Rough
proof
review

January 3, 1990

Dr. Caleb E. Finch
Ethel Perey Andrus Gerontology Center
University of Southern California
University Park MC0191
Los Angeles, CA 90089-0191

Dear Dr. Finch:

I reviewed chapter 9 and offer more in-depth information on Arctic char, Salvelinus alpinus (last paragraph, p.7). The Arctic char has a broad geographic distribution in the Holarctic of Europe, Asia, and North America. Throughout this vast range, several distinct morphological, ecological and distinct behavioral types exist. The taxonomy of Arctic char (one or several species) is controversial, but it can be used as an extreme example of a polytypic species. As the northernmost occurring freshwater fish species, examples of extreme adaptations to extreme conditions are known, including high survival to successive spawnings after extreme "reproductive drain".

Nordeng's 1983 work, to which you refer oversimplified the hereditary vs. environmental influences on life history traits such as age at maturity. Enclosed is a copy of a review I wrote of Nordeng's paper before publication. Also enclosed is a page proof of my contribution to the proceedings of an international char symposium which discusses a common phenomenon in S. alpinus of fractioning into two (or more) sympatric populations in lakes, which differ in age at maturity and life span. It seems obvious that significant hereditary differences in life history can come about with very slight genetic change--perhaps alleles at one locus modifying developmental sequences during ontogeny.

As might be suspected of a polytypic species, all Arctic char do not spawn annually (second line from bottom, p.7). Dutil (1986. Energetic constraints and spawning interval in the anadromous Arctic char. Copeia (4):945-955) describes "reproductive drain" in a high Arctic population of char (can be spelled with one (r) or two). Spawners lose up to 46% of energy reserves and require more than one year to recuperate and spawn again--but population has long life span with numerous repeat-spawnings. Virtually all energy is obtained from about 50 days per year of intense feeding in the sea.

Age at maturity and maximum life span varies enormously in S. alpinus. Some populations, especially benthic "drawfs" in southern parts of range may live only a few years. Ages to 30 (with mean age of 19 at first maturation) have been reported for anadromous char of Cresswell Bay (Somerset Is., Canadian Arctic).

It is obvious that S. alpinus is a highly heterogeneous taxon which defies any attempt to make life history generalizations without numerous exceptions to a rule.

Sincerely,

Robert S. Behnke
Professor, Fishery Biology
Dept. of Fishery & Wildlife Biology

RSB: dj

ETHEL PERCY ANDRUS GERONTOLOGY CENTER
(213) 743-6060

December 16, 1989

Dr. Robert Behncke
Colorado State University
Boulder, Colorado 80309

Dear Dr. Behncke:

Here is another excerpt from Chapter 9 that deals with variations of development. Some material overlaps with the section you've already seen. Any comments will be most welcome.

With best wishes,

Caleb E. Finch

Caleb E. Finch, Ph.D.
ARCO/William F. Kieschnick Professor
in the Neurobiology of Aging

old fish — age maturity
Campbell-79
heritable change
envirn — genetic

September 30, 1989

Section IV: Epigenetic Variations in Senescent Phenotypes

Chapter 9: Developmental Influences on Lifespan and Senescence

Chapter 9: Developmental Influences on Lifespan and Senescence

9.1. Introduction:

This chapter addresses three major ways through which the phenotypes of senescence are determined during development, with emphasis on epigenetic and environmental influences. (I) The duration of developmental stages can vary total lifespan in some species. (II) The variety of epigenetic influences on senescence that arise during oogenesis or development, including the effects of maternal age and alternative developmental pathways. (III) Finally, I discuss a difficult subject, the developmental determinents of the capacity for cell renewal and regeneration which can influence potential longevity. The wide species differences in longevity and patterns of senescence among multicellular organisms (Chapters 1-4) can be ascribed in many cases to heritable differences which are consequent to specific differentiated cell characteristics, such as the capacity for regeneration, the presence of vital organs, and adult body size.

A general question is traced through this and the next chapter: Do species differences in senescence arise from differences in the regulation of gene activities vs. differences in enzymatic activities and other protein functions that mostly arise from point mutations. Genetic elements crucial for the control of senescence could involve either, or both, coding and non-coding DNA sequences. Trans-acting regulators of transcription by which the products of one gene influence the activities of distant genes are being studied intensively and, and will soon provide powerful new approaches to investigating mechanisms of senescence through manipulating development. For the present, we can only get glimpses of these possibilities through examples of environmental influences on lifespan and senescence that act before maturation, and in some cases must penetrate to the level of gene regulation. Even at this early stage of understanding how the patterns of senescence are predestined, the evidence clearly shows extensive plasticity in the developmental determinents of senescence. The manipulation of senescence during prematurational stages also gives insight into pacemakers for senescence.

9.2.2.2. Vertebrates

Vertebrates show many variations in the age of reproduction within a species, but there are few examples in which environmental influences are proven to increase lifespan through slowed development and delayed maturation. The following examples are generally more suggestive than definitive; few vertebrates show a major link of delayed maturation to greater total lifespan that is demonstrable in lower forms.

Rigorous studies on the age of maturation in relation to lifespan are being done with platyfish (Xiphophorus maculatus); see Chapter 3.4.3. for descriptions of senescence in platyfish. Strong genetic influences on the age of maturation are linked to the sex-linked gene P. Alleles P1-P5 control sexual maturation over a 12-fold range, from 2 to 24 months. Yet, the earliest maturing fish with the P1 allele live slightly longer [redacted] (Schreibman and Margolis-Nunno, 1989). In contrast, males of Nothobranchius guentheri (an annual fish, Chapter 2) lived 25% longer if they matured later (Markofsky and Perlmutter, 1973); one suspects genetic factors, as for platyfish. The longer lifespans of later maturing fish may be related to the large metabolic demand and stress associated with reproduction in fish ("reproductive drain"). For example, Orton (1929) hypothesized that the reproductive drain is greater on larger and older fish. Since ovarian weight and fecundity increase disproportionately greater than body weight in some species (Gerking, 1959), older fish might have increased mortality at spawning. However, late maturing members in several species appear to have greater reproductive lifespans (Garrod and Horwood, 1984; Roff, 1981).

Mosquitofish (Gambusia affinis, a viviparous peocilid) vary in growth rate and lifespan between populations in Hawaii that were discussed in Chapter 6 as an example of natural selection for different reproductive schedules. Under standard conditions in the laboratory, six F1 stocks differed in their nearly

2-fold in fecundity, with smaller differences in age at maturity, size at maturity, and the interval between broods (Stearns, 1983a,b). Although the mean lifespan of about 9 months did not differ between stocks, there was a strong correlation between length at maturity and lifespan.

These results are consistent with Krumholz' (1948) observations on mosquitofish from the midwestern US, which showed two patterns of life history, early and late reproducing according to whether they over-winter before becoming gravid. In this study, maturation was evaluated by the presence of fertilized eggs, which may be more of an index of hormonal and behavioural receptivity than of anatomical maturation; males are considered promiscuous and limited only by female receptivity. Fish becoming gravid during the first summer of life (ca. 1 month) were smaller, and had fewer and smaller broods; these dissappeared soon after their last clutch was born. Those that were born later in the summer and had delayed reproduction until the second summer were larger, and had double the number of litters. In mosquitofish, there is clearly no fixed quota of ova and offspring, and the larger females are more productive. Irrespective of the reproductive schedule, all mosquitofish were observed to have a sterile postreproductive phase before death, in which the ovary was histologically "senile" and devoid of ova; further studies are needed to evaluate the relative roles of ovarian oocyte depletion (which cannot be assumed from the brief account given) and possible neuroendocrine influences. The coexistance of fish of the same size and apparent maturity in late summer populations that were gravid or were not reproductive suggests neuroendocrine variables. Although feral populations of Gambusia rarely survive more than a year in the temperate zones, they may live 4-5 years in aquaria, which Krumholz (1948) attributed to effects

of "semi-starvation"; the prevention of reproduction may also be important. These studies show that the total lifespan of female mosquitofish is more related to body size than to the age at maturation. The main factor appears to be the smaller stress of reproduction to larger females. These studies also discount the early view that "reproductive drain" is greater on larger and older fish (Orton, 1929). There are other examples of late maturing members of a population that have greater reproductive lifespans (Garrod and Horwood, 1984; Roff, 1981).

As in most vertebrates, gender is often associated with differences in the lifespan of fish. A novel study used sex steroids to cause phenotypic sex reversal in rice fish, or medaka (Oryzias latipes) that also caused reversal of lifespan differences (Fineman et al., 1974). Just after hatching, genotypic males were fed estrone; these grew to become phenotypic females with fertile ova and had shorter life expectancies that were characteristic of untreated females. Converse effects were induced in genotypic females fed methyltestosterone that had male phenotypes. Most of the effects on life expectancy were attributed to the age-independent mortality rate (Ro, equation 1.3), which is represented in the analysis of Fineman et al. (1974) as the constant hazard factor. Because the life expectancy of untreated control females (5 months) and males (11 months) were much less than the several years reported elsewhere (Chapter 3.4.3.), the conditions of this study might not have allowed enough fish to reach ages when the mortality rate acceleration was robust enough for cmparison between experimental groups. In any case, the risk factor of producing fertile ova was clearly demonstrated.

Several variations in the duration of development of salmonids merit future

consideration as possible lifespan variants. In Atlantic salmon (Salmo salar), the immature river phase of 1-3 years is followed by transformation into smolts in preparation for migration to the the sea. The sea phase, when 99% growth occurs, varies 1-2 years before they return to the river for spawning, which is associated with considerable (not universal!) post spawning mortality (Thorpe et al., 1982, 1984; Hane and Robertson, 1959). Local populations have distinct growth and mortality rates that are influenced by parental stocks in hatchery bred juveniles (Thorpe and Morgan, 1978). Indications of genetic isolation of these home-stream oriented populations are different transferrin polymorphisms and chromosomal numbers (reviewed in Thorpe and Mitchell, 1981). In further contrast to Pacific salmon which have nearly universal death after spawning in association with elevated corticosteroids (Chapter 2), Atlantic salmon have decreased plasma corticosteroids during spawning (Leloup-Hatey, 1964; Hane and Robertson, 1959); it is plausible that the reduction of corticosteroids at a stressful time favors their greater survival after spawning. Thorpe and Mitchell (1981) showed an inverse relationship between the age at migration as smolts and the time at sea before spawning; this implies that the duration of development to spawning may be relatively constant. Nonetheless, the duration of the river phase influences adult fecundity, and hence could be an aspect of natural history that is subject to strong selection. Fish that spent 3 years in the river before smoltification produced fewer eggs than after 1 or 2 river-years (Thorpe et al., 1984). Egg size increased with adult size in all groups, as did the size of the fry at hatching.

Coho salmon (semelparous Oncorhynchus kisutch, Chapter 2, Table 2.3) have a variant, the 'jack males which mature one year early (2 vs 3 years). While

coho jacks have the same universal postspawning death as the normative adult Pacific salmon (Gross, 1985), jacks of O. tschawytscha and O. masou can survive spawning (Table 2.3). Despite their smaller size and smaller teeth, the precociously mature coho jacks are reproductively competitive, because of 50% lower mortality to maturation (Gross, 1985). Jacks are also "specialized at sneaking" access for females, whereas the larger normative adult males must fight their way in past competing males. Breeding studies indicate genetic differences between the two variants that influence growth rate (Childs and Law, 1972; Iwamoto et al., 1983). Precocious maturation occurs in males of other Pacific salmon, but is rare in females. Gross (1985) described these alternate forms as a mixed evolutionary strategy, which permits a single population to produce adults that mature at different ages; this may average out fluctuations of the environment, including population size. Social dominence heirarchies also influence growth rates in salmon. In rainbow trout (O. mykiss; formerly Salmo gairdneri; conditionally semelparous; Chapter 2.2.1.5.2), subordinate fish grew more rapidly (Yamagishi, 1962). This is probably an epigenetic influence.

Arctic char (Salvelinus alpinus) often have populations with three coexisting variants that are considered alternate phenotypes: small and large freshwater residents and large anadromous forms (Nordeng, 1983). The three variants differ age at maturity (2-8 years), size at maturity (2-fold length), and color. Rearing and relocation studies proved that the three variants can be produced from any single parental type. However, genetic polymorphisms for the age of maturation are indicated in char populations that have only one form. Arctic char spawn annually (Nordeng, 1983) and live at least 22 years (Sproules, 1952). It is unknown how these variations influence mortality rates or lifespan.

Continuing to tetrapods, the age at metamorphosis of the bullfrog (Rana catesbeiana) ranges 10-fold effects of climate, from three months after fertilization in Arizona to up to three years in the north-east (Collins, 1979). During the winter, growth is continues, but is slowed. Nothing is known about the lifespans of bullfrogs which mature at different ages. Because other anurans live at least 13-15 years (Chapter 4.2), delayed maturation may amount to 20% of the bullfrog lifespan.

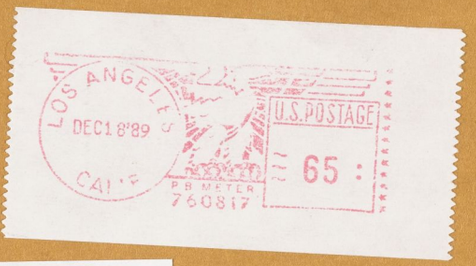
Among mammals, puberty can be delayed several-fold through restriction of diet and light (Frisch, 1985; Ojeda et al., 1980; Magee et al., 1970; McCay et al., 1939). A smaller variation of menarche is widely observed between different human populations (Tanner, 1962). Because diet restriction can interupt fertility cycles of mature adults (Frisch, 1985), the absence of fertility cycles does not necessarily prove retarded sex organ development. That is, brain regulatory mechanisms for gonadotropin regulation might mature, albeit slowly, and be masked by the effects of low body fat which are the strongest body compositional predictor of cyclicity ([redacted]). Diet restriction in adults is discussed in the next chapter.

No general relationship is established between rate of growth and adult lifespan in mammals. Two approaches have been used apart from diet restriction: increasing the growth rate by making more food available and by genetic variations in growth rates. A classic study of Widdowson and Kennedy (1962) varied the number of pups being nursed to form two experimental groups with 3 and >15 pups (small vs. large litters), which is equivalent to very early diet restriction. After weaning at 21 days, all rats were given the same diet ad libitum. Those from large litters were smaller and had relatively more fat throughout life, although they achieved some catch-up growth. While the mean lifespans were only slightly different, being 15% more for the pups from large litters, but the groups had a different pathophysiology of senescence. The larger adults from small litters had a prominent weight loss before death and a higher incidence of kidney disease, particularly in males. Thus, early diet can have a major impact on later adult diseases. The role of ad libitum early feeding on adult fat depots is discussed below.

Several studies of genetic influences have also failed to establish consistent relationships between growth rates and lifespan. A thorough analysis of growth rates in both sexes of 9 inbred Jackson Lab mouse strains and 6 F1 hybrids showed that the adult body weight, growth rate, and lifespans were positively correlated to lifespan in males, but inversely correlated in females (Ingram et al., 1982). I also mention the study of Eklund and Bradford (1977), which analyzied a strain of mice that were selected for rapid growth. The large adults of the rapidly growing strain had short lifespans (12-18 months), but also an earlier incedence of tumors (type not specified); the unselected controls had shorter lifespans than typical of most Jackson Lab strains (Eklund and Bradford, 1977).

Further insight might come from analysis of the age of puberty and the lifespan in humans or other mammals from individual records. However, the historical trends in many populations for earlier puberty (Tanner, 1962) and for greater average lifespan (Chapter 1) that both continue into this century argue

against a fixed duration of adult (postmaturational) lifespan. Thus it seems unlikely that several or more years earlier exposure to adult levels of sex steroids has adverse effects on the potential lifespan. The greater rates of growth during childhood are attributed to the reduced impact of childhood infectious disease and improved year-round nutrition (Tanner, 1962). These more favorable conditions could also enhance the immune responses throughout the lifespan.



Dr. FInch

UNIVERSITY OF SOUTHERN CALIFORNIA
UNIVERSITY PARK MC 0191
ETHEL PERCY ANDRUS GERONTOLOGY CENTER
LOS ANGELES, CA 90089-0191

Dr. Robert Behncke
Colorado State University
~~Boulder~~ Colorado ~~80309~~

FtCollins, Co

NO. 90 CLASP 9 x 12