Editorial: Basic Biological Aging Research in Canada: Time for Rejuvenation?

The twenty-third annual meeting of the Canadian Association on Gerontology (CAG) was held in 1994 from October 13–16 in Winnipeg, Manitoba. At that meeting, two of the sessions dealt with the basic biological mechanisms that contribute to the aging process. The papers presented at these sessions and published in this issue of the *Canadian Journal on Aging* constitute the subject of this editorial review.

It is reasonable to assume that individuals have pondered their own mortality ever since the evolution of abstract thought. However, it was not until the late 1800s that a framework was established that attempted to define the process of biological aging as an event unique to multicellular organisms. In an essay published in 1891, August Weismann contended that death was not an "essential attribute of living matter". He proposed that natural death only occurred in multicellular organisms as a consequence of evolutionary separation of the reproductive germ cells and the somatic cells which make up the vast majority of cells in higher organisms (1). While bacteria, yeast and many other single-celled organisms are functionally immortal, experiments described in the late 1950s by Sonneborn have shown that some strains of unicellular *Paramecium* appear to be immortal while others are not (2). Thus, it appears that the phenomenon of aging (or senescence as it is often referred to) evolved in single-celled organisms even before the separation of germ-line and somatic cells in multi-cellular organisms.

Contemporary biological aging research is carried out using a large array of unicellular and multicellular experimental organisms, including individual somatic cells that are grown independently of the host organism in artificial medium. Cells isolated and grown in this manner outside the body (in vitro: literally "in glass") appear to remember how old they are as measured by the number of times they can divide, independently of the other cells in the body (3). Combined with studies showing that cells isolated from short-lived species divide fewer times in vitro than cells derived from long-lived species (4), such observations have prompted many researchers to examine how the processes of cellular aging might affect organismal aging of individuals within a population, and have contributed to the idea that aging has a definite genetic component. The nature of the genetic component of aging was the subject of the first paper presented at the twenty third meeting of the CAG.

The first speaker of the session was Hildegard Enesco of Concordia University who pointed out that over 65 years have passed since the first scientific data were published to support the view that heredity influences human lifespan (5). Since it has proven possible to select for longevity in lower or-

ganisms that have relatively short lifespans such as fruit flies and roundworms, Enesco proposed the existence of two classes of genes that contribute to regulating lifespan. The first category contains protective genes that function to regulate physiological processes within the cell and protect the cell from physical and biochemical assaults such as ultraviolet radiation or noxious chemicals. The second category of genes control the initiation of the aging process in cells and are termed senescence initiation switches. Since changes in single genes of these classes can markedly affect lifespan in some animal models, Enesco proposed that aging might be under the control of relatively few master genes which might ultimately allow modification of the aging process by gene therapy approaches (6).

One such gene that has been termed a "master switch" (7) encodes a transcription factor which is a molecule that regulates the expression of many other genes and which decreases in activity as cells age (8,9). Karl Riabowol from the University of Calgary presented evidence that the production of this important factor within the cell is actually controlled by decreasing the activity of a second transcription factor within the cell as it ages (10). This results in a cascade effect in which the activity of a single gene product affects the production of several other proteins important for cell growth, thereby contributing to the inability of senescent cells to continue to grow. Although loss of this factor's activity can alter the "in vitro lifespan" of individual cells, it is presently unknown whether loss of this factor affects the lifespan of whole experimental animals.

Senescence, as defined by Comfort "is a deteriorative process. What is being measured, when we measure it, is a decrease in viability and an increase in vulnerability ... Senescence shows itself as an increasing probability of death with increasing chronological age. The study of senescence is the study of a group of processes, different in different organisms, which lead to this increase in vulnerability" (11). Four criteria have been proposed by Strehler that any age- or senescence-associated change should meet before being considered as potentially causal to the basic aging process (12). These are: 1) universality, 2) intrinsicality, 3) progressiveness, and 4) deleteriousness. These criteria appear to be met by the accumulation of cellular lesions due to the damaging effects of particular forms of oxygen called free radicals which are continuously produced in living cells. Jack Carlson from the University of Waterloo presented data from his own and other laboratories showing that the levels of free radicals increase during aging and that higher levels of the enzymes that protect cells from free radicals correlate with longer lifespan. In fact, a recent study in which the protective enzymes SOD and Catalase were produced at higher levels in fruit flies reported that fly lifespan can in some cases be increased by up to one third (13), suggesting that loss of enzyme activity might be a causal factor in aging! In order to link effects at the single cell level to aging changes seen in whole animals, Carlson then proposed that some cells of the body, notably nerve cells within the hypothalamus that regulate pituitary gland function might be a particularly important target of free radical damage.

The hypothalamic region of the brain was also the experimental system used in studies of reproductive aging that were presented by Eugenia Wang from the Bloomfield Centre for Research in Aging that is affiliated with McGill University. Since normal reproductive function depends upon several hormones produced in the pituitary gland and this gland is regulated by chemicals produced within specific brain cells within the hypothalamus, Wang's group examined the status of cells within this region of the brain in mice that were showing a significant drop in reproductive capacity. Evidence was presented that a process termed programmed cell death in which certain cells are programmed to self destruct might be responsible, in part, for the loss of cells observed in this region of the hypothalamus. More recently Wang's group has also made the intriguing observation that senescent human cells grown in culture appear resistant to the process of programmed cell death (14) which might be a factor contributing to the greatly increased incidence of cancers of many types in the human population with advanced age.

A number of experiments with animal models have suggested that it may be possible to modify the human lifespan or at the very least, delay the onset of age-related diseases. In order to determine whether specific treatments might affect the rate of human aging as they do in animal models, methods that accurately measure aging processes in humans need to be developed due to the relatively long lifespan of humans compared to commonly used animal models such as mice, fruit flies or roundworms (15). Working towards this goal, Robert McCulloch from the University of Regina presented an interesting overview of the effects of aging on bone mass in the elderly. While it has been known for some time that bone mass decreases in both males and females during the aging process (16), McCulloch highlighted the observation that physical activity plays an important role in maintaining bone density and strength, especially in elderly individuals. The strengths and limitations of the various protocols and techniques that are now available for the accurate measurement of bone density were also described.

The mechanisms responsible for biological aging have been pondered by philosophers for centuries and more recently have been studied by a small group of researchers, however the amount and general quality of biological aging research increased substantially in the mid 1970s due to the formation of the National Institute on Aging in the United States in May of 1974 (17). This increased quality and quantity of research has been a direct result of increased funding to support research in this area that will affect the vast majority of individuals in the population. No such institute exists as yet in Canada, and the overall level of funding for research in this country is well behind the levels seen in other industrialized countries. Even before the most recent cut in research funding announced by the Federal Government, Canada spent substantially less of its gross domestic product on research and development than any other large industrialized nation in the world! Studies reporting this embarrassing statistic have been undertaken primarily by non-Canadian research organizations with no vested interest

in the final outcomes of the studies (18). Despite these limitations to undertaking science in Canada, first-rate studies of biological aging are still done in this country as evidenced by the reports described above, but in numbers that are substantially less than should be justified based on the importance of aging and age-related diseases to the vast majority of Canadians and the greying of our population.

References

1. Weismann A. Essays upon heredity and kindred biological problems. London and New York: Oxford Univ. Press (Clarendon), 1891.
2. Sonneborn TM, Rofolko M. Aging in the *P. aurelia*-multimicronucleatum complex. J. Protozool 1957; 4:21.
3. Hayflick L. The limited *in vitro* lifespan of human diploid cell strains. Exp. Cell Res. 1965; 37:614.
4. Martin GM, Sprague CA, Epstein CJ. Replicative life-span of cultivated human cells: Effects of donor's age, tissue and genotype. Lab. Invest. 1970: 23:86.
5. Pearl R, Pearl R de W. The ancestry of the long-lived. London: H. Milford, 1934.
6. Enesco HE. Genetic control of the aging process: a review and interpretation. Can J. Aging 1996, this issue.
7. Marx JL. The fos gene as "master switch". Science 1987; 237:854.
8. Seshadri T, Campisi J. Repression of *c-fos* transcription and an altered genetic program in senescent human fibroblasts. Science 1990; 247:205.
9. Riabowol K, Schiff J, Gilman MZ. Transcription factor AP-1 activity is required for initiation of DNA synthesis and is lost during cellular aging. Proc. Natl. Acad. Sci. USA. 1992; 89:157.
10. Atadja PW, Stringer KS, Riabowol KT. Loss of serum response element-binding activity and hyperphosphorylation of serum factor during cellular aging. Mol. Cell Biol. 1994; 14:4991.
11. Comfort A. The biology of senescence. New York: Rinehart Publishers, 1956.
12. Strehler BL. Origin and comparison of the effects of time and high energy radiations on living systems. Quart. Rev. Biol. 1959; 34:117.
13. Orr WC, Sohal RS. Extension of lifespan by overexpression of superoxide dismutase and catalase in Drosophila melanogaster. Science 1994; 263:1128.
14. Wang E. Senescent human fibroblasts resist programmed cell death, and failure to suppress bcl2 is involved. Cancer Research 1995; 55:2285.
15. Dubina TL. Biological age as a tool for the determination of the rate of aging. In: Balin AK, ed. Practical handbook of human biologic age determination. Boca Raton, London, Tokyo, Ann Arbor: CRC Press, 1994.
16. Adams P, Davies GT, Sweetnam P. Osteoporosis and the effects of aging on bone mass in elderly men and women. Q. J. Medicine 1970; 39:601.
17. Strehler BL. Time, cells and aging. 2nd ed. New York, San Francisco, London: Academic Press, 1977.
18. Palc, J, Anderson A. Science in Canada: underinvestment lies at the core. Nature 1988; 333:719 .

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