OXIDATIVE STRESS: ITS POTENTIAL RELEVANCE TO HUMAN DISEASE AND LONGEVITY DETERMINANTS

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ABSTRACT
Most evidence indicates that aging is a result of normal metabolic processes that are essential for life. Thus an important approach in biogerontology is to identify specific metabolic reactions necessary for life but which could also lead to aging. A unique characteristic of this approach is an explanation of what governs aging rate or longevity of a species or even individuals within a species. These would be mechanisms that would act to reduce the long-term toxic or aging effects of the normal metabolic and developmental reactions. The reactions involving oxygen metabolism clearly fit into this model for they are essential for life yet can potentially cause many of the dysfunctions associated with aging. Such a model can also account for differences in aging rate or longevity of different animal species by differences that may exist in their innate ability to reduce oxidative stress state. Our laboratory has been testing this oxidative stress state (OSS) hypothesis of aging and longevity by determining if a positive correlation exists between OSS of an animal and its aging rate. Much of our data has found such a positive correlation, yet there is some indication that separate causative mechanisms may exist in determining aging rate as opposed to those related to age-dependent specific diseases such as cancer or cardiovascular disease.

INTRODUCTION
Nothing definite is yet known about the causes of human aging or the processes that govern aging rate of different mammalian species. Furthermore, there is the possibility that aging could be the result of many different independently-related processes and that no simple primary process exists that causes aging or governs aging rate.

Nevertheless, steady progress is being made towards answering these key questions. For example, although we do not yet have proof of a single cause of aging, we can now state with reasonable confidence that aging is the result of normal and essential products of metabolism and development (Cutler, 1991a, b, c). This is an important advance, for the other view which has been unchallenged for many years is that aging is genetically programmed, where specific genes turn on or off to cause aging for the evolutionary good of the species or individual. That this is not likely to be the case is argued by the fact that animals living in their natural ecological niche rarely live long enough to grow physiologically old or senescent. Thus, why evolve a genetic program of death or senescence if an individual in a population rarely reaches such a dysfunctional condition? So, if aging is not an "active" process it must be a "passive" process, a result of other processes that were selected to insure a minimum survival time for the organism.

So the next question we ask is: What are these hypothetical passive processes predicted to cause aging? Are they developmental or metabolically-related processes — or both? Another question is: Are there only a few primary processes causing aging or does essentially every gene and/or metabolic product contribute a little to aging?

RESULTS
Some progress has been made in answering the latter question as to the genetic/metabolic complexity of aging or the processes governing aging rate (Cutler, 1975; Cutler, 1976a, b). A series of studies comparing the life span of closely related species having substantial differences in aging rates such as human vs chimpanzee has led to the suggestion that, in spite of the vast complexity of aging processes, relatively few processes may exist that actually govern aging rate. These processes have since been defined as longevity-determinant mechanisms. Such studies have led to the suggestion that perhaps a few key regulatory genes play a global role in governing the duration general health is maintained.

These studies have led to a new approach in studying human aging and longevity, and this is to ask what normal processes essential to life could also lead to the loss of health maintenance and consequently aging. In this regard, then, we need to determine what longevity determinant mechanisms might act to reduce the effects of these aging processes. In this sense, we now ask not...
so much how a human ages, but why do humans live so long? This question is particularly interesting since humans are clearly the longest-lived of all mammalian species, yet have no great biological differences as compared to shorter-lived species. Thus, the new focus is on longevity, not aging mechanisms.

DISCUSSION

Of the many different developmental and metabolic processes we have to choose in investigating what key developmental or metabolic programs might play a role in causing aging, we have selected to study oxygen metabolism as a "passive" aging process. This appeared to be an ideal area to study since oxygen metabolism is clearly an essential part of life, providing efficient means of generating energy - but at the same time producing well known by-products called reactive oxygen species (ROS) that could conceivably cause aging. Moreover, an exciting aspect on suggesting that ROS act as a primary cause of aging is that we easily arrive at a class of mechanisms potentially important in governing aging rate. These are mechanisms acting to reduce oxidative stress state, such as in lowered metabolic rate, more efficient mitochondria, higher levels of DNA repair or concentrations of antioxidants. I have more recently called this idea the "Oxidative Stress State hypothesis of aging" or "OSS hypothesis of aging" to bring the concept more in line with current concepts of oxidative stress mechanisms.

If this hypothesis is correct, then we would predict, as a function of longer life span of different species, a less oxidative stress state in an animal's tissues. There are, of course, many different mechanisms that could have evolved to reduce oxidative stress, but clearly one simple means would be to increase the concentration of the same antioxidants that are commonly found in all mammalian species. Such an increase would likely be a result of simple genetic modifications of regulatory genes, a mechanism also thought to be a principle genetic mechanisms in the evolution of different species (Wilson, 1976).

EXPERIMENTAL PROCEDURES

The first study undertaken to test the OSS hypothesis of aging was to measure the specific activity of superoxide dismutase (SOD) in different tissues of mammalian species having different life spans. Since, of course, we were really interested in measuring net oxidative stress state in a cell, it is important to realize that it was argued that antioxidant concentration reflects indirectly the steady state levels of oxyradical concentration or the OSS of the cell (Cutler, 1982). To make this possible, it is necessary to normalize the antioxidant activity by dividing SOD activity by the specific metabolic rate. For example, Fig. 1 shows typical data of SOD activity per mg protein of liver tissue as a function of life span of different species. These data show a general increase with life span in SOD activity with human clearly having the greatest amount.

However, as shown in Fig. 2, by normalizing the data on a per specific metabolic rate basis, this correlation becomes remarkably linear.

Thus, we find that:

$$\text{SOD/SMR} = k\text{MLSP}$$

where SOD is superoxide dismutase (units/mg protein), SMR is specific metabolic rate (c/g/d) and MLSP is maximum life span potential (yrs).

Now we can also estimate oxidate stress state (OSS) within a cell, as:

$$\text{OSS} = \frac{\text{SMR}}{\text{SOD}}.$$

Thus our correlation of SOD/SMR with MLSP does relate to MLSP $\propto 1/\text{OSS}$, as expected. Further experiments were then carried out to determine if other antioxidants showed a similar positive correlation with life span. This was found to be the case for many antioxidants, as...