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25 Years after *age-1*: Genes, Interventions and the Revolution in Aging Research

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Abstract

This communication will briefly review more than 30 years of research on aging using the nematode *Caenorhabditis elegans* ("The Worm") as carried out in the labs of Tom Johnson. We will highlight research directions initiated in the 1980's, which were exciting for those of us trying to turn over a new leaf in aging research. In this narrative, I will discuss primarily the science that I and my lab have been involved with for the last 30 years. This area has been fascinating to those studying the sociology of science as modern aging research has moved to replace the simplistic, poorly controlled and outright fictitious approaches seen in much of the previous aging research.

Initial Considerations

As requested, this communication will briefly review more than 30 years of research on aging using the nematode *Caenorhabditis elegans* ("The Worm") as carried out in the labs of Tom Johnson. We will highlight research directions initiated in the 1980's, which were exciting for those of us trying to turn over a new leaf in aging research. In October of 1979, having recently received funding of a small NIH grant ($27,000 annually for 2 years), I began to work on aging while still a postdoc in the laboratory of Dr. William B Wood, at the University of Colorado, Boulder. Much of the initial work on the genetics of *C. elegans* was funded by the National Institute on Aging, which was founded in 1974, although it had little to do with aging. (Dr. Don Murphy, an NIA program director was responsible for much of this funding and has never been adequately acknowledged.) Few of the Principal Investigators of these grants were interested in aging and even fewer ever published papers in the aging field. Four exceptions to this trend were David Mitchell, David Hirsh (and Michael Klass), Dick Russell (and Lou Jacobson) and myself.

In this narrative, I will discuss primarily the science that I and my lab have been involved with for the last 30 years. This area has been fascinating to those studying the sociology of science as modern aging research has moved to replace the overly simplistic, poorly controlled and outright fictitious approaches seen in much of the previous aging research. (This hubris is typical of the early researchers using The Worm in many different studies and seems to have been rewarded by many Nobel Prizes.) This transition is documented in

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two excellent recent books targeted at the lay audience (Stipp, 2010; Anton, 2013); these books convey the excitement, the competition and collaboration that followed some of the initial studies. More detailed reviews of the published literature in this era are available in a series of Annual Reviews of Biological Research in Aging (published by Alan R. Liss from 1983 through 1990, and edited by Mort Rothstein. Several reviews of studies of the aging worm were published that also contain unpublished material and historical summaries (Johnson, 1983; 1985; Johnson and Foltz, 1987; Johnson and Hutchinson, 1990). The times were wide open. (This communication ignores many contributions from many former students, current colleagues and friends, too numerous to cite.)

2. Classical and Quantitative Genetic Studies

2.1. The early days

By the mid seventies it became apparent that the biology-of-aging field was in dire need of an experimental system in which well-controlled experiments on aging could be carried out in a period of time much shorter than the three or so years required for rodents to age and die. Michael Klass and his mentor David Hirsh had published two papers that served to stimulate my initial interest in using *C. elegans* as a genetic model for dissecting the process of aging (Klass and Hirsh, 1976; Klass, 1977). Prior to beginning systematic studies we established certain conditions for performing aging experiments. These included the use of a control typically the wild type N2 (we use the CGCb strain of the Worm; see Gems and Riddle, 2000) in every experiment to control for uncontrolled environmental effects which cause a wide variation of lifespans seen between experiments (Johnson and Hutchinson, 1996?). We also used a liquid bacterial medium devoid of FUdR (fluorodeoxy uridine) for performing longevity experiments (Johnson and Wood, 1982) and defined non-parametric statistical tests for comparing survivals. We put forward life extension as a surrogate marker of slowed aging and developed a definition that would encompass both quantitative genetic and mutational approaches to longevity:

> "Genetic variants that live longer than parental strains seem more likely than shorter-lived variants to be altered in primary rate-limiting processes that determine life-span."
>
> (Johnson and Wood, 1982).

2.2. Heritability and heterosis for life span

I took a quantitative genetic approach to the study of longevity; this approach was facilitated by the lack of heterosis/inbreeding depression in *C. elegans* (Johnson and Wood, 1982; Johnson and Hutchinson, 1993), as is expected in an inbreeding hermaphrodite. My lab initially focused on quantitative genetic approaches, which included inter-strain crosses, selective breeding, and the establishment of recombinant inbred strains (a suggestion of John DeFries), which we used to dissect aging/longevity. We demonstrated that longevity is a surrogate marker of the aging phenotype, that it is heritable (Johnson and Wood, 1982), and that various life-history traits (longevity, fertility, rate of development) are independently specified (Johnson, 1987); *i.e.*, different genes segregating in these crosses control length of development, length of fertility and longevity.

2.3. Genetic Mapping and Cloning of age-1

By the middle of the 1980's it was clear that there was significant heritability of longevity in yeast, worms, and flies. The fundamental aspects of the mutational approach to the genetics of aging were laid, primarily in the nematode *C. elegans*, through the efforts of my colleague Michael Klass, who identified mutations that increased longevity (Klass et al., 1983). We furthered the analyses of these mutants, when Mike went to private industry. I thought Mike

was wrong and that there were multiple mutational events responsible for the extended longevity, but he was correct. First, all the longevity mutations were recessive and failed to complement and thus were probably in the same gene (Friedman et al., 1988a). This extended longevity phenotype, which we called "Age", mapped to chromosome 2 (Friedman et al., 1988b) and both the Age phenotype and a reduced-fertility phenotype mapped to the same locus which we termed *age-1*. We were attempting to clone the *age-1* gene when it was shown to be allelic with *daf-23* which had been recently cloned (Morris et al., 1996) and shown to encode a phosphatidylinositol-3-OH kinase. This positioned *age-1* into the most important pathway found to specify length of life and rate of aging which has been further clarified by subsequent studies in several labs (reviewed in Kenyon, 2010). We developed two strategies for identifying Age mutants in *C. elegans* (de Castro et al., 2004; Duhon et al., 1996), but neither was widely applied due to the laborious nature of their application. (However, the use of stress resistance as a surrogate marker coupled with transposon-tagging has recently been used to identify putative longevity mutants directly in mouse embryonic stem cells (Chick et al., 2009; Chick and Johnson, unpublished).

2.4. Genetic Effects on Mortality Rate

It has been suggested that a way to demonstrate that the rate of aging has been changed is to examine age-specific mortality rates, which increase exponentially with increasing chronological age in humans and in most species studied (Sacher, 1978). I demonstrated that mortality rates in the wild-type worm increased exponentially with a doubling time of about 2.8 days. Importantly the mortality rate continued to increase exponentially with increasing age and the rate of mortality was changed in both the long-lived RI strains and in the *age-1* mutant (Johnson, 1987; 1990) but there was no change in the initial mortality rate, suggesting that the "rate of aging" has been altered in these mutants. We developed strategies for a fine-scale analysis of daily mortality rate (Johnson et al., 2001). We found that mortality rates were best fit by a two-stage Gompertz model. Mortality in all strains leveled off late in life. Most startling was the finding that mortality was segmentally affected. That is, different Age mutants showed lower mortality at various ages but not at all. The largest genetic effect on mortality was that of an *age-1* mutation, which lowered mortality more than fivefold at most later ages. In contrast, a *spe-26* mutant had a tenfold lower mortality until approximately 2 weeks of age but ultimately achieved a higher mortality, whereas *clk-1* mutants showed slightly higher mortality than wild type during the fertile period, early in life, but ultimately leveled off at lower mortality.

We were able to initiate studies in RI strains in which we identified and mapped QTLs for longevity, fertility and temperature sensitivity as well as mortality (Shook et al., 1988). There was insufficient power to map mortality.

2.5. Movement as a biomarker of aging

Movement decreases with increasing life span, which led us to determine if movement rate serves to predict subsequent differential longevity of individual worms or strains of worms. Using both recombinant inbreds (Johnson, 1987; Brooks et al., 1994; Vaupel et al., 1994) and mutant strains (Duhon and Johnson; Brooks and Johnson, 1991), we found that quantitative measures of movement are very noisy and we were not able to predict life span in individual worms. However, using RI populations of worms with different genotypes and life expectancies, we were able to predict subsequent longevity using the rate of decline of movement (Johnson, 1987).

3. Changes in Gene Expression with Age

3.1. Background

A nagging question in aging research has been whether aging is simply an extension of development. Although many have made the assumption that there is no difference between what goes on in development and what goes on in aging, there are major differences arising from the basic fact that aging is not selected for. In a lack of selective value the post-reproductive, aged organism enters an unknown state with regard to alterations in gene expression (Johnson, 1986). Throughout the studies described in this section, we were asking about changes in gene expression during the senescent phase of life and how it might vary from the changes seen during development.

3.2. Lack of 5-methyl cytosine

To quote our original paper (Simpson et al., 1984):

> "The association between cytosine methylation and altered eukaryotic gene expression or X-chromosome inactivation is well documented. The association between cellular or organismic senescence (and cytosine methylation is less clear. Levels of 5-methylcytosine as high as 14 mole percent have been reported in DNA isolated from senescent populations of the nematodes *C. elegans* but not in DNA isolated from the first larval stage of life (Klass et al., 1983). A generalized hypermethylation of cytosine residues could result in decreased transcription and thereby explain the large decreases in rates of protein biosynthesis reported in senescing populations of *C. elegans* (Johnson and McCaffrey, 1985) and *Turbatrix aceti* (Sharma et al., 1979). We report here a detailed analysis of purified DNA from several strains of *C. elegans* both during development and at several times in later life. These studies involved high performance liquid chromatographic (HPLC) analysis of total organismic DNA, as well as analysis by restriction endonuclease digestion. … We detected no 5-methylcytosine at any time during the life-span of this nematode species."

This was an unfortunate state of affairs and stopped cold the various studies I had thought of doing during the first years of my position as an Assistant Professor at University of California, Irvine. Although little credited with this primary observation, it has stood the test of time and genomics.

3.3. The proteome

Quoting from Johnson and McCaffrey (1985):

> "Major theories of metazoan senescence can be conveniently divided into two major classes: programmed or stochastic theories. Theories of programmed senescence suggest that aging is caused by an ordered series of molecular events which are genetically coded in ways that may be similar to the ways developmental processes are coded. Stochastic theories, on the other hand, propose that aging is the result of environmental insult which eventually destroys the organisms' ability to maintain homeostasis. One subclass of stochastic theories is that of error catastrophe. Theories of error catastrophe propose that senescence is caused by the accumulation of errors or faults in one or more systems which the organism needs to maintain homeostasis. Such errors lead to decreased homeostasis and consequently to increased error frequency. One subclass of these theories suggests that errors in the transmission or maintenance of genetic information lead to positive feedback producing more errors and leading to a breakdown of the homeostatic process and eventually to organismic death. Although originally

proposed by Orgel (1963) at the level of protein synthesis, breakdowns at the DNA level due to altered replication or repair, during transcription, RNA processing and transport, or post-translational changes also could lead to the synthesis of polypeptides with altered pls or apparent molecular weights.

"We examined some of the predictions of each of these theories at the level of *in vivo* protein synthesis, as displayed by two dimensional polyacrylamide gel electrophoresis (2D PAGE). Development involves the synthesis of many new proteins. In *C. elegans*; Johnson and Hirsh (1979) have shown that 113 of the approximately 700 proteins detected by 2D PAGE techniques were developmentally controlled. If similar processes occur in senescence as occur in development, we might expect to observe similar changes in the spectrum of proteins synthesized over the life span. Conversely, if error catastrophe at one or more levels of gene expression drives the senescence process, we would expect to detect the incorporation of wrong amino acids in newly synthesized proteins. Such misincorporation should produce a broadening of bands or the production of satellite spots in the isoelectric focusing dimension when examined by 2D PAGE. We have grown the nematode, Caenorhabditis elegans in synchronous culture conditions throughout its life span; at several points populations of worms were withdrawn from culture, pulse labeled with ^{35}S-labeled *E. coli*, chased with cold *E. coli*, and examined using fluorography following electrophoresis.

The patterns of these proteins are highly reproducible in comparisons of independent repeats of identical experiments. No new major proteins are synthesized at any time during the adult phase (4-22 days) nor are any of the most abundant proteins not made during this period. At our level of detectability (estimated as a satellite spot containing 4% of the amount of label in a major spot) we see no misincorporation of radioactive amino acids into newly synthesized proteins. These data are inconsistent with predictions by any one of several, so called, "error catastrophe" models of senescence and also show that modulation of the highest abundancy classes of proteins are also not involved in senescence."

3.4. The transcriptome

We performed a whole-genome analysis of changes in gene expression during aging in worms that provides a molecular description of *C. elegans* senescence. We performed this analysis beginning at the first day of adult life and covering six age groups, ending at an age when 90% of the worms were dead. Using a rigorous statistical model with multiple replicates, we found 164 genes (a relatively small number) that showed changes during aging (Lund et al., 2001).

Most notable was the fact that heat-shock proteins decreased in expression levels over the life span and some transposases increased expression at older ages. This is not consistent with a damage theory of aging where many repair enzymes would be expected to increase with age, rather that decrease as we observed. These findings are more consistent with an interpretation wherein increased mortality risk results from failure in homeostenosis and destabilization of the genome at old ages. These results do clearly show a distinct difference between aging and development in that most of the genome shows changed expression during development but only 1% changes during aging.

We assessed changes in tissue specific aging by selecting genes known to be expressed in specific tissues. First, we looked at the expression of 44 known muscle and 112 known neuronal genes. Muscle and neuronal transcripts showed an apparent increase in expression during aging. Germline gene expression increases during days 4–16 and then decreases at the oldest age. The age when these changes occurred did not correlate with the time when

oocyte production ceased, indicating that these are controlled by separate causal events. It would be interesting to see if late-life mating with males, which restores oocyte generation and fertility even very late in life (Mendenhall et al., 2011), causes an activation of transcripts encoding proteins that are involved in reproduction.

4. Conclusion

I have reviewed work carried on in my lab from its beginnings in 1979, while a postdoc in the lab of Bill Wood at the University of Colorado at Boulder (UCB). The work was continued first as an Instructor at UCB in the Institute for Behavioral Genetics (IBG), then as an Assistant Professor at the University of California, Irvine and then again at IBG. I want to thank all of the people who worked with me during this period but especially one of the first: David Friedman who is now a Research Associate Professor at Vanderbilt University and Pat Tedesco and Jim Cypser who are both still working with me, even in the light of the reduced funding that leaves me without any NIA support for the first time since 1977.

Further communications will review other work from the Johnson lab as we began studies of the role of stress in the specification of lifespan (Lithgow et al., 1995; Melov et al., 1995; Johnson et al., 1996; Murakami and Johnson, 1998; Henderson and Johnson, 2001), hormesis (Cypser and Johnson, 2003), dietary restriction (Park et al., 2009), and stochastic effects (Rea et al., 2005), all in *C. elegans*, as well as our very recent work on dietary restriction in the mouse (Liao et al., 2010) and the selection of mutants in the mouse, using embryonic stem cells (Chick et al., 2009).

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Highlights

- Reviews more than 30 years of research on aging using the nematode *Caenorhabditis elegans*
- Focus is on work carried out in the labs of Tom Johnson
- Highlights research directions initiated in the 1980's, trying to turn over a new leaf in aging research
- Fascinating to those studying the sociology of science as modern aging research
- Review identification of age-1 the first mutant to prolong life in C. elegant
- Reviews differential gene expression over the life of the worm
- Reviews quantitative genetic approaches to aging
- Reviews early hormetic studies
- Reviews mortality and prediction of the life span