ISSN 0006-2979, Biochemistry (Moscow), 2012, Vol. 77, No. 7, pp. 795-798. © Pleiades Publishing, Ltd., 2012.
Published in Russian in Biokhimiya, 2012, Vol. 77, No. 7, pp. 955-960.

REVIEW

Phenoptosis, Another Specialized Neologism, or the Mark of a Widespread Revolution?

G. Libertini

Independent researcher; E-mail: giacinto.libertini@tin.it

Received February 12, 2012
Revision received February 22, 2012

Abstract—The classical approach of evolutionism is based on the concept of the survival of the fittest individuals. More and more data indicate that natural selection often acts with supra-individual mechanisms favoring genes and actions harmful for the individual. The most striking type of cases is when an individual kills himself or his offspring by actions genetically determined or favored. The neologism "phenoptosis" describes these events and implicates that they are not evolutionary anomalies but physiological phenomena determined by natural selection. The most important and familiar kind of phenoptosis, the "slow phenoptosis" or aging, which is currently considered an inevitable and scarcely changeable event, is transformed by this different interpretation into a function, in principle modifiable and manageable. Perhaps, the neologism "phenoptosis" will represent, together with the term supra-individual selection, the mark of a vital enrichment of evolutionism, conceived in broader terms of which the individual selection is just a particular case, and will be referred to as the brand and the standard for the start of a new era.

DOI: 10.1134/S0006297912070139

Key words: phenoptosis, slow phenoptosis, apoptosis, aging, proapoptosis, supra-individual selection

In the classic formulation of Darwinism, evolution follows from the survival of the fittest to live and reproduce. It is clearly a concept based primarily on the selection at the individual level. But, from its initial conception, the idea of selection only at the individual level was impossible. In fact, reproduction necessarily requires actions involving two parents – or at least one in the cases of parthenogenesis – and one or more young, and even with only two individuals the selection is no longer about a single individual. As trivial example, a mother breast-feeding a child subtracts resources for herself to allow the survival of the child, and she should limit this loss of resources to increase her possibilities of survival and of future reproduction, while the child has opposite needs. A simplistic remedy is to consider the offspring as a genetic extension of the individual, which remains the object of selection, and the problem seems solved, albeit with some bias.

However, the situation quickly becomes much more complex, with quite disconcerting consequences, even for apparently very simple cases. Let us consider the black eagle (*Aquila verreauxii*) that can successfully breed only one chick at a time because the difficulties of finding food for two or more young would cause the death of all offspring. In a hasty assessment, the most logical action may seem – in evolutionary terms – to lay a single egg and provide the best of nutrition and survival for that single offspring only. On the contrary, the bird lays two eggs and one of them hatches before the other. The young that is born first kills its brother with blows to the face and body until it lies inert or dead, all without the mother trying to stop him in any way [1]. This behavior seems strange and unnecessarily cruel but has its own logic. The second egg has a backup function; it is used in cases where the first egg does not hatch or in cases where the first born is unable to offend or defend itself. The elimination of the other young of the brood is essential for the survival of the first. The apparent waste of resources and the cruelty of the action can be justified in evolutionary terms only by appealing to super-individual causes.

This case is not limited to black eagles or even to birds as a category: "Pandas routinely give birth to twins but nurse only one. The second is dropped to the ground and left to die. ... In a variety of predatory birds – pelicans, eagles, boobies, cranes – siblings play the role of executioner. Two eggs are laid, and they hatch at unusually long intervals for birds, several days apart. The first chick to hatch gains an immediate size and strength advantage over its younger sibling. When the second chick hatches, it faces an unrelenting assault from its brother or

sister that ends only when one, almost always the younger, dies" [2]. In sand tiger sharks, the first to hatch in the maternal uterus searches for and kills all its own brothers and sisters [3].

Our species is also strongly involved in this type of phenomena.

At menarche, it is estimated that a woman has 300,000 egg cells, or oocytes. Each month, a group of oocytes is stimulated by a follicle-stimulating hormone, but the egg cell that first reaches a certain dimension eliminates all other oocytes by biochemically inducing their suicide by apoptosis. Furthermore, in the early stages of embryo formation, only those fertilized eggs without genetic defects are allowed to implant in the womb. In other words, there are many early abortions, which are generally not recognized as such. In the next weeks, many fetuses are eliminated because they are somehow defective, or even simply because they are one of a couple of twins: "Multiple births are rare in humans, but multiple conceptions are not. As many as one in every eight pregnancies begins as twin conceptions, though few survive intact to birth; twins constitute only one in every 80 to 100 live births ..." [2].

Other fetuses are eliminated because they have scarce antigen variability and this reduces the resistance to infective diseases [4]. Evidence of this phenomenon ("cryptic female choice" [5]) was well documented in an isolated community [6-8].

After birth, the killing of the offspring continues. In the study of 60 primitive societies, 112 circumstances (not single cases!) in which newborns were habitually killed were reported. There were various motivations for these killings, including inadequate parental resources (40), deformed or ill newborns (21), or the birth of twins (14) [9].

This series of phenomena is just one of many categories of events for which the selection conceived in individual terms is clearly inadequate. In fact, the countless forms of grouping and social behavior at all levels and types, and in particular the so-called eusociality of many species of ants, bees, and termites, are utterly inexplicable without using mechanisms of supra-individual selection. In many cases, to explain these phenomena one has to appeal to group-level- or even species-level-benefits. These arguments were challenged in general [10, 11], but a new model was formulated that solved many of these difficulties and seemed to give a conclusive answer.

This new theory, "kin selection" [12-14], no longer regarded the individual as the central point of the selection but the gene. From this perspective, the researcher must consider the fact that a gene is present both in the individual where it acts and in related individuals upon which its actions have an impact. The advantages and disadvantages for all these individuals must be taken into account when assessing whether or not a gene is favored by natural selection.

Kin selection is a powerful explanatory tool, and it can shed light on many behaviors with relative ease. For this reason, it is considered to be the theory that founded sociobiology, and for a time it was considered the key to explaining the eusociality observed in many species of insects (bees and ants, in particular) [15, 16].

However, justifying insect eusociality by appealing to haplodiploidy – as kin selection does – has since been disputed. This is because many non-haplodiploid species (e.g. termites) are eusocial and the association between eusociality and haplodiploidy does not seem statistically significant. Moreover, models of population structure appear to be a better approach to justify and study eusociality [17].

Besides, kin selection for demes in competition composed by one or few clones in fact is group selection. Thus kin selection cannot always be considered an alternative to the taboo of group selection.

There are other hypotheses, models, or types of mathematical approach that have also been proposed to account for supra-individual selection (e.g. selective mechanisms that increase the rate and the possibilities of evolution, or evolvability [18, 19]).

All these considerations are not at all a careful and accurate description of the theoretical debate that is about the analysis of evolutionary mechanisms regarding supra-individual selection. Their aim is simply to highlight that evolutionism has been gradually transformed from an evaluation of selective mechanisms formulated exclusively, or primarily, in terms of individual selection, into a more extensive supra-individual evaluation, of which the strictly individual level of selection is only a special case.

As part of this transformation, a very important fact was missing and, vice versa, the consequent inclusion of this fact in a much broader context was lacking.

It is well known that many species of animals and plants have a lifespan that is strictly and clearly planned. In his authoritative textbook, Finch dedicated a whole long chapter to these species [20]. The fact that for many species the death of individuals is genetically programmed and favored by natural selection is therefore nothing new. But, it is also well known that for many species, including our own, there is from a certain age (30 years for our species), a time-related gradual decline of fitness, that is an age-related increase in mortality rate. The current opinion is that this phenomenon is the result of weak selection at ages in which few individuals survive, or alternatively of selection of characters that are advantageous at young ages but harmful at older ages. Overall, the current view is therefore that this age-related increasing mortality is a phenomenon caused by unavoidable factors, which are either not directly favored by selection or insufficiently opposed by it. However, there are a number of lines of evidence against these mainstream views – evidence, which suggests that the

phenomenon is planned and directly favored by selection. This evidence includes:

1) The existence of many species in which the phenomenon does not exist and there is equal fitness at any age [21, 22], species defined as having "negligible senescence" [20], or even an age-related increase of fitness, called "negative senescence" [23]. This is not explained by current theories.

2) According to the current view, there should be a positive correlation between high environmental (or extrinsic) mortality and intrinsic mortality, but empirical data show that the correlation is inverse [24], as it should be if the phenomenon was programmed and favored by selection [25, 26]. Not one of the supporters of current theories has ever attempted to explain this contradiction, or even admitted that a problem exists.

3) The interpretation of the phenomenon as something programmed necessarily requires the existence of specific mechanisms, genetically determined and regulated, which leads to the fitness decline. Conversely, if the phenomenon is not programmed, the existence of aging-causing mechanisms is not expected and indeed they would be in total conflict with this interpretation [26]. In regard to these mechanisms, there is increasing documentation and awareness that the decline of physical functions is determined by limitations in cell turnover, which in turn are controlled by the telomere–telomerase system and by the progressive activation of a specific on/off program defined as cell senescence [27]. In particular, cell senescence, which has been considered a "fundamental cellular program" [28], is reversed to the off state, with the return to youthful conditions and the reactivation of duplication capacities, by telomerase introduction in somatic cells [29-32]. Moreover, telomerase reactivation in aged mice with artificially blocked telomerase shows a marked reversal of all degenerative manifestations, even for the nervous system [33]. These results are hardly justifiable in keeping with the non-programmed hypotheses of senescence: the justification of the telomere–telomerase system as a general defense against cancer, the only proposed explanation, is weak and contradicted by empirical data and theoretical arguments [26, 34].

4) Moreover, the current evolutionary interpretations of aging (specifically, antagonistic pleiotropy and disposable soma hypotheses) are based on the assumption that the beneficial effect of a longer life span cannot be obtained without incurring a cost [35]. But, this should be proven. Currently the evidence in support of this assumption is not only lacking, but there is clear evidence against it in particular important cases. For example, a) there is a clash between the predictions of disposable soma theory and the association of caloric restriction with a greater longevity [36]; b) there is the possibility of evolving "both a long life and alternative anti-cancer defenses" [34].

To mark (and emphasize) the idea that individuals are sacrificed by supra-individual selective mechanisms, the neologism "phenoptosis" was coined [37].

Strangely, no one before Skulachev – who is not an evolutionary biologist – had thought to unify under a single term phenomena very different from each other in the mechanisms and expressions but firmly united by a common and well-known evolutionary logic: the individual is completely expendable if supra-individual selective mechanisms require this.

With the same logic, the age-related growth of mortality in species such as ours has been defined as "slow phenoptosis", a beautiful expression coined by the same Scholar [38, 39], marking the evolutionary analogy with many other forms of phenoptosis that are entirely different in their specific causes and mechanisms.

The analogy between the terms phenoptosis and apoptosis (the word which inspired the neologism) is not just semantics. By considering a multicellular organism as an immense clone highly organized and differentiated (and it should be noted that the first multicellular organisms derived from clones that have gradually acquired an increasing cellular specialization and organization), the apoptosis of a cell in a multicellular organism is phylogenetically similar to the phenoptosis of an individual within a clone.

Moreover, if we consider that bacterial proapoptosis [40], sometimes expressed in the form of mass suicide [41] and modulated by mechanisms clearly phylogenetically related to apoptosis in unicellular eukaryotes [42], which also show forms of single [43] and mass suicide [44], the underground ties and the analogies among bacterial proapoptosis (alias phenoptosis in these unicellular organisms), apoptosis of single-cell eukaryotes (alias phenoptosis in this case too), apoptosis in multicellular organisms, and phenoptosis of multicellular organisms, become even more evident.

How is it possible to mark with symbolic words the distinction between an idea of evolution focused on the individual and a different conception based mainly on mechanisms of supra-individual selection (and of which the individual selection is only a special case)?

The term "kin selection" is too restrictive and only indicates a method, although very important, of analysis of supra-individual selection. The expression "selfish gene" has too much of the flavor of a selection based on the single gene, rather than the single individual, and does not reflect well the assumed central importance of the supra-individual selection.

Perhaps, there are two words that best interpret the new concept in the distinction from the old idea. The first is the expression "supra-individual selection" that describes a category of tools of analysis and evaluation (here not precisely defined) in contrast to the oversimplified view of the first conception. The second is the very expression "phenoptosis", both because it pinpoints the

sacrifice of the individuals as a pivotal characteristic of evolution, and because it places in the center a particular category of phenoptosis, the slow phenoptosis, indicating too that, being a genetically programmed and regulated function, it is also open to modifications and control.

In a more general framework, in particular outside the scientific world, the transition from methodologies focused on individual selection to others focused on supra-individual selection does not appear capable of arousing noteworthy attention. But, if we consider that this step involves the transformation from the concept that aging is an inevitable and scarcely changeable event to a new outlook for which aging is a function, in principle modifiable and manageable, this will certainly be object of the greatest interest.

For these reasons, the neologism "phenoptosis", to which the name of this journal has been dedicated, is not just another technical term to use in a small circle of specialist scholars, but potentially a term to be referred to as the brand and the standard for the start of a new era.

REFERENCES

1. Gargett, V. (1990) *The Black Eagle*, Acorn Books, Randburg.
2. Forbes, S. (2005) *A Natural History of Families*, Princeton University Press, Princeton-Oxford.
3. Gilmore, R. J., Dodrill, J. W., and Linley, P. A. (1983) *Fishery Bull.*, **81**, 201-225.
4. Apanius, V., Penn, D., Slev, P. R., Ruff, L. R., and Potts, W. K. (1997) *Crit. Rev. Immunol.*, **17**, 179-224.
5. Loisel, D. A., Alberts, S. C., and Ober, C. (2008) in *Evolution in Health and Disease* (2nd Edn.) (Stearns, S. C., and Koella, J. C., eds.) Oxford University Press, Oxford, pp. 95-108.
6. Ober, C. (1992) *Exp. Clin. Immunogenet.*, **9**, 1-14.
7. Ober, C., and van der Ven, K. (1997) *Curr. Top. Microbiol. Immunol.*, **222**, 1-23.
8. Ober, C., Hyslop, T., Elias, S., Weitkamp, L. R., and Hauck, W. W. (1998) *Hum. Reprod.*, **13**, 33-38.
9. Hausfater, G., and Hrdy, S. B. (1984) *Infanticide: Comparative and Evolutionary Perspectives*, Aldine, New York.
10. Maynard Smith, J. (1964) *Nature*, **201**, 1145-1147.
11. Maynard Smith, J. (1976) *Quart. Rev. Biol.*, **51**, 277-283.
12. Hamilton, W. D. (1964) *J. Theor. Biol.*, **7**, 1-52.
13. Hamilton, W. D. (1970) *Nature*, **228**, 1218-1220.
14. Trivers, R. L. (1971) *Quart. Rev. Biol.*, **46**, 35-57.
15. Wilson, E. O. (1975) *Sociobiology, The New Synthesis*, Harvard University Press, Cambridge.
16. Trivers, R. L., and Hare, H. (1976) *Science*, **191**, 249-263.
17. Nowak, A. M., Tarnita, C. E., and Wilson, E. O. (2010) *Nature*, **466**, 1057-1062.
18. Earl, D. J., and Deem, M. W. (2004) *Proc. Natl. Acad. Sci. USA*, **101**, 11531-11536.
19. Colegrave, N., and Collins, S. (2008) *Heredity*, **100**, 464-470.
20. Finch, C. E. (1990) *Longevity, Senescence, and the Genome*, The University of Chicago Press, Chicago-London.
21. Comfort, A. (1979) *The Biology of Senescence* (3rd Edn.) Churchill Livingstone, Edinburgh-London.
22. Congdon, J. D., Nagle, R. D., Kinney, O. M., van Loben Sels, R. C., Quinter, T., and Tinkle, D. W. (2003) *Exp. Gerontol.*, **38**, 765-772.
23. Vaupel, J. W., Baudisch, A., Dolling, M., Roach, D. A., and Gampe, J. (2004) *Theor. Popul. Biol.*, **65**, 339-351.
24. Ricklefs, R. E. (1998) *Am. Nat.*, **152**, 24-44.
25. Libertini, G. (1988) *J. Theor. Biol.*, **132**, 145-162.
26. Libertini, G. (2008) *TheScientificWorld J.*, **8**, 183-193.
27. Fossel, M. B. (2004) *Cells, Aging and Human Disease*, Oxford University Press, New York.
28. Ben-Porath, I., and Weinberg, R. (2005) *Int. J. Biochem. Cell. Biol.*, **37**, 971-976.
29. Bodnar, A. G., Ouellette, M., Frolkis, M., Holt, S. E., Chiu, C., Morin, G. B., Harley, C. B., Shay, J. W., Lichsteiner, S., and Wright, W. E. (1998) *Science*, **279**, 349-352.
30. Counter, C. M., Hahn, W. C., Wei, W., Caddle, S. D., Beijersbergen, R. L., Lansdorp, P. M., Sedivy, J. M., and Weinberg, R. A. (1998) *Proc. Natl. Acad. Sci. USA*, **95**, 14723-14728.
31. Vaziri, H., and Benchimol, S. (1998) *Curr. Biol.*, **8**, 279-282.
32. De Lange, T., and Jacks, T. (1999) *Cell*, **98**, 273-275.
33. Jaskelioff, M., Muller, F. L., Paik, J. H., Thomas, E., Jiang, S., Adams, A. C., Sahin, E., Kost-Alimova, M., Protopopov, A., Cadinanos, J., Horner, J. W., Maratos-Flier, E., and Depinho, R. A. (2011) *Nature*, **469**, 102-106.
34. Milewski, L. A. (2010) *Biosci. Horizons*, **3**, 77-84.
35. Goldsmith, T. (2008) *Rejuvenation Res.*, **11**, 847-848.
36. Mitteldorf, J. (2001) *Evolution*, **55**, 1902-1905.
37. Skulachev, V. P. (1999) *Biochemistry (Moscow)*, **64**, 1418-1426.
38. Skulachev, V. P. (2002) *Ann. N. Y. Acad. Sci.*, **959**, 214-237.
39. Skulachev, V. P. (2010) *The Talk at the "From Homo sapiens to Homo sapiens liberatus" Workshop*, May, 26, 2010, Moscow.
40. Hochman, A. (1997) *Crit. Rev. Microbiol.*, **23**, 207-214.
41. Lane, N. (2008) *Nature*, **453**, 583-585.
42. Koonin, E. V., and Aravind, L. (2002) *Cell Death Differ.*, **9**, 394-404.
43. Buttner, S., Eisenberg, T., Herker, E., Carmona-Gutierrez, D., Kroemer, G., and Madeo, F. (2006) *J. Cell Biol.*, **175**, 521-525.
44. Granot, D., Levine, A., and Dor-Hefetz, E. (2003) *FEMS Yeast Res.*, **4**, 7-13.