f15 Mitosis, meiosis and mutations < diploid, haploid; Haldane >

> ... linguistic analysis cannot tell us how the [Asiatic] invaders treated the indigenous people. Remarkably, that detail of the ancient invasion is revealed in the DNA of Finnish boys alive today. The foreigners killed all the local men and settled down to have babies with the local women.
> —excerpted from Lee M. Silver's review of *The Autobiography of a Species*.[3]

> [The] now largely forgotten work on cytological genetics by Walter Sutton and Edmund B. Wilson ... established that different chromosomes carry different hereditary factors, yet occur in pairs that become separated during the formation of gametes in meiosis, giving essential physical support for Mendel's laws. —Jerry A. Coyne.[4]

François Jacob (1965-) quipped that "the dream of every cell is to become two cells."[5] Cell division (fission) was first described by Lazzaro Spallanzani (1729–1799).[6] In 1841 by Robert Remak (1815-1865) persuaded that every cell owes its existence to the division of a pre-existing cell.

Mitosis is cell body (***Footnote f15.1***) division that results in duplication.[7] A mutation will unavoidably (not so for meiosis, see below) be inherited, unless a mutation occurs for it, by duplicate descendants of a single-celled organism. In a cell nucleus, chromosomes exist decondensed (not individually visible) while in "interphase"[8] but condense (become highly compacted and visible as in familiar genome cut-out pictures of the 46 human mitotic chromosomes) when duplication of the chromosomes occurs and a fibrous network (mitotic spindle) dividingly pulls sister chromosomes, anchored to it by their centromeres, to opposite poles in preparation for mitosis.[9]

Meiosis (Gk. *meioun,* to diminish) is diploid germ cell division that results in haploid sex cells (sperm, egg). To begin, each chromosome in a cell is duplicated and a first meiotic division separates their lateral parts to produce *different* pairs of *identical* (homologous) haploid chromosomes each with a randomly assigned half share of the parent cell's genes (***Figure f15.1***). This could be the end of the process that produces haploid cells. However, what is found is that the chromosomes of each pair move together and come to lie side by side (process is known as synapsis). In this intimate association, by a mechanism so far unidentified, crossing-over sometimes occurs. It is to take advantage of this event that evolution has established a second meiotic division; thus a total of four *unidentical* haploid cells, each with a *different* single-stranded chromosome, can come to be.

Chance can cause alleles to be lost or passed on. These alleles may be ancestral or mutant (good, bad, or indifferent as regards the success of the individual). Mutation can occur in either parent germ cell as a legacy of its coming into being by mitosis, or at the time of meiosis, or at the time of zygote (initial somatic cell) formation. In multicellular organisms each individual cell divides to give rise to two lineages of cells: somatic cells that create and maintain our entire body and are doomed to extinction at death (a mercy that denies the corpus being as Struldbrugs immortals; imagined by Jonathan Swift persisting in decrepit senility), and germ cells that give rise to eggs or sperm that may foster a new generation.[10] In the laboratory, ionizing radiation and chemical treatments demonstrably can induce mutations. This must be true, also, in the natural world, but in a muted way.

Cyril Dean Darlington (1903-1981) in *Recent Advances in Cytology*, 1932,[11] clarified many basic biological issues and provided essential evidence for the evolutionary synthesis of the 1940s. In Rena Selya's words: "His description of the way chromosomes line up with their homologous copies before cell division settled a long-running debate among cytologists over whether chromosomes pair up end to end [no] or next to each other, and accounted for the phenomenon of crossing over [yes]."[12]

In 1947, J. B. S. Haldane (1892-1964) hypothesized that DNA-code copying mistakes during cell replication is a major source of mutations. A test for this would be to find higher mutation rates in males than in females as cell divisions over two months for each sperm's spermatogenesis number more than in oogenesis.[13]

Working strongly against mutations are in-cell sensors of DNA change. These are proteins of the MutS family (in eukaryotic cells detection and repair is by the "MSH2–MSH6 complex"). Mismatch errors in DNA recognized by this complex, and routinely corrected are:[14]

- mispaired bases that arise as a result of DNA-replication errors.
- mislocated similar chunks of chromosomes swapped for each other during recombination.

Also,

- when recombining chromosome segments are too dissimilar, recombination is prevented.
- when unreparable chemical damage in DNA is detected, cell-death pathways are activate.

In humans: from stem cells there are about 205 divisions, taking some two months, from roundish zygote (XY) in the testes to spermatogenesis (the product an elongated, tail whipping, spermatozoan) and 33 from zygote (XX) formation to oogenesis (the product an egg—all formed before birth in a female and no new are added later). Mutation rates derived from a study of sequences of genes on the X and Y chromosomes of mammals (exampled in studies of primates and rodents) are higher for males than females. However, while this datum is in keeping with Halden's hypothesis, it *does not* rule out a competing hypothesis that the difference in mutation rates exist because there is no machinery to ensure accurate replication of Y chromosomes. In mammals deleterious mutations in the Y chromosome, which the heterogamic XY males have, are recessive (unless they are sex determining genes) and natural selection cannot work to minimize them in the male line.[15] In birds, as in mammals, more somatic cell divisions lead to the male germ cell than to the female germ cell. However, in birds it is the males which have two identical sex chromosomes ZZ and females are heterogametic ZW. Thus the competing hypothesis to Haldan's *is* ruled out by confirming his prediction in the case of birds. This was achieved in 1997 by H. Ellegren and A. -K. Fridolfsson.[16]

Species of multicellular organisms evolve from mutations of germ cells that ultimately result in an offspring. In sexual replication, a female germ cell (an egg with surface microvilli to hold a sperm) and a male germ cell (a sperm with digestive enzymes, activated on contact, to enter the egg) form the initial cell (zygote) of an offspring. Asexual replication of a germ cell, male or female, produces a clone as offspring. (In 1903, H. J. Webber, a botanist who had examples from grafting, defined, without a nod to Philoponus (***Footnote f15.2***), a clone (Gk. *clonos*, twig) to be "any group of cells or organisms produced asexually from a single sexually produced ancestor." Of maternal twins, one is a clone of the original zygote.)[17]

In 1996, Ian Wilmut and Keith Campbell at the Roslin Institute in Scotland, cloned from the nucleus of an adult differentiated cell taken from the mammary tissue of a six year old ewe, Dolly (name inspired by singer/actress Dolly Parton's large endowment). This dispels forever (*if* the cell that was cloned was not inadvertently a stem cell, which review has shown it was not) the received opinion that although the genes to make any kind of cell are in every kind of cell, something will have happened to those genes that forever stops them and their descendants from programming any kind of cell other than the one they are. Thus if one were to clone the genes from a ewe's udder, one would get just that: an udder. And a whole new sheep? Certainly not. Dolly is an identical (monozygotic) twin of the original (except for its mitochondrial chromosomes). Similarly could a human be so cloned. For those who may tut-tut and ponder the day when the order might be "Beam several of me up Scotty," is the existing reality of Margaret Buckingham's sober remark: "a genocopy is not necessarily a phenocopy."

The methodology for embryo reconstruction of species (now successfully for sheep, cattle,[18] goats, pigs,[19] and mice[20] and, of these, clones of clones, and clones of the mother as, for example, the foal dubbed Promethea born in 2003 by its dam twin [21]) is: diploid donor nuclei transplanted into enucleated MII oocytes that are activated on, or after transfer. In the present state of somatic-cell cloning art, the receiving egg apparatus has but a few hours to remove all previous inhibitors to the

inserted DNA code, which before kept its expression to that say of a skin cell (hence anomalies are often in the product). The reconstructed embryos are then cultured, and selected embryos are transferred to surrogate recipients for development to individuals (***Comment f15.1***) on the way to term, and say Dolly, the successful of 277 starts.[22] Charles Siebert who made a pilgrimage to see Dolly writes: "The decidedly unspiritual nature of her immaculate conception notwithstanding, there is an aura of otherworldliness about Dolly [and] when her 12- to 14-year life span is complete [she was put down on 2003.02.14, suffering from a virus caused tumor on her lung],[23] into a kind of immortality: a taxidermist is to despatch Dolly to her own private diorama at the Museum of Scotland in Edinburgh." He found her with two of her not "headlined" naturally conceived and birthed lambs and asked if the scientists intended to name them. "We're not" was the reply. "It makes it easier to turn them out to pasture." [24]

Sexual reproduction does not guarantee the retention in a species of a mutation (as its fate under those circumstances will be a matter of happenstance, of natural selection, and, increasingly, of biotechnology for domesticated species and ourselves). Extinction of a species, with the reality of Dolly, is now a reversible option. The gaur (Indian bison) comes back! are headlines (though disappointingly the baby, called *Noah*, died of bacterial intestinal infection 48 hours after his birth to a normal cow in Illinois).[25] So will the Giant Panda return. And clones of the recently extinct Pyrenees bucado mountain goat (using normal goats to carry the embryos)[26] will live.

On their native Mediterranean islands of Sardinia, Corsica, and Cyprus, herds of rare wild mouflon sheep, *Ovis orientalis musimon*, are vanishing. In 2001, Pasqualino Loi and coworkers substituted nuclei from 23 cells of two dead mouflon ewes for nuclei in egg cells from a domestic sheep. Seven of these developed enough for transfer to surrogate domestic sheep mothers. The happy result—a mouflon lamb and first viable clone of an endangered species. ❑

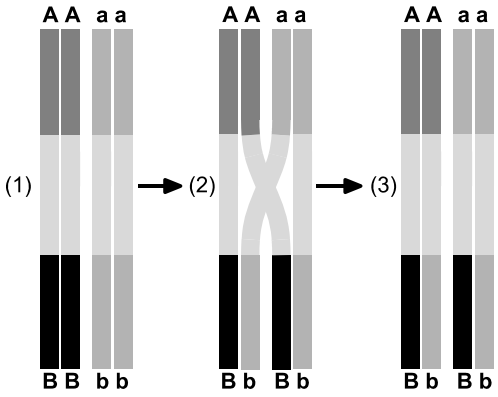

Figure f15.1 **Schematic model of crossing-over**
(1) The two homologous double-stranded chromosomes, one bearing alleles A and B and the other alleles a and b, lie side by side in synapsis.

(2) Portions of an AB chromatid and an ab chromatid exchange positions.

(3) After breakage of the crossed chromatids, the fragments fuse in the exchanged configuration, with the result that one chromatid of the first chromosome bears alleles A and b and one chromatid of the second chromosome bears alleles a and B.

Footnote f15.1 The autonomous and self-reproducing unit of eukaryotic life, has long been the *cell* (named for the cellulose walled-boxes, like monk "cells," that the microscope showed Hooke in cork bark in 1665, and by Nehemiah Grew in 1682, and, after long debate by cytologists, for the protein-membrane sacks containing cytoplasm in animals) but, as cell-to-cell channels and supracellularity refute the concept, better is *cell body* (originally proposed for animal cells by the Daniel Mazia in 1993) which is just the nucleus and a set of perinuclear radiating microtubules. The cell body pervades the whole interphase cell and condenses into a mitotic apparatus during mitosis. It represents the smallest autonomous and self-reproducing unit of eukaryotic life.[27]

Footnote f15.2 Joannes Philoponus, an Alexandrian philosopher of the sixth century CE, commenting on Aristotle's *On Animal Generation*, observed: "If someone cuts a twig from a walnut tree in Athens and plants it in [distant] Patras, two or three years later it will bear nuts that are the same in every aspect, in size and taste and color and every other character, with the ones from the walnut tree in Athens." Commenting on this, A. A. Diamandopoulos and P. C. Goudas, point out that "Philoponus probably used a walnut tree rather than, say, an olive tree, intentionally. The word *karyo* (nut) also meant 'testicle', then as now."[28]