28th August, 1963

ROUGH DRAFT OF FIRST HALF OF THE PAPER

"ON THE INHERITANCE OF LONGEVITY" BY LEO SZILARD

Progress in medicine has greatly reduced infant mortality but extending the life expectancy of the adult is more and more becoming an uphill fight. In order to see what we are up against in this regard, let us consider what would happen if one of these days medical science were to find a miraculous cure for a disease, such as cancer, which is currently responsible for, say, 25% of the deaths in adulthood or old age. The age specific death rate of most diseases doubles, roughly speaking, every eight years and so does the total death rate from all causes. It follows that if we plot for a cohort, within a population that has been freed from this disease, the number of deaths occurring per year as a function of the age, and also plot the same data for a population from which this disease has not been eliminated, we obtain two identical curves, except that the curve relating to the population freed from the disease is shifted towards the higher ages by 3.3 years. Thus it may be seen that by eliminating a disease which is responsible for about 25% of the deaths in adulthood or old age, the life expectancy of the adult could be increased only by about three years.

Moreover, even though some increase in the life expectancy of the adult might still be obtained through further advances in medical science, this would presumably mean only that people would die when they are somewhat older, but it would not be likely to mean that people would keep young longer.

As shown below, we could hope to be able substantially to prolong the life of adults and, conceivably, not only to prolong their life, but also to slow the rate at which they age, if the observed scattering of the ages at death were due to a substantial extent to the genetic differences of the individuals who make up the population.

In a population, like that of the United States, the ages at death are widely scattered within a cohort around a median value. If one plots for a cohort of women the number of deaths, per year, as a function of the age, one obtains a curve which resembles a Gaussian, with its maximum at 80 years. The standard deviation, $\sigma_o[ab]$, of the observed curve is about 10 years.

The observed scattering of the ages at death around the median is presumably due in part to the genetic differences of the individuals, and in part it is due to environmental factors. As shown below, $\sigma_o[ge]$, the standard deviation of the Gaussian that would describe the distribution of the ages at death, if their scattering were due only to genetic differences of the individuals (i.e. if none of the scattering were due to

environmental factors), sets a lower limit for the number of years by which the median of the ages at death could be raised, through selective breeding practised for a number of generations.

If $\sigma_0 [ab]$, the observed scattering of the ages at death around the median, were wholly due to genetic differences of individuals, then presumably it would be possible to increase, through selective breeding over a number of generations, the median of the ages at death in toto by at least

Today, the productive life of an adult covers a period of 45 years, stretching from the age of about 20 to about 65. If the median age at death could be raised by 15 years and if people would not only die at a higher age, but would also keep young longer, then selective breeding over a number of generations would increase the productive period of the adult by about one third. If the theory of the aging process which I have presented in an earlier paper[1.)] were correct, then one would indeed expect that by eliminating from the population mutant alleles of wild type genes which shorten the life span, one would also correspondingly slow down the rate of physiological aging.

The increase that could be obtained through selective breeding in toto could be conceivably much greater than the lower limit given above, but on the other hand this lower limit might

have been set too high, since a substantial portion of the observed scattering of the ages at death might be due to environmental rather than genetic factors.

In these circumstances the standard deviation, of the observed distribution of the ages at death does not in itself permit us to set a lower limit for Δ , the increase in the median of the ages at death, that could be achieved through selective breeding over a number of generations.

For the purposes of our discussion we shall now assume that there has come about a change in social customs, that artificial insemination has become the general practice and that women choose the father of their children freely out of a catalogue of donors. Let us further assume, for the sake of argument, that onward from some point in time, it is decided to market only sperm of donors who have lived to a high age, (to the age which is reached only by about 2½% of the males). We may then ask:

a) by what factor would this increase, in the first generation, the proportion of people who live to such a high age,

b) by how much would the median of the ages at death be increased in the first generation, and

c) can we set a lower limit for what could be gained in this regard in toto, by practising selective breeding for a number of generations.

We shall assume that there are present in the population "abnormal" alleles of a variety of wild type genes, which shorten the life of those individuals who carry them. We shall further assume that none of these "abnormal" alleles involved is sex linked, and that they do not in some subtle way influence the choice of the mate.

The phenotypic expression of these "abnormal" alleles could be different for males and for females. However, on the basis of the observed distribution of the ages at death of males and of females, we shall assume that for any given genotype, the distribution of the "ages" at death of males and females would be the same, provided we define the "age" of a male as the number of years he has lived, plus δ, where δ is about 3 years. Thus we may write for man

(1) $$\text{"age"} = \text{age} + \delta$$

Let us now consider the offspring that would be produced in matings where the female has been picked at random, but the male has been selected on the basis of having lived to a high age, say the age which is reached by only about $2\frac{1}{2}\%$ of the males. We wish to compare this offspring with the offspring that would

be obtained in matings where the male has been selected at random, but the female has lived to a high age, (the age which is reached by only about 2½% of the females). From the assumptions stated above, it follows that the distribution of the ages at death is the same for these two populations of offsprings. Therefore, we could answer the questions formulated under a) and b), if we knew the distribution of the ages at death of children of women who have lived to a high age and who picked their mate at random.

We may further say on the basis of a general theorem, formulated below, that the distribution of the ages at death of the children of such women is the same as the distribution of the ages at death of their mothers. This general theorem may be formulated as follows:

Let us consider a phenotypic character which can be measured quantitatively, the quantity of the character being designated by λ. Let us further assume that there are present in the population "alleles" of a variety of wild type genes, which influence this phenotypic character. Let us now consider a population in which mating is at random with respect to the alleles which influence the phenotypic character in which we are interested and which is in a state of equilibrium, remaining stationary in every respect from generation to generation. Let us designate the distribution function for λ in such a population with $p(\lambda)$, where $p(\lambda)d\lambda$ gives the probability that for an individual λ may be found between the limits of λ and $\lambda + d\lambda$.

In its more general form our theorem also states that the distribution function for λ of the "granddaughters" of the selected females is the same as the distribution function of the "grandmothers" of the selected females.

We shall be content to let this general theorem stand here as a "conjecture", but I shall indicate in the Appendix how the theorem may be proven.

If none of the "alleles" involved are sex linked and if the phenotypic expression of the character in which we are interested is quantitatively the same for "males" and for "females", then the theorem holds for "fathers" as well as for "mothers", and for "sons" as well as for "daughters".

In the following we assume that the "abnormal" alleles which shorten the life span of those individuals who carry them are not sex linked and we assume that - provided we define the "age" of men as stated under (1) - the expression of these alleles in terms of longevity is the same for men and women.

By selecting out of a cohort, from within the general population, men and women who are sufficiently old and by finding out when their fathers and mothers have died, we can determine the distribution of the ages at death of the parents of these "selected" people. Regarding the distribution of the ages at death of their parents we may ask two questions which are of particular interest:

a) The selected people who live to a high age represent a certain proportion of the general population. For the

purposes of our discussion, we shall select people who live to the age which is reached by only one-fortieth (i.e. 2½%) of the cohort. If the number of people who die within any given year, plotted as a function of the age, is described by a Gaussian, the fraction of the cohort living beyond two standard deviations is just slightly less than one-fortieth of the population. The proportion of their parents who live to the same high age is increased by a certain factor k . How large is this factor k ?

b) The median of the ages at death of the parents of the selected people may be higher by a certain number of years, z , than the median of the ages at death of the general population, out of which the "selected" people were picked. How large is z ?

Having found k and z for the parents of the selected people, we may then expect to have the same values of k and z for the first generation of children, if a population goes over to the practice of the kind of selective breeding described above.

file: aging

E/1351

COMMONWEALTH BUREAU OF ANIMAL BREEDING AND GENETICS

Heterospermic insemination in Livestock

ARZUMANJAN, V.I. 1957. [The effectiveness of double mating of sows.] Svinovodstvo, 11 (4) : 43-44. [A.B.A., 25, No. 1983.]

CAMPBELL, R.C., and JAFFE, W.P. 1958. The motility of mixed semen. J. agric. Sci., 50 : 64-65. [A.B.A., 26, No. 750.]

DŹUGOSZ, J., and MARCHLEWSKI, T. 1956. [The Lipitsa horse at the Zootechnical Institute.] Pam. Inst. zootech. Polsce, 1955 : 95-102. [Russian and English summaries.] [A.B.A., 24, No. 957.]

DUN, R.B. [? 1962.] Insemination. In Artificial breeding of sheep in Australia. Pp. 149-154. [Meet.: See No. 1271.] [A.B.A., 31, No. 1275.]

FRAPPELL, J.P., and WILLIAMS, G. [1956.] A study of heterospermic insemination in cattle. Pap. 3rd int. Congr. Anim. Reprod. [Camb.], 1956, Sect. 1 : 65-67. [French summary.] [A.B.A., 24, No. 1636.]

GIGINEĬŠVILI, N.S. 1955. [Attempts to increase the viability of grey Karakuls.] Karakulevodstvo i Zverovodstvo, 8 (3) : 13-20. [A.B.A., 24, No. 214.]

GLUHOVSCHI, N., BURUIANĂ, L.M., NAFORNIŢĂ, M., and SCHMIDT, K. 1960. [The artificial insemination of sheep with a heterologous sperm mixture.] Probl. zooteh. vet. [Bucureşti], 1960 (9). From abstract in Med. vet., 1961, 17 : 441-442. [A.B.A., 30, No. 1851.]

GORJAŠIN, V.A., and EFIMOV, A.E. 1955. [Characteristics of Black Pied-Jersey crossbreds.] Trud. Puškin. naučˇ.-issled. Lab. Razved. sel.-hoz. Životn., No. 7 : 88-102. From abstract in Referat. Ž., Biol., 1956, No. 23, No. 102676. [A.B.A., 25, No. 1128.]

HÁMORI, D. 1960. [Fecundation of chronically barren mares by mating consecutively with a stallion and a jack.] Zuchthyg. FortPflStör. Besam. Haustiere, 4 : 136-145. [Russian and English summaries.] [A.B.A., 29, No. 664.]

HAMRAEV, S. 1958. [The effect of insemination with mixed smen on the fertility of ewes and the development of progeny.] Ovcevodstvo, 4 (8) : 28-30. [A.B.A., 27, No. 308.]

HESS, E.A., LUDWICK, T.M., RICKARD, H.E., and ELY, F. 1958. Some of the effects of heterospermic processing on semen quality and bovine fertility. Fertil. & Steril., 9 : 238-242. [A.B.A., 27, No. 775.]

KARELIN, V.N., and TREĬJA, O.A. 1954. [Commercial crossbreeding of pigs on collective and state farms of the Latvian S.S.R.] Sborn. Trud. Inst. zooteh. zoogig. [Riga], 5 : 13-41. [A.B.A., 23, No. 761.]

KAZAKOV, /

KAZAKOV, V.M. 1960. [The effectiveness of double insemination of ewes.] Ovcevodstvo, 6 (9) : 37-39. [A.B.A., 29, No. 288.]

KUMANOV, S., ALEKSIEV, A., and TANEV, D. 1962. [The effect of type of ration of stud rams studied by selective fertilisation.] Izv. cent. nauč.-izsled. Inst. Životn. "G. Dimitrov" Kostinbrod, 14 : 5-17. [Bulg. with Russ., Ger. summs.] [A.B.A., 31, No. 1258.]

KUŠNER, H.F. 1954. [The efficacy of heterosperm insemination of livestock and its biological nature.] Izv. Akad. Nauk SSSR, Ser. biol., 1954 (1) : 32-52. [B.] [A.B.A., 22, No. 1276.]

KUŠNER, H.F. 1953. [Results of experimental and genealogical studies on selection in animal breeding.] Naučnaja Sessija po Voprosam Biologii i Seljskogo Hozjaĭstva, Riga, 22-26 oktjabrja 1951 g. Moscow : Academy of Sciences of U.S.S.R. Pp. 385-410. [B.] [A.B.A., 24, No. 23.]

KUŠNER, H.F. 1961. [Some genetical premises for increasing the production of animals.] Izv. Akad. Nauk SSSR, Ser. biol., 1961 (5) : 785-797. [English summary.] [A.B.A., 30, No. 1307.]

LADAN, P.E. 1960. [Interspecific hybridisation in pig breeding.] Trud. novočerkassk. zooteh.-vet. Inst., No. 12 : 3-6. [A.B.A., 30, No. 2695.]

LAPPOWA, H. 1954. [The results of using mixed semen in pig breeding.] Przegl. hodowl., 22 (2) : 50-52. [A.B.A., 23, No. 261.]

LEMCKE, B., GASTMEIER, W., and SCHAAF, A. 1955. [The effect of double mating on fecundity of sows and subsequent weight of piglings.] Tierzucht, 9 : 117-122. [A.B.A., 23, No. 1289.]

LIBIZOV, M.P. 1956. [The use of a sexual mentor in stud pig breeding.] Životnovodstvo, 1956 (3) : 58-65. [A.B.A., 24, No. 1226.]

MANN, T. 1957. [The biochemistry of semen.] Zuchthyg. FortPflStör. Besam. Haustiere, 1 : 138-150. [English summary.] [A.B.A., 28, No. 676.]

MARCHLEWSKI, T. 1952. Vegetative segregation in mammals. Bull. int. Acad. polon. Sci. Lett., Cl. Sci. math. nat., B (II), 1951 : 281-283. [A.B.A., 23, No. 262.]

MARCHLEWSKI, T. 1955. Changes in the sex ratio as a result of external conditions.] Przegl. hodowl., 23 (3) : 42-43. [A.B.A., 24, No. 871.]

MARCHLEWSKI, T. 1956. [General results obtained by the application of heterospermic methods at the Zootechnical Institute.] Pam. Inst. zootech. Polsce, 1955 : 5-11. [Russian and English summaries.] [A.B.A., 24, No. 948.]

MARCHLEWSKI, T. 1958. [The process of fertilisation in higher organisms and the possibility of the practical application of heterospermy.] Przegl. hodowl., 26 (6) : 36-38; (7) : 57-61. [A.B.A., 27, No. 543.]

MARCHLEWSKI, /

MARCHLEWSKI, T., and MAJEWSKA, E. 1958. Note on heterospermic effects on colorations and body development in the domestic pig. Folia biol. [Warsz.], 6 : 139-143. [Polish and Russian summaries.] [A.B.A., 27, No. 356.]

MATVEENKO, D.V. 1955. [The insemination of female livestock with mixed semen from several males.] Životnovodstvo, 1955 (3) : 97-101. [A.B.A., 23, No. 1242.]

MIJAVEC, M. 1961. [Insemination with mixed semen.] Vet. Glasn., 15 : 491-496. [English summary.] [A.B.A., 29, No. 2072.]

ROWSON, L.E.A. 1956. Recent developments in artificial insemination. Vet. Rec., 68 : 484-485. [A.B.A., 24, No. 1465.]

† SAVČENKO, P.E. 1962. [The effect of heterospermic insemination of sows on the development of the progeny.] Nauč.-Trud. ukr. nauč.-issled. Inst. Životn. stepn. Raĭon. (Askanija-Nova), 10 : 60-66. [Russ.] [A.B.A., 31, No. 2229.]

SESTIPEROV, A.A. 1958. [The use of crossbred pigs for fattening for meat.] Trud. Puškin. nauč.-issled. Lab. Razved. Sel.-hoz. Životn., No. 8 : 94-97. [A.B.A., 27, No. 902.]

ŠIPILOV, V.S. 1961. [Physiological basis of a new system in the insemination of cows.] Izv. Timirjazev. sel.-hoz. Akad., 1961 (1) : 105-120. [A.B.A., 29, No. 1419.]

SMUŠKOVA, V.V., and DOLMATOV, T.S. 1959. [Development of piglings obtained by double mating.] Nauk. Praci Ljvivsjk. zoovet. Inst., 10 : 85-89. [Russian summary.] [A.B.A., 29, No. 1583.]

SUMPTION, L.J. 1961. Multiple sire mating in swine; evidence of natural selection for mating efficiency. J. agric. Sci., 56 : 31-37. [A.B.A., 29, No. 1584.]

SUMPTION, L.J., REMPEL, W.E., and WINTERS, L.M. 1959. Multiple sire mating in swine. I. General considerations. J. Hered., 50 : 293-298. [A.B.A., 28, No. 2113.]

STAHL, W., and TRIEBLER, G. 1957. [The effect of single- and double-mating of breeding sows on fertility and rearing performance.] Tierzucht, 11 : 340-343. [A.B.A., 26, No. 1487.]

STOJANOVSKAJA, V.I., and MESJACEV, A.S. 1957. [Methods of increasing the productivity of Karakul ewes with a delicate constitution.] Karakulevodstvo i Zverovodstvo, 10 (4) : 10-14. [A.B.A., 26, No. 276.]

THIBAULT, C. [1956.] [Reproductive physiology in relation to artificial insemination.] Plenary Pap. 3rd int. Congr. Anim. Reprod. [Camb.], 1956 : 89-104. [B.] [A.B.A., 25, No. 552.]

THIBAULT, C. 1956. [Reproductive physiology in relation to artificial insemination.] Élevage et Insém., No. 38 : [28 pp.] [A.B.A., 25, No. 1669.]

TIMČENKO, /

TIMČENKO, P.F. 1955. [The sex-ratio in the progeny of Karakul sheep.] Karakulevodstvo i Zverovodstvo, 8 (6) : 11-14. [A.B.A., 24, No. 1185.]

VARADIN, M. [1962.] [Some observations on the artificial insemination of ewes by the semen of different rams.] Proc. IVth int. Congr. Anim. Reprod. [The Hague], 1961, Vol. IV (Sect. A.I.): 889-894. [Fr. with Ger. summ.] [A.B.A., 31, No. 437.]

ZELFEL, S., and GOTTSCHALK, I. 1962. [Investigations on the use of mixed semen in artificial insemination in cattle.] Zuchthyg. FortPflStör. Besam. Haustiere, 6 : 42-53. [Ger. with Russ., Eng. summs.] [A.B.A., 31, No. 1162.]

26th September 1963

COMMONWEALTH BUREAU OF ANIMAL BREEDING AND GENETICS

Heterospermic Insemination of Laboratory Mammals

BEATTY, R.A. 1957. A pilot experiment with heterospermic insemination in the rabbit. J. Genet., 55 : 325-347. [A.B.A., 25, No. 2027.]

BEATTY, R.A.1960The birth weight of rabbits born after heterospermic insemination. Genet. Res. [Camb.], 1 : 39-49. [A.B.A., 28, No. 1549.]

BEATTY, R.A. 1962. Recent research on fertilization and the phenotype of mammalian gametes. Atti Simp. int. Biol. sper. [Pavia], 1959. Symp. genet. biol. ital., 9 : 328-338. [Eng. with Ger., Fr., It. summ.] [A.B.A., 31, No.783.]

CHANG, M.C., and BEDFORD, J.M. [1962.] Effects of various hormones on the transportation of gametes and fertilization in the rabbit. Proc. IVth int. Congr. Anim. Reprod. [The Hague], 1961, Vol. II (Sect. Physiol.): 367-370. [Eng. with Ger. summ.] [A.B.A., 31, No. 608.]

EDWARDS, R.G. 1955. Selective fertilization following the use of sperm mixtures in the mouse. Nature [Lond.], 175 : 215-216. [A.B.A., 23, No. 843.]

LEBEDEV, M.M. 1958. Influence exercised on characteristics of offspring by premating treatment of animals and fertilization conditions. Proc. Xth int. Congr. Genet. [Montreal], 1958, Vol. II (Abstr.) : 160-161. [A.B.A., 26, No.2258.]

NAPIER, R.A.N. 1961. Fertility in the male rabbit. III. Estimation of spermatozoan quality by mixed insemination, and the inheritance of spermatozoan characters. J. Reprod. Fertil., 2 : 273-289. [A.B.A., 30, No. 485.]

RAJU, K.K. 1953. A survey of different lactation performances of Kangayam cows in Palayakottai Cattle Farm. Indian vet. J., 30 : 229-233. [A.B.A., 22, No.900.]

26th September 1963

COMMONWEALTH BUREAU OF ANIMAL BREEDING AND GENETICS

Heterospermic Insemination of Poultry

HARRIS, G.C. (Jr.], HOBBS, T.D., BROWN, J.E., and WARREN, L.B. 1963. The storage of turkey spermatozoa in sodium citrate and carbon dioxide extenders. Poult. Sci., 42 : 536-538. [A.B.A., 31, No. 3240.]

MERKURJEVA, E.K. 1951. [Characters of progeny of female livestock in which mixed semen and repeated inseminations were used.] Agrobiologija, 1951 (1) : 85-98. [A.B.A., 21, No. 41.]

MERKURJEVA, E.K. 1951. [The appearance of characters of two sires in progeny of hens inseminated with heterosperm.] Agrobiologija, 1951 (3) : 94-97. [A.B.A., 21, No. 441.]

PIKÓ, L., and SUSCHKA, A. 1956. [Interspecific hybridisation with poultry.] Agrártud. egy. Állattenyészt. Karának Közl. [Gödöllő-Budapest], 1956 (2) : 103-109. [Russian, German and English summaries.] [A.B.A., 26, No. 406.]

VAN DRIMMELEN, G.C. 1951. Artificial insemination of birds by the intra-peritoneal route. - A study in sex physiology of pigeons and fowls with reports upon a modified technique of semen collection, and a new technique of insemination, and observations on the spermatozoa in the genital organs of the fowl hen. Onderstepoort J. vet. Res., Suppl. No. 1 : 212 pp. [B.] [A.B.A., 19, No. 1953.]

26th September 1963

COMMONWEALTH BUREAU OF ANIMAL BREEDING AND GENETICS

The Use of Heterosperm

ABULJHANOV, F.H. 1950. [The effect of artificial insemination with mixed semen from two rams on fertility of ewes and viability of lambs.] Socialist. Životn., 1950 (8) : 84-86. [A.B.A., 19, No. 210.]

ABULJHANOV, F.H. 1950. [Data on the effect of inseminating ewes with mixed semen.] Agrobiologija, 1950 (6) : 104-106. [A.B.A., 19, No. 1782.]

ARZUMANJAN, V.I. 1951. [Three-breed crossing of pigs by double service.] Socialist. Životn., 13 : 88-91. [A.B.A., 20, No. 265.]

ASLANJAN, M.M., and ČAMUHA, M.D. 1950. [Selective fertilisation in sheep by insemination with mixed, stored and fresh semen.] Sovetsk. Zooteh., 1950 (12) : 65-70. [A.B.A., 19, No. 724.]

ČAUSOVSKIĬ, A.A. 1952. [The artificial insemination of ewes with mixed semen of two rams.] Socialist. Životn., 14 (11) : 45-48. [A.B.A., 21, No. 790.]

KUDRJAVCEV, P.N. 1952. [Commercial crossing in pig breeding.] Sovetsk. Zooteh., 7 (2) : 38-60. [A.B.A., 20, No. 1160.]

LEBEDEV, M.M., and PITKJANEN, I.M. 1951. [Increasing fertility in pigs.] Sovetsk. Zooteh., 6 (9) : 34-43. [A.B.A., 20, No. 269.]

MAMEDJAROV, S.G. 1952. [Inseminating sheep with mixed semen from two rams.] Socialist. Životn., 14 (9) : 71-73. [A.B.A., 21, No. 275.]

MARCHLEWSKI, T. 1951. [An attempt to apply the agrobiological "mentor" method in the formation of a new type of pig.] Roczn. Nauk rol., 56 : 7-32. [Russian and English summaries.] [A.B.A., 20, No. 761.]

MERKURJEVA, E.K. 1951. [Characters of progeny of female livestock in which mixed semen and repeated inseminations were used.] Agrobiologija, 1951 (1) : 85-98. [A.B.A., 21, No. 41.]

MILOVANOV, V.K. 1952. [Fertility, viability and sex of livestock.] Z. obšč. Biol., 13 : 105-121. [A.B.A., 21, No. 584.]

REDJKIN, A.P., and KOZLOVSKIĬ, V.G. 1952. [The use of Mangalitsa pigs for commercial crossing.] Sovetsk. Zooteh., 7 (8) : 53-62. [A.B.A., 20, No. 1751.]

ROBERTS, E., and CARROLL, W.E. 1939. A study of hybrid vigor in a cross between Poland China and Duroc Jersey swine. J. agric. Res., 59 : 847-854. [A.B.A., 8 : 397.]

SENZE, /

SENZE, A. 1952. [The practical use of the nervous stimulus and of polyspermy in the treatment of sterility.] Med. wet., 8 : 72-73. [A.B.A., 21, No. 1239.]

WILKE, A. 1952. [Fertilisation of livestock with heterosperm.] Tierzucht, 6 : 410-411. [A.B.A., 21, No. 1830.]

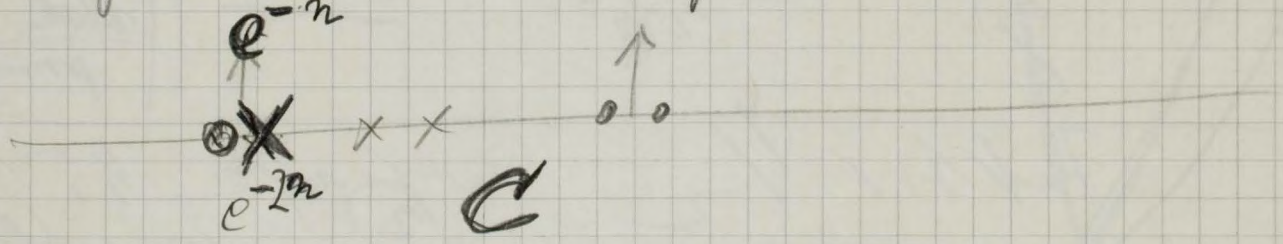
file: aging

If a man reaches age a with prob. $= \alpha$
and if probab of both parents reaching age a is $\frac{1}{2}\alpha^2$
what is probability that one of his parents (and mother) reached age a? Is this a function of n?

A = probab of $0 = \sum_r \frac{(n)^r}{r!} \cdot e^{-n} \cdot e^{-r}$

B = probab of 0 if one parent perfect $= \sum_r \frac{(n)^r}{r!} e^{-n} e^{-r}$

Offspring showed reduction of 50% per unbalanced generation
if sperm not saved reduction of 25% per unbalanced generation



$\left[1-(1-e^{-n})(1-e^{-n})\right]$ = prob that either one

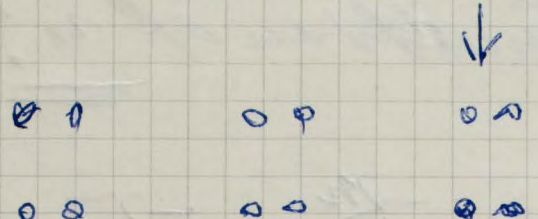
$e^{-\frac{n}{2}} C$ is prob of with one parent offsp. or other perfect

e^{-2n}

$e^{-n} = \frac{1}{20}$

probable that both parents

$\frac{1}{20}$



$\frac{1}{2} N$ is number of parents

$\frac{1}{2} N e^{-2n}$

∴ that an individual selected is long lived comes from one family has probability of $e^{-2n} = \frac{1}{20}$ $\frac{1}{20}$

that an individual in the population is long lived is $\frac{1}{20}$

95

Father + Mother each longer than 95

2,000

$\frac{2000}{2} = 1000$ | 50 dead parents

$\frac{1}{2}$ Factor $\frac{1}{2}$ ② age 95 exactly proved

i.e 25 old parents

a

C is
probability that from a couple either
one, ~~is~~ perfect:
or both are
probab. that none is ~~perfect~~ imperfect

$$1 - e^{-n}$$

probab that both are imperfect

$$(1 - e^{-n})^2$$

probab that one is perfect or
the other ~~perfect~~ or both imperfect

$$C = \left[1 - (1 - e^{-n})^2\right]$$

probab that an offspring of
such a couple is perfect

~~$\frac{1}{2} e^{-\frac{n}{2}}$~~ ; $D = C e^{-\frac{n}{2}}$

---

this must be compared
with probability of (2c)
that an individual is perfect:

$$A = e^{-n}$$

---

for small e^{-n} we may write for C

$$C = \left[1 - (1 - 2e^{-n} + e^{-2n})\right]$$

$$= \left[1 - 1 + 2e^{-n} - e^{-2n}\right] \cong 2e^{-n}$$

and $D = 2e^{-n} e^{-\frac{n}{2}}$

$$\frac{A}{D} = \frac{1}{2} e^{\frac{n}{2}}$$

or more accurately:

$$C = 2e^{-\frac{n}{2}} - e^{-\frac{n}{2}} e^{-n} \qquad D = e^{-\frac{n}{2}}\left[2e^{-\frac{n}{2}} - e^{-n-\frac{n}{2}}\right.$$

$$\frac{D}{A} = \left[2 - e^{-n}\right] e^{-\frac{n}{2}}$$

$$\frac{A}{D} = \frac{1}{2 - e^{-n}} e^{+\frac{n}{2}}$$

$\frac{A}{D} = \frac{f(x)}{g(x)}$

$\frac{A}{D} \approx$

$n =$

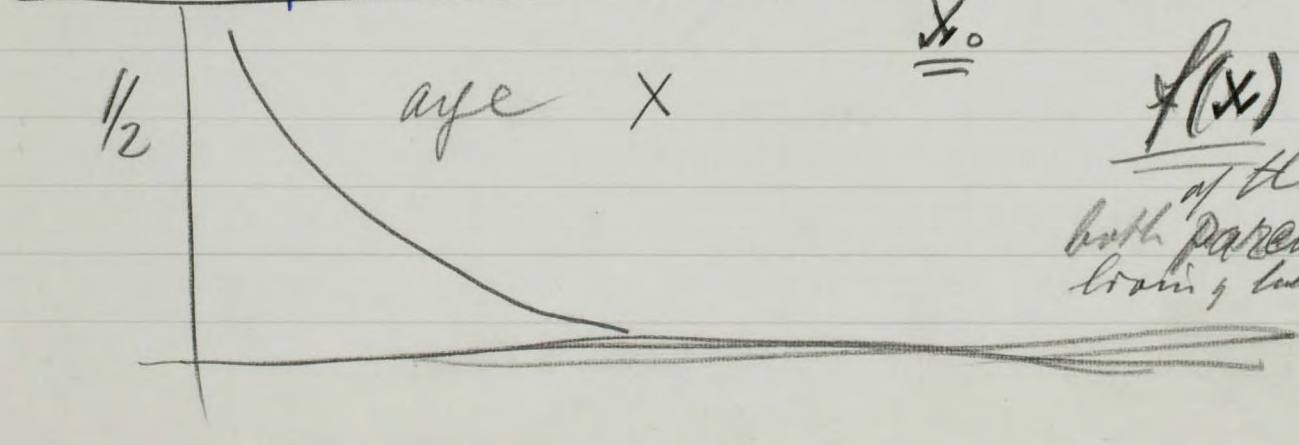
for $n = 3$ $\quad \frac{A}{D} \simeq 2$

or roughly $\frac{1}{2}$ of long lived parents / packet two's for meaning not cancel out

Sensitive for n

Measure of A and D

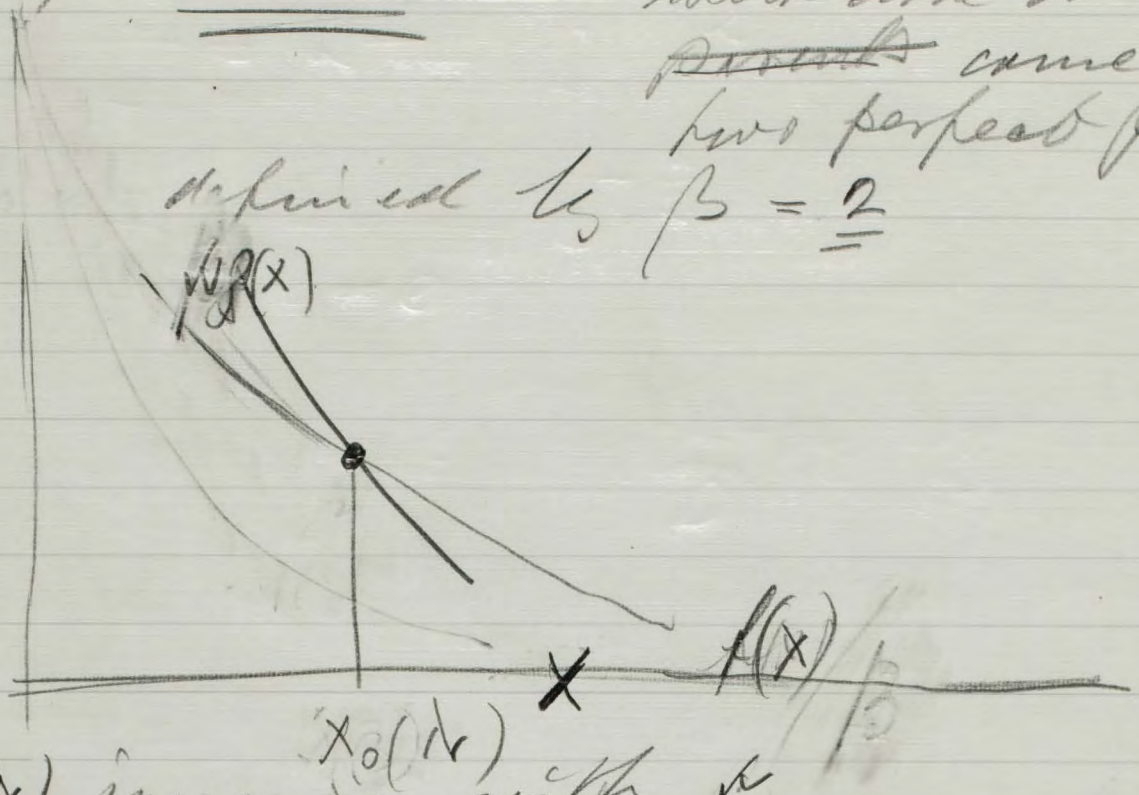
$f(x)$ and $g(x)$ (new designation)



$f(x)$ is number of perfects

$[f(x)]^2$ is number of perfects who ~~have both parents~~ come from two perfect parents

defined by $\beta = 2$



$x_0(\nu)$ increases with ν

number of perfect parents
of perfect individuals

looking at parents of ~~perfect individuals~~ individuals living at age ν one finds $g(x)$ such couples; number of perfect couples is lower by a factor. What is this factor? It is β^2

$$\nu^2 g(x) = \nu f(x)$$

so for each ν one finds an $x(\beta)$ for $\nu = 2$

Scratch Work

$$x(x)f(x) = x^2 g(x)$$

DRAFT August 13th, 1963

ON THE INHERITANCE OF LONGEVITY *

by

Leo Szilard

The University of Chicago, Chicago, Illinois

In a population, such as for instance the population of the United States, there is a considerable scattering of the ages at death, around the median value. This scattering must at least in part be due to environmental factors, but in part it might be due to the genetic differences between the individuals who make up the population.

One of the several problems which we propose to discuss below is the following: Let us postulate a society in which artificial insemination has been adopted as a general practice and in which at first women choose the father of their children by selecting a donor from among a random sample of donors. Let us then further postulate that at some point in time, the donors are chosen not from a random sample, but from among males who (a) have themselves lived to a high age, or (b) are the sons of a couple where both the male and the female have lived to a high age, or (c) have 4, 3, 2 or 1 grandparents who has lived to a high age.

One may then ask whether, by introducing some such selection

---

* This work was performed under a research grant of the National Institutes of Health.

g/f will be shown below that α

the life span of the population could be substantially increased. It is shown below that this question can be answered by ~~determining~~ comparing $f(x)$, the probability that a "daughter" ~~female~~ lives to a high age x, ~~and comparing it~~ with $g(x)$, the probability that her mother has lived to the same high age x (i.e. died at the age x, or at an age higher than x).

~~As will be seen below~~ the ratio $g(x)/f(x)$ would be 1, or just slightly ~~the~~ larger than 1, if most ~~a large portion~~ of the scattering of the ages at death in the population were due to environmental factors and only a small portion of it were due to genetical factors. ~~In~~ found that case, it would be difficult or impossible to increase the life span of the population through the kind of selective breeding described above. ~~However it will be shown below. However, if~~ the ratio $g(x)/f(x)$ is substantially larger than 1, then a substantial increase of the life span of the population (as defined for instance by the median of the ages at death) could be accomplished by carrying on the selective kind of selective breeding described above for a few generations. ~~by this kind of selective breeding. Moreover, in the circumstances defined below, such an increase in the life span could be accomplished within a few generations.~~

It is conceivable that there are present in the population mutant alleles of a variety of wild type genes, which cause a substantial reduction of the life span of the individual. We shall refer to the mutant alleles of wild type genes, which cause a substantial reduction of the life span of an individual who carries the mutant alleles, as "large markers". If several of these are carried by an individual, the life shortening effect of these markers would be expected to be cumulative and presumably it would be roughly speaking, additive. A substantial portion of the scattering of the ages at death around the median value, might be due to

Whether further substantial additional increases of life span could be obtained by continuing with selective breeding described above, beyond a few generations, would depend on whether the scattering of the ages at death is mainly due to genetical factors present in the population in a large number per individual, each of which factors have only a small life shortening effect, or whether it is mainly due to deleterious factors present in the population in a comparatively small number per individual, each of these factors having a large life shortening effect. In the latter case nothing much will be gained by carrying on the selective breeding described above after the first few generations, whereas in the former case, substantial additional lengthening of the life span should be maintained by continuing with selective breeding over many generations. An analysis presented in this paper deals with the latter case, rather than the former one.

It is conceivable that there are present in the population mutant alleles of a variety of wild type genes, which cause a substantial reduction of the life span of the individual. We shall refer to the mutant alleles of wild type genes, which cause a substantial reduction of the life span of an individual who carries the mutant alleles, as "large markers". If several of these are carried by an individual, the life shortening effect of these markers would be expected to be cumulative and presumably it would be roughly speaking, additive. A substantial portion of the scattering of the ages at death around the median value, might be due to

the presence in the population of such "large markers," in a comparatively small number per individual, and their presence might be responsible for a substantial shortening of the life span of the population. Below, I describe a method that should permit us to determine whether this is the case, and if it is the case, then the method should permit us to compute the number of "large markers" per individual present in the population, and to appraise by how much the median age at death could be increased within a few generations, by eliminating from the population, through selective breeding, these large markers.

I should add that by finding out whether large markers, present in the population in a comparatively small number per individual, are responsible for a substantial portion of the scattering of the ages at death around its median value, we might also learn something about the nature of the ageing process[1].

For the purposes of our discussion, we shall now assume that the age at death of an individual is in part determined by the life shortening effect of the "large markers" carried by the individual and in part it is determined by the more or less accidental environmental factors. We shall, for the time being, disregard the possibility that the age at death of an individual might also be influenced by mutant alleles of wild type genes, which have a small life shortening effect, but which might be present in the population in a comparatively large number per individual.

We assume that the "large markers" are distributed in the population at random

and that we have the same average number n per individual, both for males and for females.

Let us now consider a large sample taken from a stationery population. For the sake of maximum conceptual simplicity, we shall include in our sample only females who have reached adulthood and who have given birth to a daughter who has reached adulthood, and further, we shall include in our sample at random only one of several such daughters born to the same mother. ~~Further we should include in our sample at random, only one of several such daughters born to the same mother.~~

consider a cohort of 10^5

We shall ~~designate with N, the number of~~ females ~~in our sample~~ who reach adulthood, say the age of 30 years, in any one year.

Furthermore

~~We~~ shall designate females who carry no large markers as "genetically perfect." Because we may assume that the number of "large markers" carried by an individual follows the Poisson distribution, therefore we may write for N_0, the number of "genetically perfect" females, who reach adulthood in any given calendar year:

(1) $$N_0 = N e^{-n}$$

If we select an age x, which is sufficiently high, then we may assume that all females who reach that age are genetically perfect. The reverse, however, is not true: not all females who are genetically perfect reach the age x. Rather we may write for $f(x)$, the probability that a female reaches the age x:

(2) $$\lambda(x) f(x) = e^{-n}$$

where $\lambda(x)$ is larger than 1 and increases with increasing x.

The value of x, for which we have $\lambda = 2$ is the median of the ages at death of the genetically perfect females. For us it would be of particular interest to find out by how many years this median exceeds the median of the ages at death of the general population of females.

Let us now consider within a population of females, a sub-group of females, to which we shall refer as the "select group" x, which reach in a given year the age x, and let us consider where x is chosen sufficiently high to exclude all females who are not genetically perfect. We may then ask what is the probability $g(x)$ that the mother of a female within this select group x has died at an age x or at an age higher than x. We shall presently see that we might write for this probability:

$$\lambda(x)g(x) = e^{-n/2} \tag{3}$$

In order to see this, let us assume, for the sake of maximum conceptual simplicity, that of several siblings, each time only one, taken at random, was included in our initial population sample and that, therefore, our select group contains no siblings. The group of the mothers of the females who are included in the select group consists, in this case, of so many females and we want to know how many of them are genetically perfect.

This may be seen as follows:

Since we assumed that the average number of large markers carried by the males in the population is the same as the average number of large markers carried by the females, and since we may assume, that as far as large markers are concerned, mating is a random process, it follows that the probability that a genetically perfect mother has a genetically perfect daughter, is given by $e^{-n/2}$. Therefore, the number of genetically perfect females, reaching adulthood each year who are daughters of a genetically perfect mother, is given by:

$$N e^{-n/2} e^{-n} \tag{4}$$

it follows that p , the probability that a genetically perfect female has a genetically perfect mother is given by:

(5) $$p = \frac{N e^{-n/2} e^{-n}}{N^*}$$

and by substituting the value of N^*, from (1), we obtain for p :

(6) $$p = e^{-n/2}$$

Accordingly we may write for $g(x)$ the probability that a genetically perfect female has a mother who lived beyond the age x ~~is given by:~~

(7) $$g(x) = \frac{p}{\lambda(x)}$$

and ~~then~~ we obtain

(8) $$\lambda(x)\, g(x) = e^{-n/2}$$

as stated above (3).

We may compute n and also $\lambda(x)$ for any given age x , if we know how many of the mothers of the females who form the "select group x", have lived to the age x, (i.e. have died at an age x , or at an age larger than x), from their number $f(x)$, we may compute the probability $g(x)$, that a female within the "select group x" has a mother who lived to the age x , or beyond ~~that~~ age ~~x~~. We have:

(9) $$g(x) = \frac{f(x)}{N \lambda(x)}$$

Since the probability that the mother of a female in the "select group x" is a genetically perfect female is given by $e^{-n/2}$ and since according to ( ) ~~this~~ the probability ~~must be~~ that a genetically perfect mother lives up to the age of x is $\frac{1}{\lambda(x)}$ ~~we may therefore write:~~ we may write

(10) $$\lambda(x)\, g(x) = e^{-n/2}$$

From this equation and (2) it follows that we have

(11) $$\frac{g(x)}{f(x)} = e^{n/2} \quad \text{or} \quad n = 2 \ln \frac{g(x)}{f(x)}$$

and (12) $$\lambda = \frac{f(x)}{[g(x)]^2} \quad \text{or} \quad \frac{1}{g(x)} \cdot \frac{f(x)}{g(x)}$$

Let us illustrate these equations by looking at two numerical examples. Let us first assume that we have a population in which n , the average number of larger markers per individual, is about 3. We then have $e^{+n} \approx 20$ and $e^{+n/2} \approx 4.5$. Accordingly we would have:

$$\frac{g(x)}{f(x)} \cong 4.5$$

and since we may write from (2)

$$(13) \quad f(x) = e^{-\frac{x}{\lambda}}$$

and for $\lambda = 2$ we would obtain $f(x) \cong 1/40$. This means that the median of the ages at death of genetically perfect females in such a population would be at the age to which only 2 1/2 % is reached of the general population survived.

Let us next assume that all the scattering of the ages at death of the population is due to environmental factors and that no genetical factors are involved. In this case we have a population in which n , the average number of large markers per individual, is zero. We then have $e^{-n} = 1$ and $e^{-n/2} = 1$. Accordingly we would have

$$\frac{g(x)}{f(x)} = 1$$

Further, from (13) for $\lambda = 2$ we obtain and thus we would have $f(x) = \frac{1}{2}$, which means that the median of the ages at death of the perfect females in the population is the same as the median of the ages at death of the population as a whole, which is just what one would expect, since the whole population is assumed to be genetically perfect ($n = 0$)

If the number of large markers per individual is 3, as we have assumed above, then for a value of $\lambda = 2$, the select group x of females who are genetically perfect, would amount to $2\frac{1}{2}\%$ of the population, i.e. for a population sample of $n = 100{,}000$, 2,500 females would fall each year into the select group x. If we were to assume that n is considerably larger, say for instance 9, then for $\lambda = 2$, we would obtain:

(14) $$f(x) = \frac{1}{2}\left(\frac{1}{20}\right)^3$$

This means that if we choose age x high enought to make certain that those living beyond that age are genetically pure, the size of our select group x would amount only to about 6 daughters. It may be seen from this that if n is too large, then it is not possible to have a workable sample size for the select group x and, at the same time, to have x high enough to ensure that the select group x consists of genetically perfect daughters.

If we choose the value for x so as to have $f(x) = \frac{1}{40}$ then the group of daughters who will survive to age x will not be genetically perfect and will not form a genetically homogenous group, as far as the longevity markers. If we were then to compute the number of markers from such an equation, starting with $f(x) = \frac{1}{40}$ and for a number of decreasing values of $f(x)$ and corresponding increasing values of x, we would have no right to expect that the ratio which determines the value of n remains constant. Rather we would presumably find that this ratio increases with increasing x. In these circumstances we may regard the rate of increase of the ratio that we may find as a measure for the validity of the number n given by the ratio.

If n is not too large and if those daughters who survive to the age x, ~~which we have~~ chosen as high as we can go, without reducing the size of the select group x to a point where our results would no longer be statistically significant, then we would find that the ratio: ~~$\frac{f(x)}{f(x)}$~~ ~~$\frac{f(x)}{f(x)}$~~ remains constant, if we go from the chosen value of x to successively higher values of x, x+1, x+2, x+3, etc. If this ratio remains constant, we may write:

(15) $$\frac{d}{dx}\frac{f(x)}{f(x)} = 0$$

and we may write (15) also in the form of

(16) $$\frac{f'(x)}{f(x)} = \frac{\varphi'(x)}{\varphi(x)}$$

Since $f'(x)/f(x)$ represents the death rate of the daughters and $\varphi'(x)/\varphi(x)$ represents the death rate of the mothers, who lived up to the age x, (16) may be expressed by saying that the death rate of the daughters who lived up to the age x is the same as the death rate of those of their mothers who lived up to the same age x. This is what one would, of course, expect, ~~since~~ if the select group x ~~of~~ and the sub-group of their mothers who live up the age x ~~had~~ have the same genetical composition, with regard to longevity markers, (which would be the case if both groups contain only genetically perfect individuals).

At this point we shall now turn to consider the fathers of those "daughters" who belong to the select group x. If one plots the ages

at death as a function of the age for the males and the females of the population, one finds two curves which are displaced by

(17) $\Delta \approx 3$ years

The male population is shorter lived than the female population and we may write for $f^*(x)$, the fraction of the male population which survives to the age x

(18) $$f^*(x) = f(x-\Delta)$$

Similarly we may write for the fraction of the genetically perfect males which survives to the age x

(19) $$f^*(x) = e^{-\nu^*(x)}$$

where we may write home

(20) $$\nu^*(x) = \nu(x-\Delta)$$

We now propose to determine the probability $f(x)$ that both the mother and the father of a daughter contained in the select group, survive to a high age, the mother having died at age x or higher, the father having died at age $(x-\Delta)$ or higher. We may compute this probability $f(x)$ in the same manner as we have computed the probability that the mother, whose daughter is included in the select group x, survives to an age x, or higher and find:

(21) $$f(x) = \varphi^2(x)$$

This may be seen as follows: The probability that both the father and the mother of a daughter are genetically perfect is given by:

(22) $$e^{-2n}$$

and since according to ( ) the probability of a daughter being genetically perfect is given by e^{-n}, it follows that a probability that the genetically perfect daughter had both a genetically perfect mother and a genetically perfect father is given by:

(23) $$e^{-n}$$

Therefore, the probability that the mother of a daughter contained in the select group x (and therefore genetically perfect) survived to the age x or higher and that the father also survived to a high age, the age of $(x-\Delta)$ or higher, of that daughter is given by:

(24) $$\lambda(x)\, e^{-n}$$

From this we obtain (21) by taking into account that the value of $f(x) = \lambda(x)\, e^{-n/2}$ see equation ( )

Aug 28, 1963

Rough draft of first half of the ~~Wiener~~ paper

~~D R A F T~~

~~28th August, 1963~~

"ON THE INHERITANCE OF LONGEVITY"* by Leo Szilard

by

Leo Szilard

The University of Chicago, Chicago, Illinois

Progress in medicine has greatly reduced infant mortality but extending the life expectancy of the adult is more and more becoming an uphill fight. In order to see what we are up against in this regard, let us consider ~~(for example)~~ what would happen if medical science were to find (one of these days) a miraculous cure for a disease (such as cancer), which is currently responsible for, say, 25% of the deaths in adulthood, or old age. The (age specific) death rate of most diseases doubles, roughly speaking, every ~~8~~ eight years and so does the total death rate (from all causes). It follows that if we plot for a cohort, within a population that has been freed from this disease, the number of deaths occurring per year as a function of the age, and ~~then~~ also plot the same data for a population from which this disease has not been eliminated, we ~~shall~~ obtain two identical curves, except that the curve relating to the population freed from the disease is shifted towards the higher ages by 3.3 years. Thus it may be seen that by eliminating a disease ~~such as cancer~~, which is responsible for about 25% of the deaths in adulthood or old age, the life expectancy of the adult could be increased only by about 3 years.

---

* This work was performed under a research grant of the National Institutes of Health of the U.S. Public Health Service.

Moreover, even though some increase in the life expectancy of the adult might still be obtained through further advances in medical science, this would presumably mean only that people would die when they are somewhat older ~~and~~ but it would not be likely to mean that people would keep young longer.

As shown below, we ~~x~~ could hope to be able substantially to prolong the life of adults and, conceivably, not only to prolong their life, but also to slow the rate at which they age, if the observed scattering of the ages at death were due to a substantial extent to the genetic differences of the individuals who make up the population.

In a population like that of the United States, the ages at death are scattered within a cohort around a median value. If one plots for a cohort of women the ~~ages at~~ number of deaths per year, as a function of the age one obtains a curve which resembles a Gaussian, ~~which has as~~ with its maximum at 80 years. The standard deviation of this curve is about 10 years.

The observed scattering of the ages at death around the median is presumably due in part to the genetic differences of the individuals, and in part it is due to environmental factors. As shown below, σ_g, the standard deviation of the Gaussian that would describe the distribution of the ages at death, if their scattering were due only to genetic differences of the individual (i.e. non of the scattering were due to environmental ~~factors~~ factors) sets a lower limit for the number of years by which the median of the ages at death could be raised through selective breeding practised for a number of generations.

~~As shown below,~~ If σ_{obs} the observed scattering of the ages at death around the median, were wholly due to genetic differences of individuals, then presumably it would be possible to increase in toto, through selective breeding over a number of generations, the median ages at death by at least $\sigma_{obs}\sqrt{2.5} \cong 15.8$ years

Today, the productive life of an adult covers a period of 45 years, stretching from ~~about~~ the age of about 20 to about 65. If the median age at death could be raised by 15 years and if people would not only die at a higher age, but would also keep young longer, then selective breeding over a number of generations would increase the productive period of the adult by about one third. If the theory of the aging process which I have presented in an earlier paper (1) were correct, then one would indeed expect that by eliminating from the population mutant alleles of wild type genes which shorten the life span, one would also correspondingly slow down the rate of physiological aging.

The increase that could be obtained through selective breeding in toto could be conceivably much greater than the lower limit given above, but on the other hand this lower limit ~~itself~~ might have been set too high ~~above~~, since a substantial portion of the observed scattering of the ages at death might be due to environmental rather than genetic factors.

In these circumstances ~~the~~ the standard deviation, σ_{obs}, of the observed ~~scattering~~ distribution of the ages at death does not in itself permit us to set a lower limit for the ~~rise~~ increase in the median of the ages at death, that could be achieved through selective breeding over a number of generations.

For the purposes of our discussion we shall now assume that there has been brought about a change in social customs, that artificial insemination has become the general practice and that women choose the father of their children freely out of a catalogue of donors. Let us further assume, for the sake of argument, that onward from some point in time, it is decided to market only sperm of donors who have lived to a high age, (to an age which is reached only by about 2½% of the males). We may then ask:

(a) by what factor would this increase in the first generation the proportion of people who live to such a high age,

(b) by how much would the median of the ages at death be increased in the first generation, and

(c) can we set a lower limit for what could be gained in this regard in toto, by practicing selective breeding for a number of generations.

We shall assume that there are present in the population "abnormal" alleles of a variety of wild type genes, which shorten the life expectancy of those individuals who carry them. We shall further assume that none of these "abnormal" alleles involved is sex linked, and that they do not in some subtle way influence the choice of the mate.

The phenotypic expression of these "abnormal" alleles could be different for males and for females. However, on the basis of the observed distribution of the ages at death of males and of females, we shall assume that for any given genotype, the

distribution of the "ages" at death of males and females ~~is~~ would be the same, provided we define the "age" of a male as the number of years he has lived, plus δ, where δ is about 3 years. (There may be for men "age" = age + δ)

(11) Let us now consider the offspring that would be produced in matings where the female has been ~~selected~~ picked at random, but the male has been selected on the basis of having lived to a high age, say the age which is reached only by about 2½% of the males. We wish to ~~Let us~~ compare this offspring with the offspring that would be obtained in matings where the male has been selected at random, but the female has lived to ~~a~~ the high age, (~~an~~ age which is reached only by about 2½% of the females).

From the assumptions stated above, it follows that the ~~x~~ distribution of the ages at death is the same for these two populations of offsprings. Therefore, we could answer the questions formulated under (a) and (b), if we knew the distribution of the ages at death of children of women who have lived to a high age and who picked their mate at random.

We may further say on the basis of a general theorem, ~~which is~~ formulated below, that the distribution of the ages at death of the children of such women is the same as the distribution of the ages at death of their mothers and their fathers. This general theorem may be formulated as follows:

Let us consider a phenotypic character which can be measured quantatitively, the quantity of the character being designated by x. Let us further assume that there are present in the population "abnormal" alleles of a variety of wild type genes, which influence this ~~pxx~~ phenotypic character. Let us

now consider a population in which mating is a random process with respect to the alleles which influence the phenotypic character in which we are interested, which is in a state of equilibrium and remains stationery in every respect from generation to generation. Let us designate the distribution function for λ in such a population with $\varphi(\lambda)$, where $\varphi(\lambda)d\lambda$ gives the probability that for an individual λ may be found between the limits of λ and $\lambda+d\lambda$.

Let us now select from out of one cohort of "females" those for whom λ falls into some interval between λ_1 and λ_2. The distribution function $q(\lambda)$ of the "mothers" of this group of "females" is different from the distribution function $\varphi(\lambda)$ of the general population of "females". Our theorem states that the distribution function for λ of the "daughters" of the selected "females" is the same as the distribution function $q(\lambda)$ of the "mothers" of the selected "females".

In its more general form our theorem also states that the distribution function for λ of the "granddaughters" of the selected females is the same as the distribution function of the "grandmothers" of the selected females.

We shall be content to let this general theorem stand here as a "conjecture", but I shall indicate in the Appendix how the theorem may be proven.

If none of the "alleles"involved are sex linked and if the phenotypic expression of the character in which we are interested is quantatitively the same for "males" and for "females", then the theorem holds for "fathers" and "mothers" as well as for "sons" and "daughters".

In the following we shall assume this to be the case for the abnormal alleles which shorten the life span of those individuals who carry them and we assume that this also holds - provided we define the "age" of men as stated under (1) - for the expression of these alleles in the physiological age of the individuals, which has a bearing on the age at death.

By selecting out of a cohort, from within the general population, men and women who are sufficiently old and by finding out from them when their fathers and mothers have died, we can....

Insert

a) The selected people who live to a high age represent a certain proportion of the general population. For the purposes of this discussion, we shall select people who live to the age which is reached by only one-fourtieth (i.e. $2\frac{1}{2}\%$) of the cohort. If the number of people who die within any given year, plotted as a function of the age, is described by a Gaussian, the fraction of the cohort living beyond two standard deviations is just slightly less than one-fourtieth of the population. The proportion of their parents who live to the same high age is increased by a certain factor k . How large is this factor k ?

determine the distribution of the ages at death of the parents of these "selected" people. Regarding the distribution of the ages at death of their parents we may ask two questions which are of particular interest:

a) The selected people who live to a high age represent a certain proportion of the general population. The proportion of their parents who live to the same high age is increased by a certain factor k . How large is this factor k ?

b) The median of the ages at death of the parents of the selected people may be higher by a certain number of years, η , than the median of the ages at death of the general population, out of which the "selected" people were picked. How large is η ?

Having found k and η for the parents of the selected people, we may expect to have the same values of k and η for the first generation of children if a population goes over to the practice of the kind of selective breeding described above.

If η turns out to be the same order of magnitude as σ_{obs}, the standard deviation of the Gaussian which approximates the observed distributions of the ages at death in a cohort within the general population, then we shall be in a position to set a lower limit for the number of years by which we could increase in toto the median of the ages at death, through practising selective breeding (of the kind described above) over a number of generations.

The discussion which now follows is based on these assumptions:

1.) The distribution of the ages at death, which is due to the scattering of the ages at death by non genetic factors, may be described by a Gaussian for each genotype contained in the population and these Gaussians have the same standard deviation $\sigma_0[en]$ for every genotype contained in the population.

2.) There are present in the population a variety of mutant alleles of wild type genes, which shorten the life of the individual who carries them, and the life shortening effect of each of these mutant alleles is about the same. Further, n, the average number per individual of the mutant alleles present in the population is larger than 2.5.

On the basis of the assumptions made under points (1) and (2), it is possible to compute from the observed value of η and from $\sigma_0[ob]$, the observed value of the standard deviation of the ages at death of the general population, the values of $\sigma_0[ge]$ and $\sigma_0[en]$.

The values computed will, however, be reliable estimates only, if the observed value of η amounts to at least a few years (i.e. if η is not too small compared to $\sigma_0[ob]$).

In the stationery general population the mutant alleles of the wild type genes will have a Poisson distribution which resembles a Gaussian. We may write for the average life shortening effect which is caused by the presence of the mutant alleles

If η is sufficiently large, then we shall obtain a small value for $\sigma_0[an]$ and in such a case we would have

$$\eta \approx \sigma_0[ge]$$

In the stationery general population, the mutant alleles of the wild type genes may be assumed to have a Poisson distribution which resembles a Gaussian.

By superimposing two Gaussian distributions, we again obtain a Gaussian distribution and we may write:

$$\sigma_0^2[ab] = \sigma_0^2[ge] + \sigma_0^2[en]$$

If we had, for example, $\sigma_0[ge] = \sigma_0[en]$ then we would obtain for $\sigma_0[ge]$

$$\sigma_0[ge] = \frac{1}{\sqrt{2}}\,\sigma_0[ab]$$

For a population like that of the United States, where we have $\sigma_0[ab] \approx 10$ years, we would obtain for $\sigma_0[ge]$ in this case

~~where~~

$$\sigma_0[ge] \approx 7 \text{ years}$$

We may write for Δ, the number of years by which we would increase $\bar{t}_0$, the median of the ages at death of the general population, by eliminating all abnormal alleles, through the practice of selective breeding over a number of generations:

$$\Delta \Rightarrow \sqrt{n}\,\sigma_0[ge]$$

~~where $\sigma_0[ge]$ designates the standard deviation of the distribution of the ages at death, in the absence of any scattering of the ages at death due to non genetic, environmental factors.~~

Because we do not know the number n, we cannot predict the value of Δ from this formula, but by assuming $n \geq 2.5$ we can set a lower limit for Δ by writing:

$$\Delta > \sigma_0[ge]\sqrt{2.5}$$

From ( ) we would obtain for example $\Delta >$ [illegible] years, for $\sigma_0[fe] \approx$ [illegible] years and we would obtain $\Delta >$ [illegible] years for $\sigma_0[fe] \approx$ [illegible] years.

If γ turns out to be very small compared to $\sigma_0[ab]$ $\sigma_0[ab]$, then the distribution of the ages at death of the mothers and fathers of the select group of people would not furnish a reliable , .

clue to the value of $\sigma_0[q]$ and it would not set a reliable lower limit for Δ .

If η turns out to be high enough, then it will be possible also to obtain a lower limit for Δ in another manner. ~~and if n were higher than 2.5 then we would obtain a higher value for the lower limit of than the value given by (25).~~ What ~~we~~ I have in mind is as follows:

Let us choose out of the group of selected people previously defined, a sub group composed of those individuals among them, whose fathers as well as whose mothers have reached the same high age, for which the group itself had been selected. Let us now consider the distribution of the ages at death of the siblings of this group of selected people. We may then write for Δ, the increase of the median of the ages at death that can be obtained through selective breeding practised over a number of generations,

$$\Delta > \bar{t}_s - \bar{t}_o + \sqrt{\sigma_s^2[o] - \sigma_o^2[ng]} \tag{26}$$

where $\bar{t}_s$ stands for the median of the ages at death of the siblings, ~~and~~ $\bar{t}_o$ for the median of the ages at death of the ~~xxxx~~ general population, and $\sigma_s[o]$ stands for the observed standard deviation of the ages at death of the siblings.

This holds, however, only if η turns out to be large so that $\sigma_o[ng]$ becomes sufficiently small to permit us to disregard any correlation which might be brought about by the effect ~~on the age at death~~ of environmental factors, between the longevity of the members of the above mentioned sub group and the longevity of

their siblings. (If $\sigma_0[ng]$ were large, this correlation might be significant, because, as a general rule, siblings are exposed to similar environmental factors, at least during their early childhood.)

~~Szilard~~ Mendel

9 a at mark 1

D R A F T 28th August, 1963

Rough Draft of first half of the paper.

"ON THE INHERITANCE OF LONGEVITY" * by Leo Szilard

~~by~~

~~Leo~~ Szilard

~~The University of Chicago, Chicago, Illinois~~

Progress in medicine has greatly reduced infant mortality but extending the life expectancy of the adult is more and more becoming an uphill fight. In order to see what we are up against in this regard, let us consider ~~for example~~ what would happen if medical science were to find one of these days a miraculous cure for a disease, such as cancer, which is currently responsible for, say, 25% of the deaths in adulthood or old age. The age specific death rate of most diseases doubles, roughly speaking, every eight years and so does the total death rate from all causes. It follows that if we plot for a cohort within a population that has been freed from this disease, the number of deaths occurring per year as a function of the age, and also plot the same data for a population from which this disease has not been eliminated, we ~~shall~~ obtain two identical curves, except that the curve relating to the population freed from the disease is shifted towards the higher ages by 3.3 years. Thus it may be seen that by eliminating a disease ~~(such as cancer)~~ which is responsible for about 25% of the deaths in adulthood or old age, the life expectancy of the adult could be increased only by about 3 years.

---

* This work was performed ~~under~~ a research grant of ~~the~~ National Institutes of Health of the U.S. Public Health Service.

Moreover, even though some increase in the life expectancy of the adult might still be obtained through further advances in medical science, this would presumably mean only that people would die when they are somewhat older ~~and~~ but it would not be likely to mean that people would keep young longer.

As shown below, we could hope to be able substantially to prolong the life of adults and, conceivably, not only to prolong their life, but also to slow the rate at which they age, if the observed scattering of the ages at death were due to a substantial extent to the genetic differences of the individuals who make up the population.

In a population like that of the United States, the ages at death are scattered within a cohort around a median value. If one plots for a cohort of women the ~~ages at~~ number of deaths, per year, as a function of the age one obtains a curve which resembles a Gaussian, ~~which has as~~ with its maximum at 80 years. The standard deviation ($\sigma_0[ab]$) of this curve is about 10 years.

The observed scattering of the ages at death around the median is presumably due in part to the genetic differences of the individuals, and in part it is due to environmental factors. As shown below, $\sigma_0[ge]$, the standard deviation of the Gaussian that would describe the distribution of the ages at death, if their scattering were due only to genetic differences of the individual (~~and~~ i.e. ~~no~~ none of the scattering were due to environmental ~~factors~~ factors) sets a lower limit for the number of years by which the median of the ages at death could be raised, through selective breeding practised for a number of generations.

~~As shown below,~~ If $\sigma_0[ob]$, the observed scattering of the ages at death around the median, were wholly due to genetic differences of individuals, then presumably it would be possible to increase in toto, through selective breeding over a number of generations, the median ~~ages~~ of the at death by at least $\sigma_0[ob]\sqrt{2.5} \approx 15.8$ years.

Today, the productive life of an adult covers a period of 45 years, stretching from ~~about~~ the age of about 20 to about 65. If the median age at death could be raised by 15 years and if people would not only die at a higher age, but would also keep young longer, then selective breeding over a number of generations would increase the productive period of the adult by about one third. If the theory of the aging process which I have presented in an earlier paper [1] were correct, then one would indeed expect that by eliminating from the population mutant alleles of wild type genes which shorten the life span, one would also correspondingly slow down the rate of physiological aging.

The increase that could be obtained through selective breeding in toto could be conceivably much greater than the lower limit given above, but on the other hand ~~the~~ this lower limit ~~itself~~ might have been set too high ~~above~~, since a substantial portion of the observed scattering of the ages at death might be due to environmental rather than genetic factors.

In these circumstances ~~the~~ the standard deviation, σ_{obs}, of the observed ~~scattering~~ distribution of the ages at death does not in itself permit us to set a lower limit for ~~the rise~~ increase, Δ, in the median of the ages at death, that could be achieved through selective breeding over a number of generations.

For the purposes of our discussion we shall now assume that there has been brought about a change in social customs, that artificial insemination has become the general practice and that women choose the father of their children freely out of a catalogue of donors. Let us further assume, for the sake of argument, that onward from some point in time, it is decided to market only sperm of donors who have lived to a high age, (to a high age which is reached only by about 2½% of the males). We may then ask:

(a) by what factor would this increase in the first generation the proportion of people who live to such a high age,

(b) by how much would the median of the ages at death be increased in the first generation, and

(c) can we set a lower limit for what could be gained in this regard in toto, by practising selective breeding for a number of generations.

We shall assume that there are present in the population "abnormal" alleles of a variety of wild type genes, which shorten the life expectancy of those individuals who carry them. We shall further assume that none of these "abnormal" alleles involved is sex linked, and that they do not in some subtle way influence the choice of the mater

The phenotypic expression of these "abnormal" alleles could be different for males and for females. However, on the basis of the observed distribution of the ages at death of males and of females, we shall assume that for any given phenotype, the

distribution of the "ages" at death of males and females would be the same, provided we define the "age" of a male as the number of years he has lived, plus δ, where δ is about 3 years. Thus we may write for man "age" = age + δ (1)

Let us now consider the offspring that would be produced in matings where the female has been picked at random, but the male has been selected on the basis of having lived to a high age, say the age which is reached only by about 2½% of the males. We wish to compare this offspring with the offspring that would be obtained in matings where the male has been selected at random, but the female has lived to a high age, (the age which is reached only by about 2½% of the females).

From the assumptions stated above, it follows that the distribution of the ages at death is the same for these two populations of offsprings. Therefore, we could answer the questions formulated under (a) and (b), if we knew the distribution of the ages at death of children of women who have lived to a high age and who picked their mate at random.

We may further say on the basis of a general theorem, which is formulated below, that the distribution of the ages at death of the children of such women is the same as the distribution of the ages at death of their mothers and their fathers. This general theorem may be formulated as follows:

Let us consider a phenotypic character which can be measured quantatitively, the quantity of the character being designated by λ. Let us further assume that there are present in the population "abnormal" "alleles" of a variety of wild type genes, which influence this phenotypic character. Let us

now consider a population in which mating is a random process with respect to the alleles which influence the phenotypic character in which we are interested, which is in a state of equilibrium and remains stationery in every respect from generation to generation. Let us designate the distribution function for λ in such a population with $\phi(\lambda)$, where $\phi(\lambda)d\lambda$ gives the probability that for an individual λ may be found between the limits of λ and $\lambda + d\lambda$.

Let us now select from out of one cohort of "females" those for whom λ falls into some interval between λ_1 and λ_2. The distribution function $q(\lambda)$ of the "mothers" of this group of "females" is different from the distribution function $\phi(\lambda)$ of the general population of "females". Our theorem states that the distribution function for λ of the "daughters" of the selected "females" is the same as the distribution function $q(\lambda)$ of the "mothers" of the selected "females".

In ~~a small~~ its more general form our theorem also states that the distribution function for λ of the "granddaughters" of the selected ~~x~~ females ~~is~~ is the same as the distribution function of the "grandmothers" of the selected females.

We shall be content to let this general theorem stand here as a "conjecture", but ~~will~~ I shall indicate in the Appendix how the theorem may be proven.

If none of the "alleles"involved are sex linked and if the phenotypic expression of the character in which we are interested is quantatitively the same for "males" and for "females", then the theorem holds for "fathers" ~~and~~ "mothers" ~~are interchangeable as well as~~ and for as well as for "sons" ~~and~~ as well as for "daughters".

In the following we shall assume this to be the case for the abnormal alleles which shorten the life span of those individuals who carry them and we assume that this also holds - provided we define the "age" of men as stated ~~above~~ under (1) - for the expression of these alleles in ~~the physiological age, which has a bearing on~~ the age of the individuals at death.

By selecting out of a cohort, from within the general population, men and women who are sufficiently old and by finding out from them when their fathers and mothers have died, we can....

Insert

a.) The selected people who live to a high age represent a certain proportion of the general population. For the purposes of this discussion, we shall select people who live to the age which is reached by only one-fourtieth (i.e. $2\frac{1}{2}\%$) of the cohort. If the number of people who die within any given year, plotted as a function of the age, is described by a Gaussian, the fraction of the cohort living beyond two standard deviations is just slightly less than one-fourtieth of the population. The proportion of their parents who live to the same high age is increased by a certain factor k . How large is this factor k ?

determine the distribution of the ages at death of the parents of these "selected" people. Regarding the distribution of the ages at death of their parents we may ask two questions which are of particular interest:

(a) The selected people who live to a high age represent a certain proportion of the general population. The proportion of their parents who live to the same high age is increased by a certain factor k . How large is this factor k ?

(b) The median of the ages at death of the parents of the selected people may be higher by a certain number of years, γ , than the median of the ages at death of the general population, out of which the "selected" people were picked. How large is γ ?

Having found k and γ for the parents of the selected people, we may then expect to have the same values of k and γ for the first generation of children if a population goes over to the practice of the kind of selective breeding described above.

If γ turns out to be the same order of magnitude as σ_0 [σ_{46}] the standard deviation of the Gaussian which approximates the observed distributions of the ages at death in a cohort within the general population, then we shall be in a position to set a lower limit for the number of years by which we could increase in toto the median of the ages at death, through practising selective breeding (of the kind described above) over a number of generations.

The discussion which now follows is based on these assumptions:

(1.) The distribution of the ages at death, which is due to the scattering of the ages at death by non genetic, environmental factors, may be described by a Gaussian for each genotype contained in the population and these Gaussians have the same standard deviation $\sigma_0[en]$ for every genotype contained in the population.

(2.) There are present in the population a variety of mutant alleles of wild type genes, which shorten the life of the individual who carries them, and the life shortening effect of each of these mutant alleles is about the same. Further, n , the average number per individual of the mutant alleles present in the population is larger than 2.5.

On the basis of the assumptions made under points (1) and (2), it is possible to compute from the observed value of η and from $\sigma_0[ab]$, the observed value of the standard deviation of the ages at death of the general population, the values of $\sigma_0[ge]$ and $\sigma_0[en]$.

The values computed will, however, be reliable estimates only, if the observed value of η amounts to at least a few years (i.e. if η is not too small compared to $\sigma_0[ab]$).

~~In the stationery general population the mutant alleles of the wild type genes will have a Poisson distribution which resembles a Gaussian. We may write for the average life shortening effect which is caused by the presence of the mutant alleles~~

If γ is sufficiently large, then we shall obtain a small value for $\sigma_0[en]$ and in such a case we would have

$$\gamma \approx \sigma_0[ge]$$

In the stationery general population, the mutant alleles of the wild type genes may be assumed to have a Poisson distribution which resembles a Gaussian.

By superimposing two Gaussian distributions, we again obtain a Gaussian distribution and we may write:

$$\sigma_0^2[ab] = \sigma_0^2[ge] + \sigma_0^2[en]$$

If we had, for example, $\sigma_0[ge] = \sigma_0[en]$ then we would obtain for $\sigma_0[ge]$

$$\sigma_0[ge] = \frac{1}{\sqrt{2}}\,\sigma_0[ab]$$

For a population like that of the United States, where we have $\sigma_0[ab] \approx 10$ years, we would obtain for in this case $\sigma_0[ge]$

$$\sigma_0[ge] \approx 7 \text{ years}$$

We may write for Δ , the number of years by which we would increase $\bar{t}_0$, the median of the ages at death of the general population, by eliminating all abnormal alleles, through the practice of selective breeding over a number of generations:

$$\Delta = \sqrt{n}\,\sigma_0[ge]$$

~~where designates the standard deviation of the distribution of the ages at death, in the absence of any scattering of the ages at death due to non genetic, environmental factors.~~

Because we do not know the number n , we cannot predict the value of Δ from this formula, but by assuming $n > 2.5$ we can set a lower limit for Δ by writing:

$$\Delta > \sigma_0[ge]\sqrt{2.5}$$

From ( ) we would obtain for example $\Delta > 11$ years for $\sigma_0[\varphi] = 7$ years and we would obtain $\Delta > 15.8$ years for $\sigma_0[\varphi] = 10$ years. ~~years.~~ X

If γ turns out to be very small compared to $\sigma_0[\alpha\beta]$, then the distribution of the ages at death of the mothers and fathers of the select group of people would not furnish a reliable .....

clue to the value of $\sigma_0[ge]$ and it would not set a reliable lower limit for Δ.

If γ turns out to be high enough, then it will be possible also to obtain a lower limit for Δ in another manner. ~~and if n were higher than 2.5 then we would obtain a higher value for the lower limit of than the value given by (25).~~ What ~~we~~ I have in mind is as follows:

Let us choose out of the group of selected people previously defined, a sub group composed of those individuals among them, whose fathers as well as whose mothers have reached the same high age, for which the group itself had been selected. Let us now consider the distribution of the ages at death of the siblings of this group of selected people. We may then write for Δ_1 the increase of the median of the ages at death that can be obtained through selective breeding practised over a number of generations,

$$\Delta > \bar{t}_s - \bar{t}_0 + \sqrt{\sigma_s^2[ab] - \sigma_0^2[an]} \tag{26}$$

where $\bar{t}_s$ stands for the median of the ages at death of the siblings, ~~and~~ t_0 for the median of the ages at death of the ~~the~~ general population, and $\sigma_s[ab]$ stands for the observed standard deviation of the ages at death of the siblings.

This holds, however, only if γ turns out to be large so that $\sigma_0[an]$ becomes sufficiently small to permit us to disregard any correlation which might be brought about by the effect, ~~on the age at death~~ of environmental factors, between the longevity of the members of the above mentioned sub group and the longevity of

their siblings. (If $\sigma_0[e_n]$ were large, this correlation might be significant, because, as a general rule, siblings are exposed to similar environmental factors, at least during their early childhood.)

Insert, following page 6.

We may now ask how much larger would be, for the population of genetically perfect females, the fraction $f(x)$ of the population that survives to a certain age x, than in the initial population from which the population of genetically perfect females may be obtained through selective breeding.

The fraction of the genetically perfect population which survives to a high age x is larger by a factor of k than the fraction of the initial population which survives to the same age x. The latter is given by $\frac{1}{l(x)}$ and the former is given by $\frac{1}{l(x)} e^{-x}$. Accordingly by making use of ( ) we obtain for the factor k:

$$k = l(x) \left[\frac{g(x)}{f(x)} \right]^2 \qquad (13a)$$

For $n = 3$ we have $\left[\frac{g(x)}{f(x)} \right]^2 \simeq 20$ and accordingly the fraction of the genetically perfect population which would live to any age x, chosen sufficiently high, would be ($k =$) 20 times as large as a fraction of the initial fraction which lives to the same age x.

From (12) we may determine for a genetically perfect population the median of the ages at death. The ratio $\frac{l(x)}{[g(x)]^2}$ increases with increasing age x and the age x for which this ratio is equal to 2 ($\lambda = 2$) is the median age for a genetically perfect population. Strictly speaking (12) would hold true only if the scattering of the ages at death, which is due to environmental factors, is sufficiently small. This is so because in deriving our formulae we have assumed that the age x has been chosen sufficiently high to ensure that all those living to the age x are genetically perfect. If the scattering of the ages at death due to environmental factors is made sufficiently

second page insert following page 6.

From (12) we may determine what fraction $\frac{1}{\lambda}$ of a genetically perfect population reaches any age x^*. This fraction increases with decreasing age x^* and the age x^* for which this fraction is equal to one-half ($\lambda = 2$), is the median age of a genetically perfect population. We can compare the age reached by an arbitrarily chosen fraction $\frac{1}{\lambda}$ of the genetically perfect population and then compare it with the same fraction of the initial population would reach, which is the age for which we have

$$l(x) = \frac{1}{\lambda}$$

It is of particular interest to compare the median of the ages at death for a genetically perfect population, for which we have:

$$\lambda = \frac{l(x)}{[l(x)]^2}$$

with the median of the ages at death of the initial population.

From (12) we may determine the median of the ages at death for a genetically perfect population. The ratio increases with increasing age x and the age x for which this ratio is equal to 2 ($\lambda = 2$) is the median age for a genetically perfect population. Strictly speaking (12) holds true only if the scattering of the ages at death, which is due to environmental factors, is sufficiently small. This is so because in deriving our formulae we have assumed that the age x has been chosen sufficiently high to ensure that all those living to the age x are genetically perfect. If the scattering of the ages at death due to environmental factors is too large, then we can not set the age x high enough to ensure that only genetically perfect individuals live up that age and at the same time expect that of the genetically perfect individuals, as high a proportion as one half lives up to the age x.

third page insert following page 6.

In as much as the effect of an over large scattering due to environmental factors reduces the observed value and thereby according to (12) gives a too large value for λ, such an over large scattering would tend to make the median of the ages at death of the genetically perfect population, lower than it actually is.

replaced see "Text"

Text. Top insert p. 2.

From

( ) $\frac{1}{\lambda} = f(\bar{x})$

we can find the mitotal population reaches any given age x

From

(12) $\frac{1}{\lambda} = \frac{[q(x)]^2}{f(x)} = \frac{q(x)}{f(x)} q(x)$

we can find for genetically perfect population which (high) age is reached by the same fraction of the population, since $\frac{[q(x)]^2}{f(x)} > \frac{1}{2}$ the latter is higher than one. Of particular interest is the age $\bar{x}^*(\lambda = 1/2)$ reached by the genetically perfect population according to (12) for $\lambda = 1/2$. This is the median of the ages at death of the genetically perfect population which may be even higher than $\bar{x}$. The median of the ages at death of the mitotal population that can be reached from

( ) $\frac{1}{2} = f(\bar{x})$

Text D. p. 3 of insert. (caused by)

one of the effects of ~~the~~ large scattering ~~due to~~ environmental factors is to reduce the observed value of $\frac{f(x)}{f(x)}$ below the value that it would have if the scattering caused by environmental factors were small. ~~If we~~ ~~If we put a 1~~ ~~lower the value of $\frac{f(x)}{f(x)}$ which we substitute~~ into (12) we get

~~By lowering the value of $\frac{f(x)}{f(x)}$ in (12) we raise the value of x and thus get we obtain a value of x which is higher than it~~ ~~if and~~ it really is.

By substituting into (12) ~~for~~ for $\frac{f(x)}{f(x)}$ a value ~~which is lower that it really~~ ~~will than it would be~~, ~~we obtain~~ which is lowered we obtain a value for x which is too high and thus for the median of the ages at death of the gen. perpet. population a value which is too low.

Subsidiary the genetically perfect popn. we have for the

Text ~~for insert~~

For the ~~The~~ ~~[illegible]~~ median age at death ~~of the~~

~~for the genetically perfect pop.~~

~~is given by~~

$$f(x) = \frac{e^{-x}}{2}$$

and for $x = 3$ we have

$$f(x) = \frac{1}{40}$$

If the ~~[illegible]~~ environmental scattering of ages at death is small enough so that

~~those in the individual population~~

~~[illegible] which who reach [illegible]~~

~~the age length age to which~~

~~$\frac{1}{40}$ of the pop so that~~

~~the longest lived~~ ~~[illegible]~~ most of

one may say that those in the individual population who live to ~~a length~~ an age ~~[illegible]~~ x for which we have $f(x) = \frac{1}{40}$ are genetically perfect than

~~It follows~~ we may conclude that in a genetically pure population half of the people would live to the ~~length~~ age, which is reached by only 2½% of the individual population

"drift" in the ~~median~~ ages at death ~~we can~~ [next] after

~~From σ mothers we can~~

estimate what σ_{in} would be for the ~~initial population~~ the value that σ would have for the initial pop. of ~~there were no environmental~~ non genetic scattering in the absence of any of the ages at death. ~~we shall designate this as~~

Let us now ~~If we~~ assume that ~~the~~ the non genet. scattering of the ages at death would lead to ~~the~~ a gaussian distribution of the ages at death and that σ_{ng} would be the same for all $\Sigma\,\Delta i$ ~~— s.~~ ~~Here we can compute~~ In this case we can now estimate, from the observed ~~σ of the selected mothers~~ ~~σ_{ng} for the initial population~~ ~~reduction~~ of the median of the ages of death of the "mothers" as compared to the median of the initial population

$$\left(\frac{\sigma}{\tau}\right)^2 = n \qquad \sigma = \tau\sqrt{n}$$

Test

~~[illegible]~~

selected mothers whose daughter born to 2σ ~~[illegible]~~ have mean shifted by σ.

~~daughter~~ shift [Δ_{obs}] observed

σ_{in}

[variance = n

$$\left(\frac{\sigma}{\tau}\right)^2 = n$$

$$[\sigma_{in}] - \Delta^2_{obs} = [\sigma_{ng}]^2$$

Δ^2_{obs} is σ_{gen} for the initial population

Stencil copy

Attached

28th August, 1963

ROUGH DRAFT OF FIRST HALF OF THE PAPER

"ON THE INHERITANCE OF LONGEVITY" BY LEO SZILARD

Progress in medicine has greatly reduced infant mortality but extending the life expectancy of the adult is more and more becoming an uphill fight. In order to see what we are up against in this regard, let us consider what would happen if one of these days medical science were to find a miraculous cure for a disease, such as cancer, which is currently responsible for, say, 25% of the deaths in adulthood or old age. The age specific death rate of most diseases doubles, roughly speaking, every eight years and so does the total death rate from all causes. It follows that if we plot for a cohort, within a population that has been freed from this disease, the number of deaths occurring per year as a function of the age, and also plot the same data for a population from which this disease has not been eliminated, we obtain two identical curves, except that the curve relating to the population freed from the disease is shifted towards the higher ages by 3.3 years. Thus it may be seen that by eliminating a disease which is responsible for about 25% of the deaths in adulthood or old age, the life expectancy of the adult could be increased only by about three years.

Moreover, even though some increase in the life expectancy of the adult might still be obtained through further advances in medical science, this would presumably mean only that people would die when they are somewhat older, but it would not be likely to mean that people would keep young longer.

As shown below, we could hope to be able substantially to prolong the life of adults and, conceivably, not only to prolong their life, but also to slow the rate at which they age, if the observed scattering of the ages at death were due to a substantial extent to the genetic differences of the individuals who make up the population.

In a population, like that of the United States, the ages at death are widely scattered within a cohort around a median value. If one plots for a cohort of women the number of deaths, per year, as a function of the age, one obtains a curve which resembles a Gaussian, with its maximum at 80 years. The standard deviation, $\sigma_o[ob]$, of ~~this~~ the observed curve is about 10 years.

The observed scattering of the ages at death around the median is presumably due in part to the genetic differences of the individuals, and in part it is due to environmental factors. As shown below, $\sigma_o[ge]$, the standard deviation of the Gaussian that would describe the distribution of the ages at death, if their scattering were due only to genetic differences of the individuals (i.e. if none of the scattering were due to

environmental factors), sets a lower limit for the number of years by which the median of the ages at death could be raised, through selective breeding practised for a number of generations.

If σ_o [ab], the observed scattering of the ages at death around the median, were wholly due to genetic differences of individuals, then presumably it would be possible to increase, ~~in toto~~ through selective breeding over a number of generations, the median of the ages at death in toto by at least

Today, the productive life of an adult covers a period of 45 years, stretching from the age of about 20 to about 65. If the median age at death could be raised by 15 years and if people would not only die at a higher age, but would also keep young longer, then selective breeding over a number of generations would increase the productive period of the adult by about one third. If the theory of the aging process which I have presented in an earlier paper[1.] were correct, then one would indeed expect that by eliminating from the population mutant alleles of wild type genes which shorten the life span, one would also correspondingly slow down the rate of physiological aging.

The increase that could be obtained through selective breeding in toto could be conceivably much greater than the lower limit given above, but on the other hand this lower limit might

have been set too high, since a substantial portion of the observed scattering of the ages at death might be due to environmental rather than genetic factors.

In these circumstances the standard deviation, of the observed distribution of the ages at death does not in itself permit us to set a lower limit for Δ, the increase in the median of the ages at death, that could be achieved through selective breeding over a number of generations.

For the purposes of our discussion we shall now assume that there has come about a change in social customs, that artificial insemination has become the general practice and that women choose the father of their children freely out of a catalogue of donors. Let us further assume, for the sake of argument, that onward from some point in time, it is decided to market only sperm of donors who have lived to a high age, (to the age which is reached only by about 2½% of the males). We may then ask:

a) by what factor would this increase, in the first generation, the proportion of people who live to such a high age,

b) by how much would the median of the ages at death be increased in the first generation, and

c) can we set a lower limit for what could be gained in this regard in toto, by practising selective breeding for a number of generations.

We shall assume that there are present in the population "abnormal" alleles of a variety of wild type genes, which shorten the life of those individuals who carry them. We shall further assume that none of these "abnormal" alleles involved is sex linked, and that they do not in some subtle way influence the choice of the mate.

The phenotypic expression of these "abnormal" alleles could be different for males and for females. However, on the basis of the observed distribution of the ages at death of males and of females, we shall assume that for any given genotype, the distribution of the "ages" at death of males and females would be the same, provided we define the "age" of a male as the number of years he has lived, plus δ, where δ is about 3 years. Thus we may write for man

(1) $$\text{"age"} = \text{age} + \delta$$

Let us now consider the offspring that would be produced in matings where the female has been picked at random, but the male has been selected on the basis of having lived to a high age, say the age which is reached by only about 2½% of the males. We wish to compare this offspring with the offspring that would

be obtained in matings where the male has been selected at random, but the female has lived to a high age, (the age which is reached by only about 2½% of the females). From the assumptions stated above, it follows that the distribution of the ages at death is the same for these two populations of offsprings. Therefore, we could answer the questions formulated under a) and b), if we knew the distribution of the ages at death of children of women who have lived to a high age and who picked their mate at random.

We may further say on the basis of a general theorem, formulated below, that the distribution of the ages at death of the children of such women is the same as the distribution of the ages at death of their mothers. ~~and their fathers.~~ This general theorem may be formulated as follows:

Let us consider a phenotypic character which can be measured quantitatively, the quantity of the character being designated by λ. Let us further assume that there are present in the population "alleles" of a variety of wild type genes, which influence this phenotypic character. Let us now consider a population in which mating is at random with respect to the alleles which influence the phenotypic character in which we are interested, and which is in a state of equilibrium, remaining stationary in every respect from generation to generation. Let us designate the distribution function for λ in such a population with $p(\lambda)$, where $p(\lambda)d\lambda$ gives the probability that for an individual λ may be found between the limits of λ and $\lambda + d\lambda$.

In its more general form our theorem also states that the distribution function for ν of the "granddaughters" of the selected females is the same as the distribution function of the "grandmothers" of the selected females.

We shall be content to let this general theorem stand here as a "conjecture", but I shall indicate in the Appendix how the theorem may be proven.

If none of the "alleles" involved are sex linked and if the phenotypic expression of the character in which we are interested is quantitatively the same for "males" and for "females", then the theorem holds for "fathers" as well as for "mothers", and for "sons" as well as for "daughters".

X In the following we ~~shall~~ assume ~~this to be the case for~~ that ~~holds~~ the "abnormal" alleles which shorten the life span of those individuals who carry them ~~and we assume that this also holds~~ are not sex linked - provided we define the "age" of men as stated under (1) - ~~for~~ the expression of these alleles in ~~the age of the individual at death~~ terms of longevity is the same for men and women.

By selecting out of a cohort, from within the general population, men and women who are sufficiently old and by finding out ~~from them~~ when their fathers and mothers have died, we can determine the distribution of the ages at death of the parents of these "selected" people. Regarding the distribution of the ages at death of their parents we may ask two questions which are of particular interest:

a) The selected people who live to a high age represent a certain proportion of the general population. For the

purposes of ~~this~~ our discussion, we shall select people who live to the age which is reached by only one-fourtieth (i.e. 2½%) of the cohort. If the number of people who die within any given year, plotted as a function of the age, is described by a Gaussian, the fraction of the cohort living beyond two standard deviations is just slightly less than one-fourtieth of the population. The proportion of their parents who live to the same high age is increased by a certain factor k . How large is this factor k ?

b) The median of the ages at death of the parents of the selected people may be higher by a certain number of years, ζ , than the median of the ages at death of the general population, out of which the "selected" people were picked. How large is ζ ?

Having found k and ζ for the parents of the selected people, we may then expect to have the same values of k and ζ for the first generation of children, if a population goes over to the practice of the kind of selective breeding described above.

~~If ζ turns out to be the same order of magnitude as σ_0 [σ_6], the standard deviation of the Gaussian which approximates the observed distributions of the ages at death in a cohort, within the general population, then we shall be~~ in a position to set a lower limit for Δ, the number of years by which we could increase in toto the median of the ages at death, through practising selective breeding (of the kind described above) ~~over~~ for a number of generations.

The discussion which now follows is based on these assumptions:

1) The distribution of the ages at death, which is due to the scattering of the ages at death by non genetic, environmental factors, may be described by a Gaussian for each genotype contained in the population and these Gaussians have the same standard deviation $\sigma_0[q_n]$ for every genotype contained in the population.

2) There are present in the population a variety of mutant alleles of wild type genes, which shorten the life of the individual who carries them, and the life shortening effect ~~of each~~ of these mutant alleles is additive and about the same. Further, n, the average number per individual of the mutant alleles present in the population is larger than 2.5.

On the basis of the assumptions made under points 1) and 2), it is possible to compute from the observed value of ζ and from $\sigma_0[a_6]$, the observed value of the standard deviation of the ages at death of the general population, the values of $\sigma_0[q_e]$ and $\sigma_0[e_n]$.

The values computed will, however, be reliable estimates only, if the observed value of ζ amounts to at least a few years (i.e. if ζ is not too small compared to $\sigma_0[a_6]$).

~~Straight line with slope ζ~~ (If ζ is sufficiently large, then we shall obtain ~~a small value for~~ ~~and in such a case we would have~~ $\sigma_0[q_e] \approx \zeta$)

(In the stationery general population, the mutant alleles of the wild type genes may be assumed to have a Poisson distribution which resembles a Gaussian.

By superimposing two Gaussian distributions, we again obtain a Gaussian distribution and we may write:

(2) $\sigma_0^2[ob] = \sigma_0^2[ge] + \sigma_0^2[en]$

If we had, for example, $\sigma_0[ge] = \sigma_0[en]$

then we would obtain for $\sigma_0[ge]$

$$\sigma_0[ge] = \frac{1}{\sqrt{2}}\,\sigma_0[ob]$$

For a population like that of the United States, where we have $\sigma_0[ob] \approx 10$ years, we would obtain in this case for $\sigma_0[ge]$

$$\sigma_0[ge] \approx 7 \text{ years} \quad)$$

Insert here p. 8 →

We may write for Δ, the number of years by which we could increase the median of the ages at death ~~of the general population~~ by eliminating all abnormal alleles, through the practice of selective breeding for a number of generations:

(3) $$\Delta = \sigma_0[ge]\sqrt{n}$$

Because we do not know the number n, we cannot predict the value of Δ from this formula, but by assuming $n > 2.5$, we can set a lower limit for Δ by writing:

(4) $$\Delta > \sigma_0[ge]\sqrt{2.5}$$

From (4) we would obtain for example $\Delta > 11$ years, for $\sigma_0[ge] = 7$ years; and we would obtain $\Delta > 15.8$ years, for $\sigma_0[ge] = 10$ years.