000 calories are needed to convert the rest to flesh we see that an extra pound of flesh represents about 1 days' intake of food. At 10 percent excess, 10 days should add 1 pound, 1 year 36.5 pounds, and 10 years 365 pounds, etc. We do not see many individuals that weigh more than 400 pounds even though we may be reasonably sure that many people eat in excess of 10 percent more than their daily requirement for maintenance of weight. Those of us who are old enough to remember the depression of 1929-42 know that people ate at least 10 percent less than they do now, on the average. Not many died of starvation but fat people nearly disappeared from view during the decade of the thirties.

As we shall see, the way our bodies adjust to differences in intake of food has an important bearing on our longevities and consequently on the rates at which members of a population die of senescent causes including cancer.

What mechanisms are available to ameliorate the effects of too great a caloric intake? Three things quickly come to mind: Increased physical

activity; increased conversion to heat and elimination of the excess heat; increased reproductive activity. The mechanisms for accomplishing all of these things are reasonably well known. An increased production (or altered composition) of the thyroid hormones results in what appears to be a reduced efficiency of conversion of energy to muscular activity, thus increasing the heat output relative to the muscular work done. Altered functioning of the pituitary, perhaps secondary to the need for more thyroid activity, may change the reproductive cycle, preparing for increased reproductive activity. In any case the individuals in the population must respond to the signal from the environment that indicates an abundance of food. Those species which lacked an appropriate response must have long since been crowded out by those that developed the more efficient mechanisms for responding appropriately. In humans, abundant food reduces the age at which young women become able to bear children. Also it reduces the intervals between childbirth because it reduces the length of time young must be nursed to insure their survival, and nursing inhibits conception. These responses inevitably lead to an increase in the population of early maturing, rapidly reproducing individuals relative to the late maturing, slow reproducing ones. When food is scarce (relative to the energy required to gather it) the early maturing, rapidly reproducing contingent would be most sensitive to the lack and tend to die early, while the late maturing, slow reproducing group should be able to subsist on less, and consequently, in the long-run, produce more offspring than the shorter-lived group. In this way it can be seen that reproductive rate should, through natural selection, rapidly become negatively correlated with life span. The direct observation

of this reciprocal relationship in experimental animals was probably first made by Hall and Marble (1931), who worked with laying hens.

It can readily be appreciated that the scenario outlined above could account for a population "boom and crash" cycle under certain environmental conditions. Under other conditions it might lead to a fairly steady equilibrium or to any combination between these extremes. The scheme allows for entrainment of cycles into externally driven fluctuations such as an annual cycle. It seems quite likely that the cycling between extremes, whether steady or not, is a major source of variance in life spans within populations. It should also be a source of variance in size as explained elsewhere (Totter, 1985), and a source of intermittent or continuous pressure for an increase in size over long periods of time.

RADIATION HORMESIS

If we combine the foregoing suggestions with what is known of radiation hormesis in animals we can lay a solid foundation upon which to base a hypothesis that accounts for senescence operationally. Unfortunately it does not give a solution for this problem at the molecular level but it has much to offer at the physiological level, and points to the type of research needed for progress in understanding aging at both a physiological and a molecular level.

When x or gamma rays are absorbed in water or a water containing medium, electrons are freed from the water molecules following which the water decomposes into H atoms and hydroxyl radicals as well as into H^+ and

OH^- ions. Unless it has been carefully excluded, the oxygen in solution scavenges the H atoms to produce superoxide radicals and H^+. The superoxide radicals can combine with others of the same kind and H^+ to give hydrogen peroxide and O_2. The hydrogen peroxide is a powerful oxidizing agent because at tissue pH and in the presence of traces of certain metals (iron, copper, etc.) it gives rise to hydroxyl radical that may produce Fenton-type reactions. The damage to cells and cell components caused by the products of radiolysis are called "indirect effects" because they can occur to molecules that do not suffer direct ionization through absorption of radiation. Up to about 70 percent of the measurable damage to tissue from absorption of low linear energy transfer, ionizing radiation may result from the indirect effect (Lea, 1944).

Oxidizing Radicals and Senescence

Evidence has been accumulating for the past 30-40 years that indicates the presence of, and the necessity for, oxygen radicals in metabolizing tissues. These radicals are similar to or identical with the ones produced by the absorptions of x or gamma radiation by oxygen containing water. (For reviews, see Rodgers and Powers, 1981; Gottlieb, Langmuir and Totter, 1984; Ames, 1983).It has long been believed that exposure to ionizing radiation produces many of the same biological effects as are seen to result from the passage of time (Lindop and Sacher, 1966). Several investigators have advanced the idea that "aging" is in fact, largely or entirely the result of the deleterious actions of oxidizing radicals produced during metabolism.

The well-known relationship between basal metabolic rate and life span in endotherms is in good accord with the hypothesis (Sacher, 1959).

If the conclusion is correct that oxidizing radicals are responsible for aging, then we should see some manifestation of small doses of whole-body ionizing radiation that mimic the effects of food. They are not difficult to find. One of the most universal effects of a meal is the suppresion of appetite. Reduction of appetite is a well-known effect of whole-body, head, or trunk irradiation. It is true that the dose-effect relationship for this manifestation is not well explored. However, the effect is no more likely to exhibit a threshold than any other known effect of radiation exposure. It has been suggested that this appetite effect is responsible for the hormetic effect of radiation (Totter, 1985). If appetite is supressed by nearly continuous low-level exposure to gamma rays, one would expect to see, as one result, the effects of the reduced food intake. The most conspicuous of these effects is life span extension as seen in the experiments of Lorenz et al. (1952). Their results may be compared with the food restriction experiments of McKay et al. (1939) and many others.

An abundance of food tends to "rectangularize" mortality curves as may be seen in human populations undergoing the "demographic transition." This result is also seen in the Lorenz experiments. Of course, no calories useful to the animal are obtained from the irradiation, so weights may not increase as fast as they would with more food. However, an additional physiological change consistent with the "food substitution" idea was seen by Lorenz et al. This was the increase in body fat seen in irradiated animals as compared with nonirradiated controls.

The animals receiving the larger semicontinuous radiation exposure (0.022-0.088 Gd^{-1}) had quite steep survival curves with shortened life spans, in accord with the steepened survival curves in well-fed humans.

The chief difference in results between the humans and the irradiated mice were that the largest increase in death rates in mice occurred because of cancer rather than cardiovascular diseases. It has been suggested elsewhere (Totter, 1985) that this difference may be owing to difference in normal flux levels of oxidizing radicals between the surroundings of the nucleus and those of the cell walls in tissues.

The oxygen radical hypothesis of aging offers many attractive avenues of research. It also offers a basis for understanding how longevity (or senescence) has been molded by selection. The strategies such as repair, reduction of radical flux, etc., that are necessary to promote longevity are easy to enumerate. It must be remembered that the most important natural one was increase in size, which permitted a reduction in basal metabolism--the source of the radicals.

As indicated at the beginning of this section, the key problem to the organism is to use the energy available to it to insure its own survival and that of sufficient offspring so that the species persists. There are ways to manipulate the requirements for energy to insure species survival. Those animals that were not lucky enough to find the right combination are no longer here. The very small mammal has to gather a prodigious amount of food to keep warm and have enough excess energy to produce frequent large litters of young. Its high metabolic rate ages it rapidly. It has no time

to invent ways to gather and store food for winter so that it could reduce its reproductive rate and so acquire a somewhat longer life span.

The large mammal or bird requires much less food for unit weight so it can put relatively more energy into insuring a longer life. It cares for its young and protects it against predation so it need not reproduce so many times. These savings permit improved protection against the smaller number of radicals formed so that it ages more slowly.

THE FUTURE

Humans are in a transition period now--evolution is proceeding at a prodigious rate. We are changing both in size and longevity. We have, owing to organization and mechanical transport, severely reduced the energy (our own) formerly required to gather food. Our young seldom die before reproductive age. We could reduce our reproduction so as to just maintain numbers. The energy savings could be used to increase longevity--but must we wait for the evolutionary change--could we cheat a little? The trouble with waiting for the evolutionary change is that it is likely to go in an undesired direction. If food remains abundant and easily obtained, the signal to our physiology (and the endocrine glands will respond) will be to reproduce rapidly and age quickly. One can already discern this tendency in the statistics for some developed countries. For example, the reduction in age at puberty among young women is well established (Wyshak and Frisch, 1982).

On the other hand, if we eat sparingly and exercise vigorously, the signal to the endocrines is that food is difficult to obtain and calories must be husbanded to insure that we can use them to obtain food. Consequently, our reproductive rate and our aging rate diminishes. The diseases of senescence are postponed and our lives lengthened. The adjustment of the endocrines to the environmental signal created by the scarcity or abundance of food and our "energetic" response is best seen in the slope of the life-table mortality curves that reflect the change in reproductive success of the short-lived compared with the long-lived descendants.

If we owe our longevity to the action of natural selection in eliminating the short-lived and favoring the long-lived, how does it come about that mortality curves do not follow a normal distribution as do many other attributes whose variance is governed by selection? The answer is that some do, although not many appear to behave in this manner. The reason most do not may be found in the fact that, as noted above, most populations are undergoing strong selection just at a time when most of our useful data are being gathered. Selection tends to distort curves which under relaxed conditions would be normal as depicted, for example, in Wilson and Bossert's "Primer of Population Biology," (Wilson and Bossert, 1971).

Favoring this explanation is the fact that mortality curves that largely consist of death from senescent causes are easily converted to normal curves by a simple systematic operation on the age axis. That is, the data normalized and converted to normal equivalent deviates may be compared with ages raised to some power less or greater than 1. (If the best fit is given by the power 1, then the curve is naturally a normal one.)

The degree to which the power differs from 1 to get a good fit to the curve is a measure of the degree of selective activity of the living conditions. This systematic shrinking or stretching of the age-axis is akin to the use of a logarithmic normal distribution that also shrinks the age axis as the age increases. The "agepower" method (Totter, 1981), however, is much more general than the log-normal distribution. The conversion of life table data to formulas describing the parameters of normal curves from which the life-table data may be accurately reproduced (correlation coefficients are almost always above 0.999) is a great convenience and allows many comparisons that are not easily made with other mathematical operations, such as conversion to Gompertz or Weibull curves. Figure 1 illustrates one use of the method to depict the frequency distribution of women that died of senescent diseases in England and Wales in 1901 or in 1964. Other comparisons may be seen in an earlier publication (Totter, Adler, and Storer, 1985). One can see that in spite of great differences in rates for the diseases the relationship of the fraction dying at any age is the same in 1964 as it was in 1901 except for the age displacement of 10 years, owing at least in part, to increase in longevity in the 4 or 5 generations between the old and the more recent data collection. Precisely the same display could be made for the total cancer or total cardiovascular deaths with only the median ages at death differing for the two.

The results shown in Figure 1, typical of many such comparisons that have been made do not speak in support of a chiefly "accidental" type of environmentally caused death from either cancer or cardiovascular disease. They do strongly support the idea that whatever effect the current

environment has, its expression is determined by the genetic composition of the population. The frequency distribution of deaths from both cancer and cardiovascular disease at different ages among the members of the population are largely fixed by this composition. The genetic composition was, of course, affected quite rapidly by the environment encountered by the ancestors of the current generation. The fact that the gene frequency may be rapidly changed by environmental conditions does not imply that we may be able to change the conditions at will. The quantitatively most important attribute of the environment is the accessibility of food and it is the caloric intake that is of overriding importance in affecting the life-span and the death rates from all senescent causes of death.

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The estimation of ionizing radiation effects, based on the alternate hypothesis presented here, is greatly different for low-level low-linear energy-transfer (Low LET) exposures from that made on the basis of the "classical" theories. For densely ionizing radiation that produces a much greater "direct effect" than "indirect effect" there is likely to be little difference. If there is a steady flux of oxygen radicals produced by metabolism, equivalent in terms of cancer incidence to 0.0002 to 0.001 Gy each day, then exposure to a dose of 0.01 Gy of Low LET radiation may be only equivalent to ten to fifty days of "aging" with respect to cancer. It may be much less relative to cardiovascular disease. However, there would be a much different effect if the exposure was of a nature to affect the hormonal system that controls appetite and food intake, in which case the average life of the exposed population might be extended rather than shortened. There is not enough information available to estimate how much exposure would be required to give this kind of hormetic effect in humans. The basis for extrapolation of high dose effects to low doses, in this case, does not exist.

TABLE 1. THE MEDIAN AGES AT DEATH AND THE FRACTION OF THE POPULATION DYING FROM THE LISTED CAUSES OF DEATH

ENGLAND AND WALES
WOMEN 1861

Cause of Death	Approximate Median Age at Death From Cause Listed Years	Fraction of the new-born population
Certain Diseases of Infancy	0.5	0.03986
Diarrheal Diseases	3.7	0.04603
Other Infections & Parasites	4.3	0.12199
Maternal	31.0	0.01257
Respiratory diseases and Tuberculosis	32.3	0.11618
Violence	37.0	0.01676
Certain Degenerative Diseases	50.0	0.00677
Influenza, Pneumonia, and Bronchitis	58.0	0.12495
Cancer	59.3	0.03173
Cardiovascular Disease	66.0	0.13251
Other and Unknown	71.0	0.35065
		1.0000

TABLE 2. THE MEDIAN AGES AT DEATH AND THE FRACTION OF THE POPULATION DYING FROM THE LISTED CAUSES OF DEATH

ENGLAND AND WALES
WOMEN 1964

Cause of Death	Approximate Median Age at Death From Cause Listed Years	Fraction of the new-born population
Certain Diseases of Infancy	0.5	0.00899
Diarrheal Diseases	77.0	0.00591
Other Infections & Parasites	66.5	0.00333
Maternal	31.0	0.00073
Respiratory diseases and Tuberculosis	64.5	0.00165
Violence	75.0	0.03754
Certain Degenerative Diseases	75.0	0.02180
Influenza, Pneumonia, and Bronchitis	81.0	0.09778
Cancer	70.3	0.17068
Cardiovascular Disease	80.2	0.56632
Other and Unknown	78.7	0.08527
		1.0000

TABLE 4. CHANGES WITH TIME IN MEDIAN AGE AT DEATH FROM CANCER AND FROM "SENESCENT" CAUSES*

	WOMEN			MEN		
Year	Cancer yrs	"Senescent" Causes yrs	percent*	Cancer yrs	"Senescent" Causes yrs	percent*
			Australia			
1911	66.085	73.358	(62.8)	66.035	70.964	(57.3)
1933	68.281	75.657	(68.3)	69.512	73.021	(79.3)
1964	71.291	77.880	(71.3)	69.406	72.043	(78.5)
			England & Wales			
1861	59.342	69.350	(47.2)	62.733	67.141	(42.5)
1901	62.575	69.269	(51.3)	63.767	68.883	(42.9)
1931	67.062	73.522	(65.8)	67.006	71.757	(59.4)
1964	70.338	78.381	(81.7)	68.790	72.380	(76.8)
			Italy			
1881	60.499	63.698	(34.3)	62.818	63.492	(32.0)
1901	62.324	68.344	(46.6)	64.595	68.388	(43.8)
1921	64.003	72.593	(55.7)	65.198	72.061	(53.0)
1931	64.794	73.396	(54.7)	65.725	72.453	(56.5)
1964	70.202	78.570	(75.2)	68.060	74.289	(81.4)
			Japan			
1899	59.171	65.263	(57.8)	61.499	63.290	(55.2)
1908	59.897	66.638	(53.9)	62.398	65.202	(52.5)
1940	61.126	70.054	(54.3)	62.214	66.328	(50.1)
1951	63.693	74.180	(65.9)	64.601	71.450	(59.9)
1964	68.131	77.523	(80.8)	67.686	73.434	(75.2)
			USA			
1900	61.754	68.540	(44.9)	65.553	68.889	(39.6)
1930	67.724	71.588	(59.9)	65.657	70.449	(53.9)
1964	70.044	78.663	(85.1)	68.833	72.211	(81.4)
Mean for listed Countries	64.917	72.273		65.630	69.906	
SD	4.023	4.643		2.585	3.305	
Correlation Coefficient* (r)	0.925			0.870		

*The numbers in parentheses are the approximate percentage of those surviving to age 1 that die of "senescent" causes. For this table "senescent" causes include cancer, cardiovascular diseases and other and unknown causes. Cancer is not excluded because its contribution to the total deaths is relatively small and the other and unknown category must include some cancer as well as cardiovascular disease.

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