Population: An English Selection, 2001, 13(1): 197-222.

Biodemographic Study of Familial Determinants of Human Longevity

Leonid A. GAVRILOV*, Natalia S. GAVRILOVA*

The biodemography of human longevity is a newly emerging area of multidisciplinary biosocial research (Wachter and Finch, 1997) with deep historical roots (see Gavrilov and Gavrilova, 1991; Carnes and Olshansky, 1993; Olshansky, 1998). In biodemographic studies the fundamental biological ideas frame the hypothesis-driven research on life span and mortality in human populations (Carnes *et al.*, 1999). As a result of these studies, the driving forces behind the observed mortality and life expectancy trends are better understood. The biological and genetic constraints on mortality forecasts are expected to decrease the uncertainty in our present vision of the future of human longevity. Biodemographic studies are also important for understanding the geographical, ethnic and sex differences in human life expectancy and its secular trends. Here we will discuss the perspectives and some preliminary findings for two particularly fascinating research directions in biodemographic studies:

1. the effects of parental age at reproduction on offspring life span, with special emphasis on the long-term consequences of late parenting;

2. familial transmission of human life span (in relation to the possible genetic limits of life expectancy).

This paper also summarizes our scientific discussions with the participants of three Research Workshops on "Genes, Genealogies, and Longevity" held in Belgium (Louvain-la-Neuve, October 1998), Germany (Rostock, May 1999) and France (Montpellier, October 1999).

Since methodological issues and concerns regarding data quality are of significant importance in biodemographic studies, a special discussion of this topic is also included in this article.

* Center on Aging, NORC and University of Chicago, e-mail: lagavril@midway.uchicago. edu

I. Data Resources and Data Quality Control

1. Main data source

Our study is based on the life span data for the members of European aristocratic families. The main advantage of these data is their high accuracy, reliability and completeness (to be discussed later). Another advantage of this kind of data is the relative homogeneity of this Caucasian population in respect to social class and educational background. Since this privileged social group lived in favorable conditions for many centuries, one could expect less influence of adverse social factors (poverty, for example) on life span and hence lower bias caused by these factors. This kind of data allows us to minimize the social heterogeneity of the population under study. Thus, although the sample analyzed in this study does not represent the whole human population (as laboratory animals do not represent species in the wild), it is one of the best possible samples to test biodemographic hypotheses since the effects of population heterogeneity are minimized with regard to social status.

The database on European royal and noble families (a family-linked database) was developed and used in our previous studies (Gavrilov and Gavrilova, 1997a; 1997b; Gavrilov *et al.*, 1995; 1997; Gavrilova *et al.*, 1995; 1997; 1998). To develop this database we used one of the best professional sources of genealogical data available – the famous German edition of the "Genealogisches Handbuch des Adels" (Genealogical Yearbook of Nobility). This edition is known world wide as the "Gotha Almanac" – "Old Gotha" published in Gotha in 1763-1944, and "New Gotha" published in Marburg since 1951 (see Gavrilova and Gavrilov, 1999a, for more details). Data from the Gotha Almanach were often used in early biodemographic studies of fertility (see Hollingsworth, 1969, pp. 199-224, for references) and are used now in the studies of human longevity (Gavrilova *et al.*, 1998; Gavrilov and Gavrilova, 1997a).

Each volume of the New Gotha Almanach contains about 2,000 genealogical records dating back to the 14th-16th centuries (to the founder of a particular noble genus). More than 100 volumes of this edition are already published, so more than 200,000 genealogical records with well-documented genealogical data are available from this data source. The high quality of information published in this edition is ensured by the fact that the primary information is drawn from the German Noble Archive (Deutsches Adelsarchiv). The Director of the German Noble Archive (Archivdirektor) is also the Editor of the New Gotha Almanach. Our own experience based on cross-checking the data has demonstrated that the number of mistakes (mostly misprints) is very low in the New Gotha Almanac (less than 1 per 1,000 records), so this source of data is very accurate compared to other published genealogies.

The information on noble families in the New Gotha Almanac is recorded in a regular manner. The description of each particular noble genus starts with information on two to three generations of founders of male sex only. Then three to four of the most recent generations are described in more detail, including information on individuals (e.g., first and last names; event data: birth, death, marriage dates and places; descriptive data: noble degrees, occupation if available, information on death circumstances if available), information on parents (e.g., first and last names; event data: birth and death dates and places), information on spouse(s) (e.g., first and last names; birth and death dates and places; first and last names of parents) and information on children (detailed as for each individual).

The process of data computerization was started from the most recent volumes of the New Gotha Almanac (published in 1990-1994) and has now reached the volumes published ten years earlier. The database on European aristocratic families comprises more than 20,000 personal records and is growing.

2. *Supplementary data sources*

Some other supplementary sources of data were used in the development of the database. These data sources include two computerized data files on European royalty and British peerage (computerized database Royal92 distributed on the Internet by Brian C. Tompsett at University of Hull, UK, and database on British Peerage distributed on CD by S&N Genealogy Supplies), as well as over 100 genealogical publications on Russian nobility listed elsewhere (Gavrilov *et al.*, 1996). These data were used as a supplement to the main data source since their quality was not as high as the Gotha Almanac. Although data on European royalty were recorded in computerized data sources (Royal92, British Peerage CD, see above) with sufficient completeness, data on lower rank nobility (landed gentry) were less complete and accurate. The same was true for the data on Russian nobility. All supplementary data were matched with the Gotha Almanac data, in order to cross-check the overlapping pieces of information. This cross-checking procedure allowed us to increase the completeness of the database by complementation of information taken from different sources.

3. *The structure of the database on European aristocracy*

The database approach used in this study is similar to the approach used for existing family-linked databases, such as the Utah Population Database (Skolnick *et al.*, 1979), Laredo Epidemiological Project

(Buchanan *et al.*, 1984) or other historical databases (Gutmann *et al.*, 1989). Initially the information computerized from each volume of the New Gotha Almanac is stored in two files: the Individual File and the Marriage File. Then these two files are merged into one rectangular file with information on up to four spouses. Since marriages with fifth and higher orders comprise less than 0.1% of all marriages, the potential loss of information on spouses after data merge is negligible. Then these merged files are linked to the Master File (main database).

In the Master File each record is related to the duration of an individual's life. Each record represents an individual's event data (birth and death dates and places) and descriptive information (identification number, sex, first and last names, nobility rank, occupation, birth order, cause of death (violent/nonviolent), ethnicity, marital status, data source code number, data source year of publication). Individual information is supplemented by data for parents (identification numbers, first and last names, birth, death and marriage dates, cause of death) and spouses. Thus, the database that is used in this project is organized in the form of triplets (referred to as the "ego" and two parents). This structure of records is widely used in human genetics and is adequate for studies of parent-child relationships. A similar database structure was used in the recent study of kinship networks (Post *et al.*, 1997).

4. Data quality control

Data quality control was an important part of our study, designed to develop high quality family-linked databases for longevity studies.

The genealogical data sets were checked for: (1) *completeness* in reporting birth and death dates, which is crucial for calculating individual life span – the variable of particular interest in our study; (2) *accuracy* – whether the percentage of mistakes and inconsistencies between reported dates (such as, for example, birth by a dead mother) is low enough to be acceptable; and (3) *representativeness* – whether the characteristics of investigated data sets (distribution by age, sex, marital status, age at death, etc.) is close enough to demographic characteristics of populations in similar geographic areas, historical periods and social groups. In our study we referred to the well-known publication by Thomas Hollingsworth (1962) on British peerage as a standard for European aristocracy, to check for data representativeness.

The completeness in birth and death dates reporting in the New Gotha Almanac was very high: dates of all vital events were reported for nearly 95% of all persons. Such high completeness is not common for many other genealogical data sources. For example, for British Peerage data published in Burke's almanac, in most cases there are no birth dates for women, which makes the calculation of their life spans impossible.

This problem with data for British aristocratic women was first noticed by Karl Pearson a century ago (Beeton and Pearson, 1899, 1901). He used the British Peerage data to study longevity inheritance and had to exclude women from his consideration for the following reason: "The limitation to the male line was enforced upon us partly by the practice of tracing pedigrees only through the male line, partly by the habitual reticence as to the age of women, even at death, observed by the compilers of peerages and family histories" (Beeton and Pearson, 1901, pp.50-51).

The accuracy of data published in the New Gotha Almanac is also very high: the frequency of inconsistent records is less than 1 per 1,000 records, whereas for many other genealogical data sources it falls within 1 per 300-400 records. Comparison of our data with Hollingsworth's analysis of British peerage revealed good agreement between his findings and our data on mortality patterns, including very high male/female gap in life expectancy – about 10 years (see Hollingsworth, 1962).

The genealogies for the members of European aristocratic families presented in the Gotha Almanac are of descending type, tracing almost all the descendants of relatively few founders. This is an important advantage of this data source over other genealogies that are often of ascending type (pedigrees). It is known in historical demography that the ascending genealogies are biased, over-representing more fertile and longer-lived persons who succeed in becoming ancestors, and for this reason such genealogies should be treated with particular caution (Jetté and Charbonneau, 1984; Fogel, 1993).

Thus, the genealogical data published in the Gotha Almanac are characterized by high quality and accuracy. We have, however, encountered some problems regarding the data completeness that are discussed below, along with proposed solutions.

Censored, truncated observations and missing death dates

Our study revealed that the percentage of cases with unreported death dates is rather small in our main data sources (Gotha Almanac), and is caused mainly by right censoring of long-lived persons who were still alive at the date of data collection and publication. The percentage of non-reported death dates varies from 0 to 7% in extinct birth cohorts (1800-1880), while it is higher in later birth cohorts (1880-1899): 23% for women and 8% for men, since some individuals were still alive at the date of data collection and volume publication. Note that women, who live longer, have a higher proportion of right-censored observations. The high proportion of censored observations in genealogies is not desirable, since the exact dates of censoring are often unknown. This uncertainty creates problems for data analysis, so the researchers working with genealogies prefer to use non-censored, extinct birth cohorts in their studies (Mayer,

1991; Pope, 1992; Kasakoff and Adams, 1995). We also used extinct (non-censored) birth cohorts in our study. For this purpose only those birth cohorts that were born at least 100 years before the year of data publication were used in the study (to be sure that the birth cohort under study is almost extinct).

Underreporting of women and children

In many genealogical books and databases, non-married women as well as children who died in infancy are often missed or reported with less completeness. Since genealogical records are focused on family names, which are transmitted by males only, women could be lost in genealogies when they marry and change their family names (Hollingsworth, 1976). Also, in many cases data for women do not contain information on their birth and death dates, resulting in a biased sex ratio in the sample with complete dates. We have also encountered this problem in our studies, although for somewhat different reasons. Our analysis revealed that the main cause of the sex bias in the New Gotha Almanac is related to the manner of data representation: more recent generations are presented completely, while the earlier generations are limited mainly to the male ancestors (in order to avoid repetitive publication of individuals already presented in previous volumes). That is why the sex ratio among early birth cohorts (1800-1860) is biased in favor of males, whereas for more recent birth cohorts (1880-1899) it is within normal range. Since in our study the most recent volumes of the New Gotha Almanac (published after 1980) were computerized and analyzed (in order to avoid censoring), the proportion of males in the database was substantially higher than expected. Thus, the ideal way to overcome the sex bias problem is to ensure complete coverage of all aristocratic genuses and families ever published in the Gotha Almanac. However, it may take a long time to computerize all 100 volumes of the New Gotha Almanac. The alternative way is to computerize complete data on early birth cohorts published in old volumes. In this case the data will be heavily censored, since many persons would not have a death date (being still alive) by the date of publication. We plan to continue computerization of these genealogies, which will eventually allow us to eliminate the sex bias and potential problems associated with it. Sex bias is an important issue in fertility studies, since the fertility levels are understated when daughters are underreported, but in the case of longevity studies this issue is less important when non-censored, extinct birth cohorts are analyzed (Wyshak, 1978). According to Wyshak (1978, p.318), "in the ... analysis of longevity, there is no reason to believe that women about whom information is not recorded differ from those whose records have been traced". A large-scale data computerization project is planned that eventually will allow us to eliminate the sex bias and also to check the validity of Wyshak's assumption (see above).

The underreporting of children who died in infancy may be also a serious problem, especially for studies that include fertility analysis. Fortunately, in the Gotha Almanac the noble families are described with remarkable completeness, especially those families which belong to the higher nobility rank (kings, princes, earls). In particular, all children ever born are recorded, including those who died the same day. Another indicator of data completeness is the normal sex ratio at birth (101 to 108) observed among these families (according to our sample analysis). In our database over 90 aristocratic genuses belonging to the upper nobility were recorded completely, although data for lower rank nobility were not yet completed. Underreporting of children is not a problem for this particular study, which is focused on adult life span for those who survive to age 30.

II. Parental Age at Conception and Offspring Life Span

Childbearing at older ages has become increasingly common in modern societies because of demographic changes (population aging), medical progress (e.g., in vitro fertilization (IVF) in older women) and personal choice (Kuliev and Modell, 1990). For example, in the United States the number of births to older mothers (35-39 years and 40+ years) has more than doubled since 1980 while the number of births to younger mothers (below age 30) did not increase (U.S. Bureau of the Census, 1997).

Birth rates for older fathers (ages 45-49 and 50-54) are also increasing (*U.S. Monthly Vital Statistics Report*, 1997, p.44) and this trend may even accelerate in the future due to medical progress (Viagra, for example). *What will be the health and life span of the children born to older parents?* While the detrimental effects of late reproduction on infant mortality and genetic diseases has been well documented (Gourbin and Wunsch, 1999), *little is known about the long-term postponed effects of delayed parenting on the mortality and life span of adult offspring*. The purpose of this study is to discuss and to fill the gaps that exist in our knowledge about the possible postponed detrimental effects of late parenting.

In 1997 we made a study of parental age effects for about 8,000 persons from European aristocratic families with well-known genealogy and found a strong inverse relationship between father's age at reproduction and daughter's (not son's) life span (Gavrilov and Gavrilova, 1997a; Gavrilov *et al.*, 1997). The results of that study are summarized in Table 1.

Note that daughters born by old fathers lose about 4.4 years of their life and these losses are statistically significant (p-value, $p < 0.01$; Student's test, $t = 3.1$), while sons are not significantly affected. This finding is in accord with the *mutation theory of aging* (Vijg and Gossen, 1993)

since paternal age at reproduction is considered to be the main factor determining the human spontaneous mutation rate (Crow, 1993; 1995; 1997; 1999; Vogel and Motulsky, 1997). Also, since only daughters inherit the paternal X chromosome, this sex-specific decrease in life span of daughters born to old fathers might indicate that human longevity genes (crucial, house-keeping genes) sensitive to mutational load might be located in this chromosome (Gavrilov and Gavrilova, 1997a; Gavrilov *et al.*, 1997).

TABLE 1.– HUMAN LIFE SPAN AND SEX DIFFERENTIAL IN LIFE SPAN AS A FUNCTION OF FATHER'S AGE AT REPRODUCTION

Paternal age at reproduction** (years)	Mean age at death* ± standard error (years)		Sex differential in life span (years)
	Daughters (sample size)	Sons (sample size)	
20-29	66.5 ± 0.7 (592)	61.3 ± 0.4 (1,238)	5.2 ± 0.8
30-39	65.9 ± 0.5 (1,214)	60.8 ± 0.3 (2,580)	5.1 ± 0.6
40-49	64.4 ± 0.7 (694)	60.5 ± 0.4 (1,543)	3.9 ± 0.8
50-59	62.1 ± 1.2 (206)	60.3 ± 0.7 (451)	1.8 ± 1.4

* Human life span was calculated for adults (those who survived to age 30) born in the 18th and 19th centuries. The data for those born in the 20th century were excluded from the analysis in order to have unbiased estimates of life span for non-censored, extinct birth cohorts.
** Data are controlled for father's life span (all fathers lived 50 years and more) in order to eliminate bias caused by possible association between father's early death and offspring life span.

It should be noted, however, that in the above mentioned preliminary studies (Gavrilov and Gavrilova, 1997a; Gavrilov *et al.*, 1997) possibly important covariates and confounding factors were not controlled for – such as maternal age at reproduction (which is strongly correlated with paternal age), historical trends and fluctuations in life expectancy of birth cohorts, and parental life span (age at death). Thus, the next logical step in this line of inquiry is to fill this gap and examine the previous preliminary observations on the life-shortening effects of late paternal reproduction, taking into account other important covariates mentioned above.

In this next step of our study we have increased the sample size and re-analyzed the data for the offspring born to older fathers at age 35-55 (see Tables 2 and 3). Offspring life span was analyzed for adults (those who survived to age 30) in order to study the long-term, postponed effects of late reproduction of the parents. The data for offspring born in the 20th century were excluded from the analysis in order to have unbiased estimates of life span for non-censored, extinct birth cohorts. The data for offspring born before the 19th century were also excluded in order to minimize the heterogeneity of the sample.

TABLE 2.– CHARACTERISTICS OF THE SAMPLE UNDER STUDY

Variable	Sons	Daughters
Sample size, number of cases	4,566	2,068
Offspring birth dates, years		
– range	1800-1899	1800-1899
– mean	1860.6	1864.7
– standard deviation	25.2	27.9
Offspring age at death, years		
– range	30-100	30-105
– mean	64.6	73.5
– standard deviation	14.9	15.6
Paternal age at reproduction, years		
– range	35-55	35-55
– mean	41.4	41.6
– standard deviation	5.1	5.2
Maternal age at reproduction, years		
– range	16-56	15-51
– mean	30.7	31.0
– standard deviation	5.7	5.8
Paternal age at death, years		
– range	35-99	35-96
– mean	68.2	68.4
– standard deviation	12.0	12.0
Maternal age at death, years		
– range	21-102	19-102
– mean	68.8	69.2
– standard deviation	15.6	15.8
Cohort life expectancy, years		
– range	58.0-72.5	56.1-81.6
– mean	64.7	73.2
– standard deviation	2.3	5.9

For each birth cohort the mean sex-specific expectation of life at age 30 was calculated and used as an independent variable in a multiple linear regression model to control for cohort and secular trends and fluctuations in human life span. Offspring life span for each particular sex (4,566 records for males and 2,068 records for females) was considered as a dependent variable in the multiple regression model (program 1R in BMDP statistical package) and a function of five independent predictors: paternal age at reproduction in the range of 35-55 years (where the life-shortening effect was previously detected) (Gavrilov and Gavrilova, 1997b); maternal age at reproduction (control for maternal age is important since it is correlated with paternal age); paternal age at death; maternal age at death (to control for heritability of human life span); and sex-specific mean cohort life span (control for cohort and secular trends and fluctuations). The detailed description of the sample under study is given in Table 2. Note large sex differences in life span (8.9 years) that are in a good agreement with

previous findings for British Peerage – about 10 years (see Hollingsworth, 1962). Also note a significant sex bias (male overrepresentation), typical for this kind of genealogical data (see, for example, Westendorp and Kirkwood, 1998; Gavrilov and Gavrilova, 1999a). We plan to eliminate this sex bias in our future large-scale data computerization project and to test the validity of the findings presented in this paper.

The results of this study are presented in Table 3. The regression slope for daughters' life span as a function of paternal age at reproduction is negative (–0.16 ± 0.07) and this inverse relationship is statistically significant ($p = 0.02$; $t = -2.35$) even when the effects of the other four important covariates are taken into account. In the case of sons the association with paternal age at reproduction is much weaker (–0.06 ± 0.05) and statistically insignificant ($p = 0.23$; $t = -1.20$). Thus, this study lends support to the previous preliminary observations (Gavrilov and Gavrilova, 1997a; Gavrilov *et al.*, 1995; 1997) on the sex-specific life-shortening effect of late paternal reproduction on daughters' life span.

TABLE 3.– PARENTAL PREDICTORS OF HUMAN LIFE SPAN. COEFFICIENTS (SLOPES) OF MULTIPLE LINEAR REGRESSION ± STANDARD ERROR

Variable	Sons	Daughters
Paternal age at reproduction	–0.06 ± 0.05	–0.16 ± 0.07
Maternal age at reproduction	0.03 ± 0.04	0.02 ± 0.06
Paternal age at death	0.13 ± 0.02	0.09 ± 0.03
Maternal age at death	0.03 ± 0.01	0.04 ± 0.02
Cohort life expectancy	1.07 ± 0.10	1.04 ± 0.05
Other characteristics of regression:		
Multiple R	0.2	0.4
F Ratio	37.2	86.3

The results described above were based on the assumption that the dependence between offspring life span and paternal age at reproduction could be considered as approximately linear for the paternal ages in the range of 35-55 years. Our next step of the study was to check whether this assumption was valid. For this reason we re-analyzed the data for different ranges of paternal age at reproduction. It turned out that for the subgroup of younger fathers (35-45 years) the mean loss of daughters' life span is very small (0.02 ± 0.12 years lost per each additional year of paternal age) and statistically insignificant (sample size $n = 1{,}651$; $t = 0.16$; $p = 0.87$), whereas for older fathers (45-55 years) this loss is particularly high (0.48 ± 0.21 years lost per each additional year of paternal age) and statistically significant ($n = 598$; $t = 2.34$; $p = 0.02$). These results are consistent with the general conclusion of Professor James F. Crow on *non-linear* accelerating increase of mutation rates with paternal age (Crow, 1993; 1995; 1997; 1999).

One possible explanation for this threshold effect of paternal age might be the competition among sperm cells. Since only one of a huge number of sperm cells succeeds in fertilization in each particular case, damaged sperm cells with a high mutational load may not withstand this strong competition. Only at very old ages, when the proportion of damaged sperm cells becomes higher than some threshold level, does the selection mechanism finally fail and accumulation of mutational load becomes evident (Gavrilov *et al.*, 1997).

There may be another possible explanation of the threshold nature of paternal effect on offspring life span. Since short-lived fathers can participate in reproduction at young ages only, the detrimental effect of age-related accumulation of mutational load in paternal germ cells might be compensated by selection effects (i.e., the population of old fathers is also the population of survivors compared to young fathers). In other words, the threshold behavior might be an artifact caused by the heterogeneity of the population. It is therefore important in the future to study the effect of paternal age on a more homogeneous population of longer-lived fathers.

Another interesting preliminary observation is that sex differences in human life span are a function of paternal age at reproduction. The data presented in Table 1 show that females live longer than males when fathers are young, while in the case of old fathers sex differences are very small and statistically insignificant (Gavrilova *et al.*, 1995; Gavrilov *et al.*, 1995; 1997). This preliminary observation may also have a biological explanation. Since females have two X chromosomes, they are genetically more redundant than males who have only one X chromosome. However, when the father is older and his X chromosome transferred to the daughter has a higher mutational load, there is no longer a difference in genetic redundancy between males and females, since both have only one intact (maternal) X chromosome. Thus, there is every reason to expect that, with increases in paternal reproductive age, the sex differences in offspring life span should decrease (see Table 1, the column for sex differential in life span, supporting this hypothesis). We believe, however, that this finding should be validated in future studies using a larger sample size while controlling for effects of other important factors such as secular differences in life expectancy of different birth cohorts.

III. Familial Transmission of Human Longevity

In 1999 the scientific community could celebrate the 100th anniversary of the first systematic studies on familial determinants of human longevity. In 1899 the founder of biometrics, Karl Pearson (1857-1936), and his student, Mary Beeton, published the very first study on the inheritance of human life span (Beeton and Pearson, 1899). They analyzed the correla-

tion of parent/child ages at death, based on English genealogies going back to the 17th century (three series of data were taken from the English Peerage and Landed Gentry). Owing to the limitations of their data, Beeton and Pearson dealt with only the adult males age 20 and over.

Their second study (Beeton and Pearson, 1901) was based upon more extensive pedigree records of the members of the English Society of Friends and of the Friends' Provident Association (these data included both males and females of all ages). Using such data, Beeton and Pearson (1901) measured the correlation for ages at death not only for parent/child pairs but also in the siblings. As a result of their studies, Beeton and Pearson concluded that "the expectation of life is seriously modified by the ages of death of the relatives."

The problem of familial transmission of human life span was also examined by such outstanding investigators as the telephone inventor Graham Bell (1918) on genealogical data of about 3,000 members of the Hyde family in New England and by one of the founders of biodemography, Raymond Pearl (Pearl, 1931; Pearl and Pearl DeWitt, 1934a, 1934b) who initiated the famous Baltimore Longevity Study.

Following these initial studies on familial transmission of human life span early in the century, a number of scientists have since devoted their attention to this topic (Wilson and Doering, 1926; Holmes, 1928; Yuan, 1931; Preas, 1945; Dublin *et al.*, 1949; Jalavisto, 1951; Cohen, 1964; Hawkins *et al.*, 1965; Abbott *et al.*, 1974; 1978; Murphy, 1978; Philippe, 1977; 1978; 1980; Welter, 1978; Wyshak, 1978; Glasser, 1981; Crawford and Rogers, 1982; Swedlund *et al.*, 1983; Vandenbroucke *et al.*, 1984; Desjardins and Charbonneau, 1990; Bocquet-Appel and Jakobi, 1990; 1991; Brand *et al.*, 1992; Mayer, 1991; Robine and Allard, 1997; Tallis and Leppard, 1997).

In addition to traditional familial longevity studies, one of the most powerful approaches for assessing genetic and cultural contributions to inter-individual variation in human life span has also been used – the evaluation of the relative *longevity of twins* (Kallman and Sander, 1948; 1949; Kallman, 1957; Jarvik *et al.*, 1960; Harvald and Hauge, 1965; Wyshak, 1978; Hrubec and Neel, 1981; Carmelli, Andersen, 1981; Carmelli, 1982; Hrubec *et al.*, 1984; Hayakawa *et al.*, 1992; McGue *et al.*, 1993; Herskind *et al.*, 1996; Yashin and Iachine, 1997). Studies of twins and other kinds of related individuals suggest that about 25% of the variation in adult life spans appears to be attributable to genetic variation among individuals (McGue *et al.*, 1993; Herskind *et al.*, 1996). Some research in progress by Anatoli Yashin and Ivan Iachine suggests that an additional 25% may be attributable to non-genetic characteristics that are more or less fixed by the time a person is 30 or so, characteristics such as educational achievement, socio-economic status, mother's and father's age at a person's birth, etc. (Yashin and Iachine, 1997; Vaupel *et al.*, 1998). Little, however, is known

about the relative importance of familial factors in later life and among the oldest-old in particular.

Studies on the *life span of adopted children* were also made and have demonstrated the importance of longevity of the biological parents in predicting offspring mortality at adult ages (Sorensen *et al.*, 1988; Sorensen, 1991; Nielsen *et al.*, 1992).

Does this brief historical review of scientific literature on familial longevity suggest that all of the concepts, methodology and conclusions have already been established? Surprisingly this seems not to be true, since there is still no consensus even for the most fundamental issues regarding familial longevity. For example, the role of genetics in familial longevity resemblance was challenged by some authors (Murphy, 1978; Philippe, 1978; Jacquard, 1982) who have found very weak familial resemblance and emphasized the importance of social explanations.

The mode of life span inheritance in humans is also not yet determined and there is still controversy about the relative importance of the maternal versus paternal longevity influence on offspring life span. Is human longevity inherited more strongly along the maternal line (consistent with cytoplasmic, mitochondrial inheritance: Sont and Vandenbroucke, 1993; Wallace, 1995; Tanaka *et al.*, 1998; Vandenbroucke, 1998), as would appear to be demonstrated in many studies (Pearl, 1931; Jalavisto, 1951; Abbot *et al.*, 1978; Brand *et al.*, 1992)? Or, on the contrary, is there a predominance of paternal longevity influence on offspring life span, as suggested in other studies (Bell, 1918; Cohen, 1964; Philippe, 1978; Welter, 1978; Bocquet-Appel and Jakobi, 1990; Gavrilov *et al.*, 1998)?

Recent studies suggest that it may be reasonable to revise some of the underlying assumptions behind existing controversies about some of these issues, and to develop improved methods of familial analysis of human longevity (e.g., see Gavrilov and Gavrilova, 1991). One basic assumption that is tested in this study is the premise that there is a *linear* relationship between offspring and parental life span. This assumption of linear dependence between offspring and parental traits is basic for quantitative genetics (Falconer, 1989; Lynch and Walsh, 1998). Moreover, the assumption of linearity is one of the foundations for the Path analysis used in studies of the mechanisms of familial transmission of quantitative traits (Neale and Cardon, 1989, p.91). The methods of correlation and regression analyses are also based on this assumption of linearity and were used in previous familial studies of life span (Holmes, 1928; Yuan, 1931; Dublin *et al.*, 1949; Jalavisto, 1951; Hawkins *et al.*, 1965; Abbott *et al.*, 1973; Murphy, 1978; Cohen, 1964; Philippe, 1977; 1978; Welter, 1978; Wyshak, 1978; Desjardins and Charbonneau, 1990; Bocquet-Appel and Jakobi, 1990; 1991). In this article we address this issue directly and check whether the linearity assumption is valid or not (see later).

What are the alternatives to the linearity assumption? The dependence of offspring life span on parental life span might be a *decelerating*

one, with a decreasing slope and even a leveling off in the case of an early selection out of parents who die prematurely (either for genetic or social reasons). The population of longer-lived parents may also become more homogeneous because of selection.

An alternative prediction is that dependence should be *accelerating* (more steep for the offspring of longer-lived parents) – a hypothesis derived from the evolutionary theory of aging and the mutation accumulation hypothesis in particular (e.g., see Gavrilova *et al.*, 1998a). The evolutionary theory of aging predicts that the equilibrium gene frequency for deleterious mutations should increase with age-at-onset of mutation action because of weaker (postponed) selection against later-acting mutations (Medawar, 1952; Finch, 1990; Rose, 1991; Partridge and Barton, 1993; Charlesworth, 1994). According to the mutation accumulation hypothesis, one would expect the observed (e.g. *expressed*) genetic variability in survival (additive genetic variance) to increase with age (Partridge and Barton, 1993; Charlesworth, 1994). Generally speaking, both the additive genetic component of variance and the dominant component are expected to increase with age under the mutation accumulation hypothesis (because for traits affected by rare deleterious alleles, both components increase with increasing mutant allele frequency) (Charlesworth, 1987; Falconer, 1989; Hughes and Charlesworth, 1994). The ratio of additive genetic variance to the observed phenotypic variance (the "narrow-sense heritability" of life span) could be estimated most reliably as the doubled slope of the regression line for offspring life span on *paternal* age at death (the regression of offspring on mothers is sometimes liable to give too high an estimate on account of maternal effects, as it would, for example, with body size in most mammals) (Falconer, 1989). That is why the slope of the regression line on *paternal* rather than maternal age at death would appear to be a better estimate for heritability of human life span. Thus, if longevity is indeed determined by late-acting deleterious mutations, one would expect this slope to become steeper at higher paternal ages (Gavrilova *et al.*, 1998). In this study we test the above mentioned prediction of the evolutionary theory of aging and the mutation accumulation hypothesis in particular (see later).

One important limitation in some previous studies of familial longevity is that parental age at childbirth is ignored as a possible confounding factor in the analysis of life span heritability (Beeton and Pearson, 1899; 1901; Bell, 1918; Pearl, 1931; Pearl and Pearl DeWitt, 1934b; Holmes, 1928; Yuan, 1931; Dublin *et al.*, 1949; Jalavisto, 1951; Cohen, 1964; Hawkins *et al.*, 1965; Abbott *et al.*, 1973; Murphy, 1978; Philippe, 1977; 1978; Welter, 1978; Desjardins and Charbonneau, 1990; Bocquet-Appel and Jakobi, 1990; 1991; Mayer, 1991). This position is equivalent to assuming that this variable is of no importance. However, our preliminary studies (see previous chapter of this article) have demonstrated that parental age at childbirth (paternal age in particular) is in fact an important predictor of

offspring life span (for daughters in particular). It affects significantly the estimates of life span inheritance. For this reason it is important to re-examine the estimates of familial transmission of human longevity taking into account such potentially important covariates as parental age at childbirth as well as secular changes in cohort life expectancy.

There are two other limitations in previous studies on this topic that could lead to existing controversies and biased estimates of life span heritability. First, in some studies the birth cohorts were not extinct by the date of data collection and this right-censoring of the data was not taken into account (Beeton and Pearson, 1899; 1901; Bell, 1918; Hawkins *et al.*, 1965; Abbott *et al.*, 1973; Murphy, 1978). For this reason the data were biased in favor of shorter-lived persons, because the life span data for longer-living persons were not yet available by the time of data collection (longer-living persons were still alive). The importance of this problem has already been discussed in the scientific literature (Yuan, 1932). Moreover, for those family members whose birth date is close to the censoring date of data collection, only the short-lived persons will be included in the analysis, thus producing a spurious correlation between ages at death for short-lived relatives.

Another limitation of previous studies is the lack of proper control for historical changes in human life expectancy. When the data for families (parents and their children) that lived in different historical periods are mixed in one sample and analyzed together, a spurious artifact correlation between relatives' life span is produced (since life expectancy in early historical periods was low both for parents and their children relative to more recent time periods). That is why the estimates of familial aggregation of human longevity are probably biased (overstated) in earlier studies not controlled for secular effects (Beeton and Pearson, 1899; 1901; Bell, 1918; Jalavisto, 1951). Moreover, since the secular trends for male and female life span are different, a spurious gender difference in familial transmission of human life span could be produced in such uncontrolled studies. Some authors tried to regress out the secular effects by introducing the calendar year of death as a covariate in a multivariate analysis (Wyshak, 1978; Bocquet-Appel and Jakobi, 1990). Since the calendar year of death tends to be higher for longer-lived people (the more you live the later you die), this procedure could decrease not only the noise (secular effects), but also the signal itself (human life span). Attempts were also made to use the calendar year of birth to control for secular effects, but this variable proved to be a poor predictor of individual lifespan and it made virtually no contribution into regression fitting (see Wyshak, 1978). To resolve this problem we proposed to use an improved method for data analysis that allows for the control of strong and complex historical changes in cohort life expectancy (Gavrilov and Gavrilova, 1997b; Gavrilova *et al.*, 1998). This method is based on the idea of an internal control variable: the sex-specific mean life span for each birth cohort is

calculated and included in the analysis as an independent covariate, so that any historical trends and fluctuations in human life expectancy are regressed out (Gavrilova *et al.*, 1998). This internal control variable proved to be a much better predictor than just the calendar year of birth and it improved significantly the regression fitting (Gavrilova *et al.*, 1998).

The results obtained in this study may be summarized as follows:

1. The dependence of offspring life span on parental life span appears not to be linear, as it is generally assumed. Rather, it looks like an accelerating relationship with rapid increases of the regression slope for longer-lived parents. Thus, the familial component of human life span was probably understated in previous studies, particularly in the case of longer-lived parents. The results on this issue are presented in Table 4 and demonstrate a significant increase in familial transmission of life span (regression slopes) from longer-lived fathers (75 years and above). Recently the linearity assumption was also tested for non-overlapping parental lifespan intervals with the same result (hypothesis of linearity was rejected, see Gavrilov *et al.*, 2000; 2001).

The results in Table 4 represent a significant increase in biometric estimates of the "narrow-sense heritability" of human life span at advanced paternal ages at death, so that familial transmission of longevity (regression slopes) is significantly higher from longer-lived fathers. Also, the results in Table 4 could explain the existing longevity paradox: although the heritability estimates for life span were reported to be rather low (McGue *et al.*, 1993; Wyshak, 1978; Murphy, 1978), it is also well-known that cases of extreme longevity have a strong familial association (Pearl, 1931; Pearl and Pearl DeWitt, 1934a, 1934b; Perls *et al.*, 1998). This paradox can be explained by our finding that heritability for human life span is low (12 ± 4% for daughters and 18 ± 2% for sons) only when studied in the whole range of paternal life span (30+ years), but is rather high (46 ± 16% for daughters and 38 ± 10% for sons) when estimated specifically for longer-lived fathers (75+ years, see Table 4). These data are upper bound estimates for heritability because the combined effect of both genetic and non-genetic familial factors is measured in this study.

Similar results were obtained using survival analysis. Analysis of the survival curves for daughters and sons born to fathers with different life spans has demonstrated a threshold familial transmission of human longevity. When fathers lived less than 80 years there was very weak familial transmission of life span from fathers to sons and virtually no familial transmission of life span from fathers to daughters (see Figures 1 and 2). In those cases when fathers lived more than 80 years, there was a remarkable improvement in survival of both sons and daughters (see Figures 1 and 2).

The results presented here indicate that the familial component of human life span was probably understated in previous studies, particularly in the case of longer-lived parents. Further studies in this direction on lar-

TABLE 4.– HERITABILITY OF HUMAN LIFE SPAN INCREASES WITH PATERNAL LIFE SPAN*

Paternal age at death (years)	Regression slopes ± standard error for offspring life span on paternal age at death	
	Daughters (sample size)	Sons (sample size)
30+	0.06 ± 0.02 (5,182)	0.09 ± 0.01 (11,984)
40+	0.07 ± 0.02 (5,020)	0.10 ± 0.01 (11,670)
50+	0.10 ± 0.02 (4,610)	0.12 ± 0.01 (10,676)
60+	0.13 ± 0.03 (3,758)	0.15 ± 0.02 (8,679)
65+	0.18 ± 0.04 (3,128)	0.19 ± 0.03 (7,214)
70+	0.27 ± 0.05 (2,369)	0.20 ± 0.03 (5,500)
75+	0.23 ± 0.08 (1,572)	0.19 ± 0.05 (3,638)

* The slope coefficients of linear regression of offspring life span on paternal life span represent one half of the narrow-sense heritability of human life span. The data are upper bound estimates for genetic heritability, because non-genetic familial factors may also contribute to familial transmission of lifespan.

Data sample. To determine the type of the dependence of offspring life span on parental life span, we computerized and analyzed genealogical data on longevity in *European noble and royal families* published in "Genealogisches Handbuch Des Adels" (1980-1994) and in other professional genealogical sources, listed elsewhere (Gavrilov, Gavrilova *et al.*, 1996). This kind of data for socially elite families was chosen in order to minimize the social heterogeneity of the population under study and to avoid overstating the familial component of longevity when a mixture of families with different social status is analyzed. Offspring life span was analyzed for adults (those who survived to age 30) in order to avoid underestimation of human life span associated with high infant mortality rates and high proportion of premature deaths at young ages due to infectious diseases and violence observed in the 19th century. The data for offspring born in the 20th century were excluded from the analysis in order to have unbiased estimates of life span for non-censored, extinct birth cohorts. The data for offspring born before the 18th century were also excluded in order to minimize the heterogeneity of the study population. Thus, 1800-1880 non-censored, extinct birth cohorts were studied. For each birth cohort the mean sex-specific adult life span at age 30 was calculated and used as an independent predictor variable in multiple linear regression to control for cohort and secular effects on human life span.

Heritability estimates. Heritability was estimated as a doubled coefficient of linear regression of offspring life span on father's life span (Falconer, 1989; Khoury *et al.*, 1993). Since life span of one parent (father) was used in the regression, the regression coefficients in Table 4 represent one half of the heritability estimates (Jacquard, 1983; Khoury *et al.*, 1993). Paternal rather than maternal life span was selected as a predictor variable in the regression, since it is known that maternal effects might have a much more complex nature including specific inheritance of mitochondrial DNA and strong maternal-child interaction during *in utero* development and later during the formative years of the child. For this reason mothers often have a stronger influence on the offspring, being determined not only by genetic factors (Falconer, 1989). The estimates of heritability were adjusted for paternal age at reproduction and mean cohort life expectancy. The data correspond to both genetic and non-genetic familial effects combined, and therefore, represent the upper bound estimate for genetic narrow-sense heritability of lifespan.

Characteristics of multiple linear regression. Life span was calculated for adults (those who survived to age 30) born in 1800-1880. Offspring life span for each particular sex (11,984 records for males and 5,182 records for females) was considered as a dependent variable in the multiple regression model (using SPSS statistical package) and a function of 3 independent predictors: paternal life span (for estimation of heritability of life span), paternal age at reproduction (control for parental age effects) and sex-specific cohort adult mean life span at age 30 (control for cohort and secular trends and fluctuations). The F ratio for each multiple regression was higher than 17.0 and all the regressions were statistically highly significant ($p < 0.0001$).

ger sample sizes and other data sets (for comparative analysis) could result in significant progress in understanding the mechanisms of familial determination of human longevity.

2. Our next finding is that paternal life span seems to be a more important predictor of offspring life span than maternal life span for sons (Table 5) and probably for daughters (Table 6).

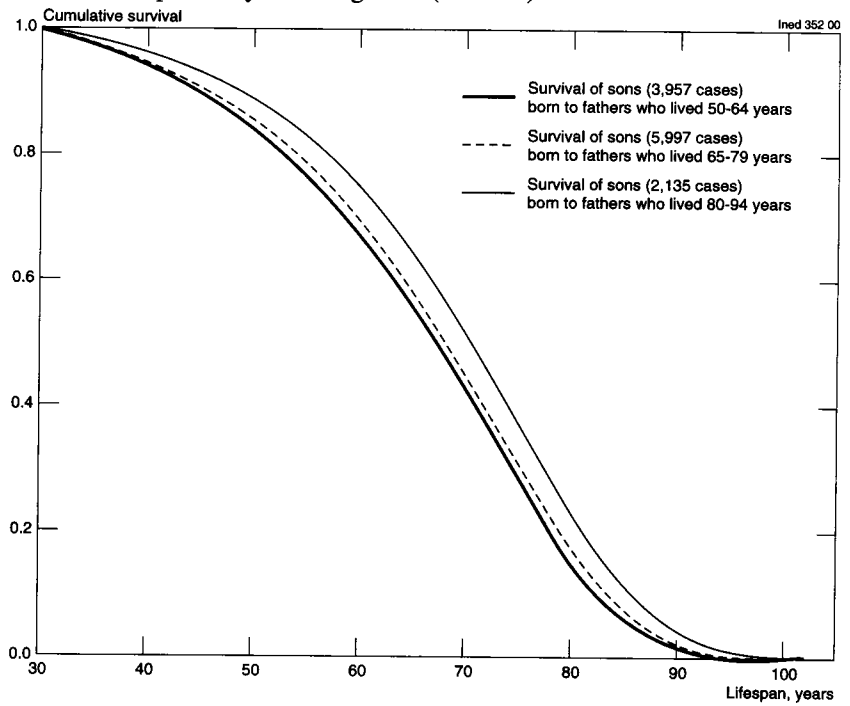

Figure 1.– Survival curves for males (sons) born to fathers with different life spans

Note that the effect of paternal life span on sons' survival is non-linear and looks like a threshold one: the survival curves for sons born to fathers who lived 50-64 years (curve 1) or 65-79 years (curve 2) are very close to each other, while for sons born to longer-lived fathers (80-94 years) there is a remarkable improvement in their survival (curve 3).

Comparison of survival curves using Log rank and Breslow tests demonstrated that the difference between survival curves 2 and 3 is highly significant (Log rank test = 44.6; $p < 0.00001$; Breslow test = 22.9; $p < 0.00001$). The difference between survival curves 1 and 2 is also highly significant (Log rank test = 12.6; $p = 0.0004$; Breslow test = 15.2; $p = 0.0001$), but the curves are very close to each other.

The data on offspring life span were adjusted for historical trends and fluctuations in life span in human birth cohorts (life span deviations from sex-specific mean cohort life span were analyzed). Thus, the adjusted life span was calculated as a deviation centered around sex-specific cohort mean life span for the studied sample (survived by age 30). In order to avoid bias in estimation of the offspring life span, only extinct birth cohorts were analyzed (born in 1800-1890). The survival curves were obtained using Kaplan-Meier procedure of SPSS statistical package. Cases of violent death were treated as censored observations.

The results of this study for *sons'* life span are presented in Table 5. Both paternal and maternal life spans have positive statistically significant effects on life span of sons. The effect is higher for longer-lived parents, especially in the case of fathers. The paternal effect (slope coefficient of

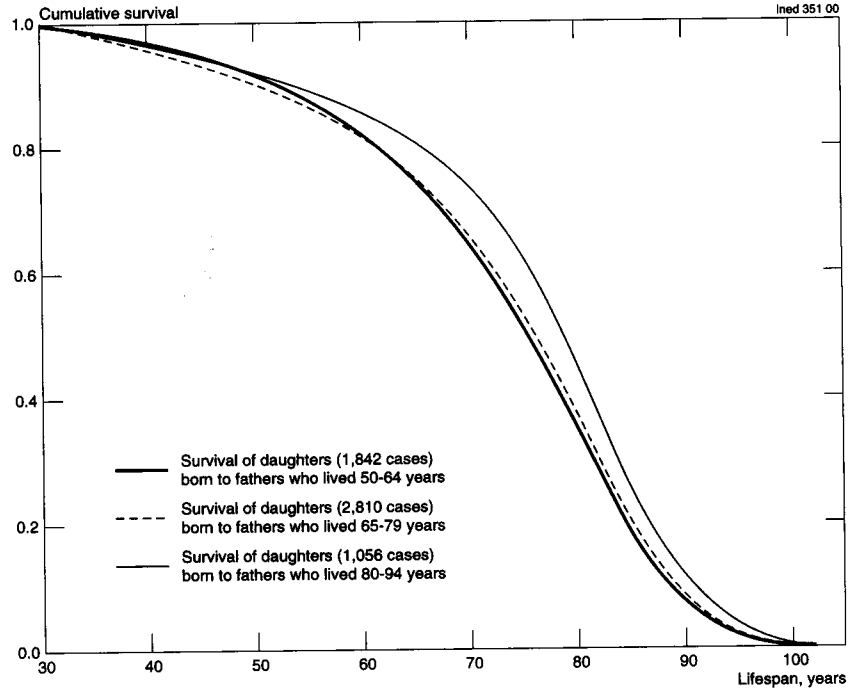

Figure 2.– Survival curves for females (daughters) born to fathers with different life spans

Note that the effect of paternal life span on daughters' survival is non-linear and looks like a threshold one: the survival curves for daughters born to fathers who lived 50-64 years (curve 1) or 65-79 years (curve 2) are virtually identical, while for daughters born to longer-lived fathers (80-94 years) there is a remarkable improvement in their survival (curve 3).

Comparison of survival curves using the Log rank and Breslow tests demonstrated that the difference between survival curves 2 and 3 is highly significant (Log rank test = 22.9; Breslow test = 25.7; $p < 0.0001$), whereas the difference between survival curves 1 and 2 is statistically non-significant (Log rank test = 1.27; $p = 0.26$; Breslow test =1.31; $p = 0.25$).

For description of data sample and methods of data analysis see footnote for Figure 1.

multiple regression model) is higher than the maternal effect at any level of parental life span and this difference is statistically significant when sample size is large enough (Table 5).

The effects of parental life span on *daughters* are presented in Table 6. Both paternal and maternal life spans are positive predictors of daughters' life span and paternal effects are particularly high in the case of longer-lived parents. In all cases the paternal effects tend to be higher than maternal ones, although the sample size should be increased in future studies in order to check the statistical significance of this observation more carefully (Table 6).

TABLE 5.– SONS' LIFE SPAN AS A FUNCTION OF PATERNAL AND MATERNAL LIFE SPAN. PARAMETERS OF MULTIPLE LINEAR REGRESSION MODEL (SLOPE COEFFICIENTS)

Parental age at death	Number of cases in regression	Linear regression slopes ± standard error		Difference between paternal and maternal effects ± standard error
		Paternal effect	Maternal effect	
30+	11,613	0.091 ± 0.010***	0.035 ± 0.009***	0.056 ± 0.013***
40+	10,403	0.102 ± 0.012***	0.050 ± 0.011***	0.052 ± 0.016**
50+	8,772	0.112 ± 0.015***	0.073 ± 0.015***	0.039 ± 0.021
60+	6,203	0.119 ± 0.023***	0.094 ± 0.022***	0.025 ± 0.032
70+	2,896	0.170 ± 0.048***	0.111 ± 0.046*	0.059 ± 0.066

* statistically significant at 0.05 level;
** significant at 0.01 level;
*** significant at 0.001 level.
NB: Data on European royal and noble families were analyzed for adults (30 years and above) born in 1800-1880. For each birth cohort the mean sex-specific adult life span at age 30 was calculated and used as an independent predictor variable in multiple linear regression to control for cohort and secular trends and fluctuations in human life span. Offspring life span for each particular sex (11,613 records for males and 5,025 records for females) was considered as a dependent variable in multiple linear regression model (using SPSS statistical package) and a function of 3 independent predictors: paternal age at death, maternal age at death and mean sex-specific cohort adult life span at age 30. The data analyses were made for 5 overlapping ranges of parental (both paternal and maternal) ages at death: 30 years and above (30+), 40 years and above (40+), 50 years and above (50+), 60 years and above (60+) and 70 years and above (70+).

TABLE 6.– DAUGHTERS' LIFE SPAN AS A FUNCTION OF PATERNAL AND MATERNAL LIFE SPAN. PARAMETERS OF MULTIPLE LINEAR REGRESSION MODEL (SLOPE COEFFICIENTS)

Parental age at death	Number of cases in regression	Linear regression slopes ± standard error		Difference between paternal and maternal effects ± standard error
		Paternal effect	Maternal effect	
30+	5,025	0.063 ± 0.016***	0.055 ± 0.014***	0.008 ± 0.021
40+	4,513	0.082 ± 0.019***	0.060 ± 0.017***	0.022 ± 0.025
50+	3,767	0.098 ± 0.024***	0.094 ± 0.023***	0.004 ± 0.033
60+	2,677	0.147 ± 0.036***	0.097 ± 0.034**	0.050 ± 0.050
70+	1,294	0.295 ± 0.069***	0.114 ± 0.066	0.181 ± 0.095

* statistically significant at 0.05 level;
** significant at 0.01 level:
*** significant at 0.001 level.
NB: see Table 5.

The most interesting result of this study is that the maternal life span effect does not exceed the paternal one – in fact, the opposite tendency is observed. This observation is surprising since the mother has many different additional influences on the offspring through specific inheritance of mitochondrial DNA, strong maternal-child interaction during in utero development and later during the formative years of the child. For this reason the maternal effect on offspring traits is usually higher than the paternal one (Falconer, 1989). It is interesting that human life span is an exception from this general observation and, in fact, the paternal effects tend even to exceed the maternal ones. Since this preliminary observation has

important implications for testing different theories of aging and longevity, it deserves to be studied more thoroughly in future on larger data sets.

Further studies are planned, including a large-scale data computerization project that will allow us to eliminate the sex bias, to validate the findings described in this paper, to analyze the data without linearity assumptions (using multivariate regression with nominal variables, see Gavrilov and Gavrilova, 1999b; 2000), and to cast more light on the biodemography of familial longevity.

Acknowledgments: We would like to acknowledge useful comments on our research work provided by the participants of three Research Workshops "Genes, Genealogies, and Longevity" held in Belgium (Louvain-la-Neuve, October 1998), Germany (Rostock, May 1999) and France (Montpellier, October 1999). We would also like to thank two anonymous reviews of this manuscript for their constructive criticism and helpful suggestions. We are extremely indebted to Dr. Victoria G. Semyonova and Mrs. Galina N. Evdokushkina for their assistance in developing the database on European aristocracy. We would also like to acknowledge the partial support from National Institute on Aging grants.

REFERENCES

ABBOTT M.H., MURPHY E.A., BOLLING D.R., ABBEY H., 1974, "The familial component in longevity. A study of offspring of nonagenarians. II. Preliminary analysis of the completed study", *Hopkins Med. J.*, 134, p. 1-16.

ABBOTT M.H., ABBEY H., BOLLING D.R., MURPHY E.A., 1978, "The familial component in longevity. A study of offspring of nonagenarians. III. Intrafamilial studies", *Am. J. Med. Genet.*, 2, p. 105-120.

BEETON M., PEARSON K., 1899, "Data for the problem of evolution in man, II: A first study of the inheritance of longevity and the selective death rate in man", *Proceedings of the Royal Society of London*. 65, p. 290-305.

BEETON M., PEARSON K., 1901, "On the inheritance of the duration of life and the intensity of natural selection in man", *Biometrika* 1, p. 50-89.

BELL A.G., 1918, *The Duration of Life and Conditions Associated with Longevity. A Study of the Hyde Genealogy*. Washington: Genealogical Records Office.

BOCQUET-APPEL J.P., JAKOBI L., 1990, "Familial transmission of longevity", *Ann. Human Biol.*, 17, p. 81-95.

BOCQUET-APPEL J.P., JAKOBI L., 1991, "La transmission familiale de la longévité à Arthez d'Asson (1685-1975)", *Population*, 46 (2), p. 327-47.

BRAND F.N., KIELY D.K., KANNEL W.B., MYERS R.H., 1992, "Family patterns of coronary heart disease mortality: The Framingham longevity study", *J. Clin. Epidemiol.*, 45, p. 169-174.

BUCHANAN A.V., WEISS K.M., SCHWARTZ R.J., MACNAUGHTON N.L., MCCARTAN M.A., BATES S.S., 1984, "Reconstruction of genealogies from vital records: The Laredo Epidemiology Project", *Comput. Biomed. Res.*, 17, p. 326-351.

CARMELLI D., 1982, "Intrapair comparisons of total life span in twins and pairs of sibs", *Hum. Biol.*, 54, p. 525-537.

CARMELLI D., ANDERSEN S., 1981, "A longevity study of twins in the Mormon genealogy", *Prog. Clin. Biol. Res.*, 69 Pt.C, p. 187-200.

CARNES B.A., OLSHANSKY S.J., 1993, "Evolutionary perspectives on human senescence", *Population and Development Review*, 19(4), p. 793-806.

CARNES B.A., OLSHANSKY S.J., GAVRILOV L.A., GAVRILOVA N.S., GRAHN D., 1999, "Human longevity: Nature vs. Nurture – fact or fiction", *Perspectives in Biology and Medicine*, 42(3), p. 422-441.

CHARLESWORTH B., 1994, *Evolution in Age-Structured Populations*, Cambridge Univ. Press: Cambridge.

COHEN B.H., 1964, "Family patterns of mortality and life span: A critical review", *Quart. Rev. Biol.*, 39, p. 130- 191.

CRAWFORD M.H., ROGERS L., 1982, "Population genetics models in the study of aging and longevity in the Mennonite community", *Soc. Sci. Med.*, 16, p. 149-153.

CROW J.F., 1993, "How much do we know about spontaneous human mutation rates?", *Environ. Mol. Mutagen.*, 21, p. 122-29.

CROW J.F.,, 1995, "Spontaneous mutation as a risk factor", *Exp. Clin. Immunogenet.*, 12, p. 121-28.

CROW J.F., 1997, "The high spontaneous mutation rate: Is it a health risk?", *Proc. Natl. Acad. USA*, 94, p. 8380-86.

CROW J.F., 1999, "Spontaneous mutation in man", *Mutation Research*, 437, p. 5-9.

DESJARDINS B., CHARBONNEAU H., 1990, "L'héritabilité de la longévité", *Population*, 45 (3), p. 603-15.

DUBLIN L.I., LOTKA A.J., SPIEGELMAN M., 1949, *Length of Life*, New York: Ronald Press Co.

FALCONER D.S., 1989, *Introduction to Quantitative Genetics*, Longman: London.

FINCH C.E., 1990, *Longevity, Senescence and the Genome*, Chicago: University of Chicago Press.

FOGEL R.W., 1993, "New sources and new techniques for the study of secular trends in nutritional status, health, mortality, and the process of aging", *Historical Methods*, 26 (1), p. 5-43.

GAVRILOV L.A., GAVRILOVA N.S., 1991, *The Biology of Life Span: A Quantitative Approach*, NY, Chur: Harwood Academic Publisher.

GAVRILOV L.A., GAVRILOVA N.S., 1997a, "Parental age at conception and offspring longevity", *Reviews in Clinical Gerontology*, 7, p. 5-12.

GAVRILOV L.A., GAVRILOVA N.S., 1997b, "When Should Fatherhood Stop?", *Science*, 277, p. 17-18.

GAVRILOV L.A., GAVRILOVA N.S., 1999a, "Is there a reproductive cost for human longevity?" *J. Anti-Aging Medicine*, 2(2), p. 121-123.

GAVRILOV L.A., GAVRILOVA N.S., 1999b, "Season of birth and human longevity", *Journal of Anti-Aging Medicine*, 2(4), p. 365-366.

GAVRILOV L.A., GAVRILOVA N.S., 2000, "Human longevity and parental age at conception", In: *Sex and Longevity*, Berlin, Heidelberg: Springer-Verlag, p. 7-31.

GAVRILOV L.A., GAVRILOVA N.S., SEMYONOVA V.G., EVDOKUSHKINA G.N., GAVRILOVA A.L., EVDOKUSHKINA N.N., LAPSHIN E.V., 1995, "Human longevity genes are located in X-chromosome", *In* Knook D.L., Dittman-Kohli F., Duursma S.A. *et al.* (eds.) *Ageing in a Changing Europe. III European Congress of Gerontology: 30 August-1 September, 1995*. Utrecht: Netherlands Institute of Gerontology, Abstract No.020.0027.

GAVRILOV L.A., GAVRILOVA N.S., EVDOKUSHKINA G.N., SEMYONOVA V.G., GAVRILOVA A.L., EVDOKUSHKINA N.N., LAPSHIN E.V., 1996, "Determinants of human longevity: parental age at reproduction and offspring longevity", *Longevity Report*, 10(54), p. 7-15.

GAVRILOV L.A., GAVRILOVA N.S., KROUTKO V.N., EVDOKUSHKINA G.N., SEMYONOVA V.G., GAVRILOVA A.L., LAPSHIN E.V., EVDOKUSHKINA N.N., KUSHNAREVA YU.E., 1997, "Mutation load and human longevity", *Mutation Research*, 377, p. 61-62.

GAVRILOV L.A., GAVRILOVA N.S., SEMYONOVA V.G., EVDOKUSHKINA G.N., KROUTKO V.N., GAVRILOVA A.L., EVDOKUSHKINA N.N., KUSHNAREVA YU.E., 1998, "The regularities of inheritance of human life span: contribution of paternal and maternal longevity to the offspring life span", *Proc. Russian Acad. Sci.* [*Doklady Akademii Nauk*], 360(2), p. 281-283.

GAVRILOV L.A., GAVRILOVA N.S., EVDOKUSHKINA G.N., SEMYONOVA V.G., 2000, "Biodemographic study of the boundaries for human longevity", Paper presented at the 2000 PAA Annual Meeting (Los Angeles, March 23-25, 2000), Abstract published in: *Population Association of America. 2000 Annual Meeting. Final Program and Abstracts*. p.187.

GAVRILOV L.A., GAVRILOVA N.S., OLSHANSKY S.J., CARNES B.A., 2001, "Genealogical data and the biodemography of human longevity", *Population and Development Review* (submitted).

GAVRILOVA N.S., GAVRILOV L.A., 1999, Data resources for biodemographic studies on familial clustering of human longevity, *Demographic Research* [Online], vol.1(4), p. 1-48. Available: http://www.demographic-research.org/Volumes/Vol1/4/default.htm.

GAVRILOVA N.S., SEMYONOVA V.G., GAVRILOV L.A., EVDOKUSHKINA G.N., GAVRILOVA A.L., LAPSHIN E.V., EVDOKUSHKINA N.N., 1995, "Biomedical basis of sex differential in human life span", *In* Knook D.L., Dittman-Kohli F., Duursma S.A. *et al.* (eds.) *Ageing in a Changing Europe. III European Congress of Gerontology: 30 August-1 September, 1995,* Utrecht: Netherlands Institute of Gerontology, Abstract No.020.0028.

GAVRILOVA N.S., GAVRILOV L.A., KUSHNAREVA YU.E., ANDREYEV A.YU., EVDOKUSHKINA G.N., GAVRILOVA A.L., SEMYONOVA V.G., EVDOKUSHKINA N.N., 1997, "Testing the evolutionary theory of longevity", In *16th Congress of the IAG [International Association of Gerontology], August 19-23, 1997. Book of Abstracts,* Adelaide, 550.

GAVRILOVA N.S., GAVRILOV L.A., EVDOKUSHKINA G.N., SEMYONOVA V.G., GAVRILOVA A.L., EVDOKUSHKINA N.N., KUSHNAREVA YU.E., KROUTKO V.N., ANDREYEV A.YU., 1998, "Evolution, mutations and human longevity: European royal and noble families", *Human Biology,* 70, p. 799-804.

Genealogisches Handbuch des Adels. Genealogisches Handbuch der Adeligen Hauser. 1953, vol.5. Van Hueck W. (ed.). Limburg an der Lahn: C.A.Starke Verlag. Ibid. 1955, vol.9, 11; Ibid. 1956, vol.12; Ibid. 1957, vol.15; Ibid. 1958, vol.17; Ibid. 1959, vol. 20; Ibid. 1960, vol.22, 24; Ibid. 1961, vol.26; Ibid. 1962, vol.29; Ibid. 1964, vol.32; Ibid. 1965, vol.34, 36; Ibid. 1966, vol.38; Ibid. 1968, vol.41; Ibid. 1969, vol.45; Ibid. 1970, vol.46; Ibid. 1971, vol.49; Ibid. 1972, vol.52; Ibid. 1974, vol.57; Ibid. 1975, vol.60; Ibid. 1977, vol.64; Ibid. 1979, vol.71; Ibid. 1980, vol.73; Ibid. 1981, vol.76, 78; Ibid. 1983, vol.81; Ibid. 1984, vol.83; Ibid. 1985, vol.86 87; Ibid. 1986, vol.89; Ibid. 1987, vol.89; Ibid. 1988, vol.93; Ibid. 1992, vol.103.

Genealogisches Handbuch des Adels. Genealogisches Handbuch der Freiherrlinhen Hauser. 1952, vol.4. Van Hueck W. (ed.). Limburg an der Lahn: C.A.Starke Verlag. Ibid. 1954, vol.7; Ibid. 1956, vol.13; Ibid. 1957, vol.16; Ibid. 1959, vol.21; Ibid. 1962, vol.27; Ibid. 1963, vol.30, 31; Ibid. 1966, vol.37; Ibid. 1967, vol.39; Ibid. 1969, vol.44; Ibid. 1970, vol.48; Ibid. 1971, vol.51; Ibid. 1975, vol.59; Ibid. 1976, vol.62; Ibid. 1977, vol.65; Ibid. 1978, vol.68; Ibid. 1979, vol.69; Ibid. 1982, vol.79, 80; Ibid. 1986, vol.88; Ibid. 1992, vol.102; Ibid. 1994, vol.106, 107.

Genealogisches Handbuch des Adels. Genealogisches Handbuch der Furstlichen Hauser. 1951, vol.1. Van Hueck W. (ed.). Limburg an der Lahn: C.A.Starke Verlag. Ibid. 1953, vol.3; Ibid. 1955, vol.8; Ibid. 1956, vol.14; Ibid. 1959, vol.19; Ibid. 1961, vol.25; Ibid. 1964, vol.33; Ibid. 1968, vol.42; Ibid. 1971, vol.50; Ibid. 1978, vol.70; Ibid. 1980, vol.74 75; Ibid. 1984, vol.85; Ibid. 1987, vol.90; Ibid. 1991, vol.100.

Genealogisches Handbuch des Adels. Genealogisches Handbuch der Graflichen Hauser. 1952, vol. 2. Van Hueck W. (ed.). Limburg an der Lahn: C.A.Starke Verlag. Ibid. 1953, vol.6; Ibid. 1955, vol.10; Ibid. 1958, vol.18; Ibid. 1960, vol.23; Ibid. 1962, vol.28; Ibid. 1965, vol.35; Ibid. 1967, vol.40; Ibid. 1970, vol.47; Ibid. 1973, vol.54-56; Ibid. 1976, vol.63; Ibid. 1979, vol.72; Ibid. 1983, vol.82; Ibid. 1991, vol.101; Ibid. 1993, vol.104, 105.

GLASSER M., 1981, "Is longevity inherited?", *J. Chron. Dis.*, 35, p. 439-444.

GOURBIN C., WUNSCH G., 1999, "Paternal age and infant mortality", *Genus*, 55(1-2), p. 61-72.

GUTMANN M., FLIESS K.H., HOLMES A.E., FAIRCHILD A.L., TEAS W.A., 1989, "Keeping track of our treasures: managing historical data with relational database software", *Historical Methods*, 22(4), 128-143.

HARVALD B., HAUGE M., 1965, "Hereditary factors elucidated by twin studies", *In* J.V.Neel, M.V.Shaw, W.J.Shull (eds.), *Genetic and the Epidemiology of Chronic Diseases,* Washington DC: US Department of Health, Education and Welfare.

HAWKINS M.R., MURPHY E.A., ABBEY H., 1965, "The familial component of longevity. A study of the offspring of nonagenarians. I. Methods and preliminary report", *Bull. Johns Hopkins Hospital*, 117, p. 24-36.

HAYAKAWA K., SHIMIZU T., OHBA Y., TOMIOKA S., TAKAHASI S., AMANO K., YURA A., YOKOYAMA Y., HAYAKATA Y., 1992, "Intrapair differences of phisical aging and longevity in identical twins", *Acta Genet. Med. Gemellol.,* 41, p. 177-185.

HERSKIND A.M., MCGUE M., HOLM N.V., SORENSEN T.I., HARVALD B., VAUPEL J.W., 1996, "The heritability of human longevity: a population-based study of 2,872 Danish twin pairs born 1870-1900", *Hum. Genet.*, 97, p. 319-23.

HOLLINGSWORTH T.H., 1962, "The demography of the British Peerage", *Population Studies*, suppl., 18, p. 3-107.

HOLLINGSWORTH T.H., 1969, *Historical Demography,* Ithaca, N.Y.: Cornell University Press.

HOLLINGSWORTH T.H., 1976, "Genealogy and historical demography", *Annales de Démographie Historique*, p. 167-170.
HOLMES S.J., 1928, "Age at parenthood, order of birth, and parental longevity in relation to the longevity of offspring", *Univ. Calif. Publ. Zool.*, 31, p. 359-367.
HRUBEC Z., NEEL J.V., 1981, "Familial factors in early deaths: twins followed 30 years to ages 51-61 in 1978", *Human Genetics*, 59, p. 39-46.
HRUBEC Z., FLODERUS-MYRHED B., DE FAIRE U., SARNA S., 1984, "Familial factors in mortality with control of epidemiological covariables. Swedish twins born 1886-1925", *Acta Genet. Med. Gemellol.*, 33, p. 403-412.
HUGHES K.A., CHARLESWORTH B., 1994, "A genetic analysis of senescence in *Drosophila*", *Nature*, 367, p. 64-66.
JACQUARD A., 1982, "Heritability of human longevity", In: S.V.Preston (ed.), *Biological and Social Aspects of Mortality and the Length of Life*, Liège: Ordina Editions, p.303-313.
JACQUARD A., 1983, "Heritability: one word, three concepts", *Biometrics*, 39, p. 465-477.
JALAVISTO E., 1951, "Inheritance of longevity according to Finnish and Swedish genealogies", *Ann. Med. Intern. Fenn.*, 40, p.263-74.
JARVIK L.F., FALEK A., KALLMAN F.J., LORGE I., 1960, "Survival trends in a senescent twin population", *Am. J. Hum. Genet.*, 12, p. 170-179.
JETTÉ R., CHARBONNEAU H., 1984, "Généalogies déscendantes et analyse démographique", *Annales de Démographie Historique*, p. 45-54.
KALLMAN F., 1957, "Twin data on the genetics of aging", In: E.Wolskenholme, M.O'Connor (eds.), *Methodology of the Study of Aging*, Boston: Little, Brown and Co., p. 131-143.
KALLMAN F.G., SANDER G., 1948, "The twin studies on aging and longevity", *J. Heredity*, 39, p. 349-57.
KALLMAN F.G., SANDER G., 1949, "The twin studies of senescence", *Am. J. Psychiatry*, 106, p. 29-36.
KASAKOFF A.B., ADAMS J.W., 1995, "The effect of migration on ages at vital events: a critique of family reconstitution in historical demography", *Eur. J. Pop.*, 11, p. 199-242.
KULIEV A.M., MODELL B., 1990, "Problems in the control of genetic disorders", *Biomed. Sci.* 1, p. 3-17.
LYNCH M., WALSH B. 1998, *Genetics and analysis of quantitative traits*, Sunderland, Mass.: Sinauer.
MAYER P.J., 1991, "Inheritance of longevity evinces no secular trend among members of six New England families born 1650-1874", *Am. J. Hum. Biol.*, 3, p. 49-58.
MEDAWAR P.B. 1952, *An Unsolved Problem in Biology*, London: H.K.Lewis (Reprinted in *The Uniqueness of the Individual*. 1957, London: Methuen).
MCGUE M., VAUPEL J.W., HOLM N., HARVALD B., 1993, "Longevity is moderately heritable in a sample of Danish twins born 1870-1880", *J. Gerontol.*, 48, B237-B244.
MURPHY E.A., 1978, "Genetics of longevity in man", In: E.Schneider (ed.), *The Genetics of Aging*. NY: Plenum Press, 261-301.
NEALE M.C., CARDON L.R., 1989, *Methodology for Genetic Studies of Twins and Families*, DorNSdrecht: Kluwer Acad.Publ.
NIELSEN G.G., GILL R.D., ANDERSEN P.K., SORENSEN T.I.A., 1992, "A counting process approach to maximum likelihood estimation in frailty models", *Scand. J. Stat.*, 19, p. 25-43.
OLSHANSKY S.J., 1998, "On the biodemography of aging: a review essay", *Population and Development Review*, 24(2), p. 381-393.
PARTRIDGE L., BARTON N.H., 1993, "Optimality, mutation and the evolution of ageing", *Nature*, 362, p. 305-311.
PEARL R., 1931, "Studies on human longevity. IV. The inheritance of longevity. Preliminary report", *Hum. Biol.*, 3, p.245-69.
PEARL R., PEARL DEWITT R., 1934a, "Studies on human longevity. VI. The distribution and correlation of variation in the total immediate ancestral longevity of nonagenarians and centenarians, in relation to the inheritance factor in duration of life", *Hum. Biol.*, 6, p. 98-222.
PEARL R., PEARL DEWITT R., 1934b, *The Ancestry of the Long-Lived*, Baltimore: The John Hopkins Press.
PERLS T., ALPERT L., WAGER C.G., VIJG J., KRUGLYAK L., 1998, "Siblings of centenarians live longer", *Lancet*, 351, p.1560.
PHILIPPE P., 1977, "La mortalite infantile: Hérédité et milieu", *Acta Genet. Med. Gemellol.* 26, p. 185-187.
PHILIPPE P., 1978, "Familial correlations of longevity: An isolate-based study", *Am. J. Med. Genet.*, 2, p. 121-129.
PHILIPPE P., 1980, "Longevity: some familial correlates", *Soc. Biol.*, 27, p. 211-19.

POPE C.L., 1992, "Adult mortality in America before 1900. A view from family histories", In: C.Goldin and H.Rockoff (eds.), *Strategic Factors in Nineteenth Century American Economic History. A Volume to Honor Robert W. Fogel,* Chicago and London: Univ. Chicago Press, p. 267-296.

POST W., VAN POPPEL F., VAN IMHOFF E., KRUSE E., 1997, "Reconstructing the extended kinnetwork in the Netherlands with genealogical data: Methods, problems, and results", *Pop. Studies*, 51, p. 263-278.

PREAS S., 1945. Length of life of parents and offspring in a rural community, *Milbank Mem. Fund Quart.*, 23, p. 180-196.

ROBINE J.-M., ALLARD M., 1997, "Towards a genealogical epidemiology of longevity", In J.-M Robine, J.W.Vaupel, B.Jeune, M.Allard (eds.), *Longevity: To the Limits and Beyond.* Berlin, Heidelberg: Springer-Verlag, p. 121-29.

ROSE M.R., 1991, *Evolutionary Biology of Aging*, Oxford: Oxford Univ.Press.

SKOLNICK M., BEAN L.L., DINTELMAN S.M., MINEAU G., 1979, "A computerized family history data base system", *Sociology and Social Research*, 63, p. 506-523.

SONT J.K., VANDENBROUCKE J.P., 1993, "Life expectancy and mitochondrial DNA. Do we inherit longevity from our mother's mitochondria?", *J. Clin. Epidemiol.*, 46, p. 199-201.

SORENSEN T.I.A., NIELSEN G.G., ANDERSEN P.K., TEASDALE T.W., 1988, "Genetic and environmental influences on premature death in adult adoptees", *New Engl. J. Med.*, 318, p. 727-32.

SORENSEN T.I., 1991, "Genetic epidemiology utilizing the adoption method: studies of obesity and of premature death in adults", *Scand. J. Soc. Med.*, 19, p. 14-19.

SWEDLUND A.C., MEINDL R.S., NYDON J., GRADIE M.I., 1983, "Family patterns in longevity and longevity patterns of the family", *Hum. Biol.*, 55, p. 115-129.

TALLIS G.M., LEPPARD P., 1997, "Is length of life predictable?", *Hum. Biol.*, 69, p. 873-886.

TANAKA M., GONG J.-SH., YONEDA M., YAGI K., 1998, "Mitochondrial genotype associated with longevity", *Lancet*, 351, 185-186.

U.S. Bureau of the Census. 1997. *Statistical Abstract of the United States: 1997.* (117th edition.) Washington, DC.

U.S. Monthly Vital Statistics Report, 1997, vol.45, No.11S.

VANDENBROUCKE J.P., 1998, Maternal inheritance of longevity, *Lancet*, 351, 1064.

VANDENBROUCKE J.P., MATROOS A.W., van der HEIDE-WESSEL C., van der HEIDE R., 1984, "Parental survival, an independent predictor of longevity in middle-aged persons", *Am. J. Epidemiol.*, 119, p. 742-50.

VAUPEL J.W., CAREY J.R., CHRISTENSEN K., JOHNSON T.E., YASHIN A.I., HOLM N.V., IACHINE I.A., KHAZAELI A.A., LIEDO P., LONGO V.D., ZENG Y., MANTON K.G., CURTSINGER J.W., 1998, "Biodemographic trajectories of longevity", *Science*, 280, 5365, p. 855-60.

VIJG J., GOSSEN J.A., 1993, "Somatic mutations and cellular aging", *Comp. Biochem. Physiol.*, 104B, p. 429-37.

VOGEL F., MOTULSKY A.G., 1997, *Human Genetics. Problems and Approaches*, Berlin: Springer-Verlag.

WACHTER K.W., FINCH C.E., 1997, *Between Zeus and the Salmon. The Biodemography of Longevity.* Washington, D.C.: National Academy Press.

WALLACE D.C., SHOFFNER J.M., TROUNCE I., BROWN M.D., BALLINGER S.W., CORRAL-DEBRINSKI M., HORTON T., JUN A.S., LOTT M.T., 1995, "Mitochondrial DNA mutations in human degenerative diseases and aging", *Biochim.Biophys.Acta*, 1271, p. 141-151.

WELTER M., 1978, *Etudes sur l'Héritabilité de la Longévité.* Thèse de Médicine, Paris: Université René Descartes.

WESTENDORP R.G., KIRKWOOD T.B., 1998, "Human longevity at the cost of reproductive success", *Nature*, 396(6713), p. 743-746.

WILSON E.B., DOERING C.R., 1926, "The elder Peirces", *Proc. Natl. Acad. Sci. USA*, 12, p. 424-27.

WYSHAK G., 1978, "Fertility and longevity of twins, sibs, and parents of twins", *Soc. Biol.*, 25, p. 315-30.

YASHIN A.I., IACHINE I.A., 1997, "How frailty models can be used for evaluating longevity limits: taking advantage of an interdisciplinary approach", *Demography*, 34, p. 31-48.

YUAN I-CHIN, 1931, "The influence of heredity upon the duration of life in man based upon a Chinese genealogy from 1365 to 1914", *Hum. Biol.*, 3, p. 157-65.

YUAN I-CHIN, 1932, "A critique of certain earlier work on the inheritance of duration of life in man", *Quart.Rev.Biol.*, 7, p. 77-83.