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Reith Lectures 2001: The End of Age

Lecture 3: Sex and Death

The greatest physical asset of any of us, even those as well endowed in other respects as Dolly Parton or Arnold Schwarzenegger, is the soft grey hemisphere that sits between our ears. The human brain is a masterpiece of evolution but it complicates our lives, and nowhere is this more apparent than when we struggle with the big questions of sex and death.

It could be said that the trouble started with Aristotle who believed that each sex act had a direct life-shortening effect. We see, many centuries later, this troubling idea surfacing in the work of the metaphysical poets. It would be hard to find gloomier expression than John Donne's mournful musing: "Since each such act, they say, diminisheth the length of life a day … I'll no more dote and run to pursue things which hath endamaged me".

Now if you were to ask the male praying mantis being eaten by his bride during the act of copulation, whether the metaphysical poets were correct that the orgasm is "a little death", he would probably agree. He might even drop the word "little". You might get the same answer from the Pacific salmon, which spawns but once and dies. But is it true of you and me?

Does sex shorten our lives? Can it be, as some have suggested, that ageing and death are the price we pay for sex? Does it make sense to think in terms of a "reproductive duty" to the species, leaving us surplus to requirement when duty is done? And what, if these worrying notions are true, are we to make of the post-menopausal woman? These are the questions I shall examine in today's lecture, and I shall hope to show you that the answers are not only reassuring (on the whole) but also that they tell us a great deal about the biological background to our revolution in longevity.

In fact, Aristotle was right; there is a relationship between sex and death, but it is even more interesting than Aristotle suspected. The catalytic insight came in 1881 from the distinguished German naturalist August Weismann. What Weismann realised was that in a multicellular body like yours and mine, there is a profound division of labour between two principal kinds of cells. On the one hand, there is the germ line - the egg- or sperm-forming cells of the ovary or testis. These are the cells that, if we have children, transmit our genes into the next generation. The rest of the cells - those that make up the other organs of the body - Weismann termed the soma.

In the early stages of life on planet earth, before the distinction between germ-line and somatic cells evolved, the responsibility for generating new individuals was shared by every cell. Indeed, most organisms were probably unicellular and their descendants are with us today - bacteria, amoebae, and the like. But as cells came to live in clumps of genetically identical clones, the separation of germ-line and soma offered wonderful new opportunities for some of the cells, freed from the need to support procreation, to become specialists.

In our bodies today we find red blood cells, specialised for transporting oxygen and other constituents around the body. We find white blood cells, designed to police the body for intruders and destroy them. We find brain and nerve cells, engineered for the conduction of electrical signals. We find the cells of the lens of the eye, uniquely translucent in order to transmit and focus light upon the retina. It would be hard to imagine how such diverse specialisms could be supported if each of these cells needed also to retain the capacity to produce a new baby.

The distinction between germ-line and soma enabled such extraordinary advances in the evolution of the higher forms of life that we might almost forgive the terrible price we have paid. For it was this, not sex, that caused us to age and die. There are species that age and don't have sex, like parthenogenetic whiptail lizards, and there are species that have sex and don't age, like the freshwater Hydra. But although Hydra are capable of sex, they often don't bother and make do instead with vegetative reproduction, by budding.

Almost any part of a Hydra can generate a new individual. Its germ-line permeates its body and it has no real soma to speak of. It is this lack of distinction between germ-line and soma that allows Hydra to evade the ageing process. The presence or absence of ageing is always associated, as far as we know, with the presence or absence of the soma/germ-line distinction.

To understand why the soma/germ-line distinction is so important for ageing, we should first observe that the germ-line simply cannot be allowed to fail in its duty of keeping going indefinitely. If it did - if, for example, it permitted cumulative damage to build up in its DNA sequence - it would rapidly become extinct. Some change to the DNA sequence must of course occur, since otherwise evolution would be stalled, but the kind of damage that builds up in the somatic cells of our bodies during our lifetime would be intolerable if it were to occur to a similar extent in the germ-line.

This immortality of the germ-line is not a theoretical concept. It is as real as life itself. Each of us could, if the records were available, trace our ancestry back to the very earliest cellular forms of life on earth. Throughout the billions of year of evolutionary history, an unbroken chain of cell divisions has made us what we are today.

When we consider the soma, however, we find that there is no corresponding requirement for somatic cells to keep their DNA in good shape indefinitely. We have nothing of either parent's soma in us, and there is nothing of our soma in our children. It just does not matter, biologically speaking, if our somatic cells eventually fall apart. The somatic cells comprise the individual and that - important as it may be to you and me - is all that they will ever be required to do.

Life in the natural world is brutish and short. All that the organism needs from its somatic cells is that they can keep the soma in good enough shape until an age when the likelihood of still being alive is negligible. When we factor in the consideration that maintenance and repair of somatic cells does not come cheap, it makes sense to trim back the maintenance of the somatic cells and divert the energy thereby saved into helping with the all-important business of reproduction.

The result was that the soma became disposable, and with that came ageing. It was in 1977 that this realisation came to me - a Eureka! moment that happened, appropriately enough, as I took my bath. At the time, the idea was highly controversial because the prevailing view then was that ageing is programmed. But in the years since, the evidence in support of the disposable soma theory - as the idea is called - has become strong. It is this idea that teaches us to understand that the primary cause of ageing is the gradual build-up of faults in the cells and organs of the body.

It is always exceptions that prove the rule, and being here in Edinburgh I should be remiss if I did not mention Dolly the sheep and the remarkable feat of somatic cell cloning. At the time this breakthrough was announced I was in Budapest, as a Visiting Fellow at the Institute for Advanced Study. I don't think I shall ever forget the glee with which my host's female secretary announced that not only were men's somas disposable, but their germ-lines were redundant too.

Like many a scientist, I was amazed at the Roslin Institute's success in transferring the nucleus from an adult somatic cell into an egg from which the nucleus had been removed and producing a viable animal. What Dolly and other cloning successes have shown is that in at least some somatic cells, the integrity of the DNA may be relatively spared. On the other hand, it was found with Dolly that the successful nuclear transfer was one among a considerable number of failures. Being random, the cellular damage that leads to the ageing of somatic tissues is by no means a uniform affair.

If the disposable soma theory is correct and ageing results from a trade-off between reproduction and maintenance, then Aristotle might have been right that romantic ardour has a life shortening effect. And if Aristotle had been a fruitfly, he would have been spot on. A life of chastity has been shown to work wonders for would-be fruitfly centenarians. Unmated flies live longer.

But in humans there is no evidence that sexual activity shortens life - indeed, quite the reverse has been suggested. Nor is there any strong indication that having children grinds you down in the longevity sense, however contrary to parents' experience this may seem. Nevertheless, there is some evidence that there is a trade-off between our genetic predispositions to long life and to fertility.

Studying human biology is complicated because, as we all know, there is a great deal that is not strictly biological which influences our lives. On the other hand, we have astonishingly full records, including details of births, deaths and marriages, which have accumulated over many years. So it was to this rich resource that I turned, together with Rudi Westendorp, an epidemiologist from the University of Leiden, in order to ask whether there might be buried evidence of a trade-off between human fertility and longevity.

The records we used had been compiled on a commercially available genealogical database, containing records of British aristocrats going back to the 8th century. The database contained records for 33,497 individuals. We chose to study aristocrats for a combination of reasons. First, their records have been better preserved. Secondly they tended to enjoy the best living conditions which, in earlier times, would have given them the greatest chance of living a long life. There are many ways in which poverty

adversely affects both fertility and survival, and these might have masked the patterns we were looking for.

What we found was very curious. There was, of course, a trend over time towards increasing life spans and smaller family sizes. As others had observed before, these trends among the aristocracy were about 150 years ahead of the general population, confirming the privileged status of aristocrats as a group. After making allowance for these underlying trends, we found that the longest-lived aristocrats tended, on the average, to have had the greatest trouble with fertility. So, taking the pattern as a whole, we concluded that a predisposition to above-average longevity may be linked to below-average fertility.

Perhaps the oddest thing about human reproduction, something that sets us apart from the rest of the animal kingdom, is the menopause. The mystery of menopause is this: why should women invariably lose their fertility when they are far short of showing advanced signs of biological ageing, and when it happens neither to monkeys nor men? To be sure, there is talk of a male menopause, or andropause. But neither in men nor in female apes is there a universal loss of fertility at such a relatively early age. Male reproductive ageing is variable. Some men may experience early loss of reproductive functions. Others retain fertility and may indeed father children at a great age. There is no such spectrum of possibilities for women. Menopause shuts the door to motherhood with blunt finality at around the age of 50. Fertility declines ahead of this for 5-10 years.

Reproduction is so important for Darwinian fitness that anything which impedes fertility should make us ponder the evolutionary stakes that may be at play. Menopause is a unique feature of the human female life history and its explanation is most likely to be found among the other elements that distinguish human evolution from our companion species on this planet. Just last month, my colleague Daryl Shanley and I published an evolutionary analysis that throws new light on the factors which may be responsible.

During the evolution of our hominid ancestors, two unprecedented developments took place. First, the size of the human brain underwent a very rapid enlargement. Secondly, we acquired the capacity for a level of advanced social and cultural interaction not previously seen. In concert with these developments, we evolved increased life spans, presumably because of evolutionary pressure to make the soma a bit less disposable. After all, there is little point in evolving a big brain and using it to make your life safer, if your DNA falls apart before you have been able to reap the benefits of these advantages. Such a process might happily continue - brains getting bigger and lives getter longer - but for one worrisome snag. The baby's brain still needs to pass through the mother's pelvis at the time of birth. Worse still, the physical dimensions of the pelvis are tightly constrained by the mechanics of the increasingly upright human gait.

Natural selection is a master of compromise. While a design engineer might suggest that the birth canal be rerouted, perhaps via the abdomen, such radical redesign rarely occurs. What happened instead was that babies came to be born with their brains half grown. Compared to other placental mammals, the human infant is unusually incomplete at birth. A lamb, calf or foal walks with its mother within hours of its

birth. A human baby takes more than a year to accomplish this feat. On the other hand, in order not to extend the period of such high dependency even longer, birth is delayed until the baby's brain is as big as possible. The result is that humans have unusually difficult deliveries, which increases the dangers if things go wrong. The dangers are tragically clear from the high levels of maternal mortality that occurred - and still occur in the developing countries - in the absence of modern obstetric care.

So there we were, the pinnacle of evolution, but reproductively speaking in a fine old mess. Social and cultural evolution was occurring fast, and life expectancy was growing rapidly. For perhaps the first time in our evolutionary history, significant numbers of women began surviving to an age when the signs of senescence were starting to be felt.

Initially, it may have been only a small number surviving past fifty, but it brought a new challenge. If females retained fertility indefinitely, and if those who survived to older ages continued to become pregnant, the already difficult business of giving birth would become downright dangerous. There is some truth, at least in natural circumstances, in the idea that the fifty year old body is too old to give birth properly.

The solution, as you might have guessed, was to limit fertility to ages when it was relatively safe, even though this meant forgoing the genetic advantages of having as many children as possible. However, there were compensatory benefits.

The older mother would be spared the risks of a late pregnancy and her dependent children would be protected from becoming orphans. And with an increasing tendency for living in extended kin groups, the post-reproductive female could assist her daughters with their reproduction, perhaps by relieving them of some of the burdens of providing for their dependent offspring. There is good evidence from hunter-gatherer societies, particularly the Hadza of East Africa, that the fulfilment of such a role by the grandmother enhances the child-raising capacity of their daughters and decreases the mortality of grandchildren.

An important concept in evolutionary biology, developed by the late Bill Hamilton, is the idea of "inclusive fitness" - that one's genetic contribution to future generations should be measured in terms of the survival and reproductive success of kin other than just one's immediate offspring. What Daryl Shanley and I showed in our paper, is that it requires all these factors to be bundled together before it becomes clear that the menopause serves a genuine evolutionary advantage. It is this stringent requirement that explains the uniqueness of the human menopause and it tells us that post-menopausal women, far from being, in Darwinian terms, worn-out biological has-beens, are actually very special.

If it is correct that the menopause represents a distinct evolutionary advantage, as I believe to be the case, this was a hugely significant step. For probably the first time ever, an adaptation arose that specifically reflected the new value of older organisms. After aeons of largely neglecting the fate of the disposable soma, natural selection finally woke up to the fact that older women were so valuable that late fertility became dispensible instead.

As we celebrate the longevity revolution and look to the future, it helps to understand where we came from and where we may be headed. The evolutionary insights that throw light on the relationship between sex and death are an important part of explaining why and how we age. They may also help us understand the directions in which the forces of natural selection, slow but resolute as a glacier, may be directing us. The circumstances under which we now procreate and die are very different from those which shaped our present-day life-history. It will be interesting to ask where natural selection may steer our descendants, even if we are not around to see.

Finally, no discussion of sex and death would be complete without visiting the intriguing question of why it is that women live longer than men. The fact that having a Y-chromosome instead of a second X-chromosome shortens life by almost 10% is one of life's oddities, made all the stranger by the fact that among birds the chromosomal determination of sex works the other way around, yet still it is the females that live longer. There is, as yet, no completely satisfactory answer why things should be so, but I believe that the existence of a female menopause and the absence of a male menopause offers a clue.

Males and females make an equal genetic contribution to their offspring, but females make a more direct physiological contribution to their young, by nurturing the foetus in her womb and suckling the young in the case of a mammal, or by forming and provisioning the egg in the case of egg-laying species like birds, reptiles, insects and amphibians.

There is therefore a sense in which the state of the female soma makes an important contribution to the success of her reproduction, and the female soma may therefore be less disposable than the male. The difference appears to be enough, in humans, to tip the balance between evolving menopause or not. As for the mechanisms through which the difference is produced, the sex hormones appear the likely culprits. High testosterone levels are associated with risk-taking and aggression in younger males, and with heart disease and prostate cancer in later life. Castration in males, as judged from data on domesticated animals, appears at least partially to equalise male and female longevity.

So sex and death are indeed deeply connected, if not quite in the way the poets thought. The longer life and shorter reproductive span of the human female point, I believe, to the superior biological usefulness of older women. Science is leading us to see new and crucial differences between the sexes - differences that take on a growing significance in the context of our longevity revolution.