

A theory of how we age

from JOHN LEAR, our American correspondent

AGEING is plainly a matter of arithmetic. We add one year to another until our time expires. Everyone knows this, and insurance salesmen earn a pleasant living by averaging out the figures and cajoling the rest of us into wagering where we as individuals fit into the scheme. But only a very imaginative man would think of systematizing these mathematics into one equation to comprehend the interval between the cradle and the grave. In all of American science, there are few minds creatively abundant enough to put such a thought into action if the idea did strike. One of these rare intellects graces the disarming corpulence of Dr. Leo Szilard, who has used it to work out mankind's first scientific theory of how we grow old.

It seems to me inevitable that this latest of the Hungarian-born theorist's long line of brilliances will in time be recognized as a major contribution to human thought. It appears, however, with almost innocuous modesty in the pages of the January, 1959, *Proceedings of the National Academy of Sciences*. A dry and frugal footnote tells us that the work was done while Dr. Szilard—ordinarily occupied with the affairs of the University of Chicago's Enrico Fermi Institute of Nuclear Studies—was serving as a consultant to the basic research programme of the National Institute of Mental Health at Bethesda, Maryland. The NIMH is, of course, keenly conscious of the relationship between advancing age and mental illness at a time when the population of this country is ageing markedly.

"This paper represents an attempt to describe a hypothetical biological process that could account for the phenomenon of ageing", the introductory sentence says. "Ageing manifests itself in much the same general manner in all mammals, and we are in a position to learn enough about the ageing of mammals to be able to test the validity of a theory that leads to predictions of a quantitative kind—as does the theory here presented."

Dr. Szilard's thinking takes off from the fact that the basic hereditary unit in our makeup, the gene, can be responsible for the synthesis of a specific protein molecule, and that this molecule in many instances has a specific catalytic function

in one of the chemical processes of the body. When the gene mutates, the change renders the gene incompetent to bring about the process for which it ordinarily would be responsible. When the bundle of changes inside us grows sufficiently large, we are incapacitated, we are crippled, and ultimately we die.

How do we begin to die? Just where does the mysterious stroke of death originate? The theory assumes not one all-powerful, felling blow but a series of minor hits. The hits occur at random, with a speed that remains constant from the moment we are born. One hit disables one chromosome, to the extent of knocking out one of the working partners of a pair of genes harnessed to a given biological task. The chromosome continues to function, however, until the second partner also suffers a hit.

Each of us possesses altogether about 15,000 genes. The Szilard theory assumes that only 3,000 of these are important to the healthy life of an adult. To distinguish these effective operatives from all the other genes, the 3,000 are dubbed "vegetative" genes and the mutants of these "vegetatives" are called "faults".

If this were the whole story, the variation in the length of our lives would depend entirely on accidents, murders and wars. But this is not the whole story. The whole story begins generations before we are conceived. It is handed down in the genes of our forebears. By the time the chromosomes containing the 3,000 "vegetative" genes reach us, a certain number of hereditary "faults" have already occurred. In terms of age, it is as though we have already been scraped by the edge of Father Time's scythe before we emerge from the womb. Some of us are born relatively old people.

Whatever individual age one of us has at the beginning of his own phase of the eternal process known as life, that age increases progressively with the number of "vegetative" genes that are disabled by the mysterious hits of time against the species. The progression is not entirely steady, for the really "old" newborn die off rapidly in the first year of existence and then at a slower rate to the age of ten years. After that time, inherited "faults" increase the death rate "only in conjunction with the hits of time, and they increase it appreciably only above 40 (years

of age)". From then on, the surviving fraction of vital genes "decreases with age at an accelerating rate".

Here Dr. Szilard begins his ageing equation by writing the symbol "f" to represent the surviving fraction of genes. When "f" reaches a certain critical value, symbolized as "f*", "the individual . . . dies . . . within the year".

"Thus, in its crudest form," Dr. Szilard notes, "the theory postulates that the age at death is uniquely determined by the genetic makeup of the individual."

This, however he adds at once, "cannot be strictly true, for, if it were true, identical twins would die within one year of each other". And the fact is that female identical twins die at differing intervals averaging out to three and a half years. So the reasoning has been refined to account for the variance in manifold ways, including the shielding effects of environmental conditions "prevailing at present in the United States, where essentially no adult dies for lack of food or shelter and no adult has a reduced propensity to procreate because of his inability to provide food or shelter for his offspring".

In underpinning his theory mathematically, Dr. Szilard takes a hypothetical, genetically perfect, white female and designates her age of death as the "life-span of the (human) species". He finds that she, at 50 years of age, would have the same physiological age as today's average woman of 35 years. Her most probable age of death would be 92 years, twelve years greater than the age at which the average woman dies today.

The Szilard equation encompasses other women by postulating a basic time interval of the ageing process and defining this interval as the difference between the life-expectancy of the genetically perfect woman and a woman whose genetic makeup includes one "fault".

Dr. Szilard stipulates that genes "vegetatively" incapacitated by the hits of age are not thus rendered impotent in their power to duplicate themselves in future generations.

Experiments are now under way in mice to provide supporting evidence for the ageing theory, mice being better than hamsters or dogs for the purpose because the number of their chromosome pairs is closer to the number of man's.