AFTER THE NEW "YEAR OF DARWIN"

Luigi Rossini* and Paola Rossini°

*Farmacologia Neuroscienze, Sezione di Farmacotossicologia umana-Centro Interuniversitario I.M.O., Servizio di Farmacologia e Tossicologia Clinica, UPM and Azienda Ospedali Riuniti di Ancona, Via Tronto 10 A, 60129 Ancona Torrette, and °Psichiatria, Ospedale S. Giacomo, ASL 22, 15067 Novi Ligure

Summary

Perusal of the papers on Charles R. Darwin's *Origin of Species* published in 2009 by the American Association for the Advancement of Science in Science Magazine and in News Focus, the celebrations by the Members of the New York Academy of Sciences and by the National Geographic, and the challenges of the enigmatic 19th century scientist suggest some considerations on his errors, which may be related to what he ignored, or is sustained by the partisan incompetence of hyper-evolutionsts and critics. So, let us simply continue to study, and do fundamentally associated, basically independent, evolutionary and developmental research in genetics, molecular biology, biomedical and social sciences. Celebrating Darwin, let us say: "Darwin is dead. Long live evolution!".

Key words: Origins; Evolution; Darwin' Year 2009

---

* Corresponding author, retired October 31, 2008. Manuscript Completed January 31, 2010. References listed in inverse temporal order. Books, full papers and "journal papers" of all References available from the authors' archives, tel +39 071 31920, fax +39 071 31900; e mail rossiniluigi@hotmail.it

"Uniformity, reproducibility – this is the obliged ground of science, what is unrepeatable in death has been sought by poets, non physicians". Varlam Šalamov, Cherry-Brandy, I racconti della Kolyma (1978-1992). Gli Adelphi 153, 1999-2009, p 70. Adelphi Ed. SpA Milano, 1995.

"Einstein, don't tell God what to do". Niels Bohr, replying in a letter to Albert Einstein, 1926.

While according to Science Magazine the breakthrough of 2008 was cell reprogramming [1], for the Editorial of the American Academy for the Advancement of Sciences (AAAS) [2] the breakthrough of 2009 was *Ardipithecus ramidus*, a 4.4-million-year-old female African found in 1994, held to be the oldest direct ancestor of man since Lucy was discovered (for modern out of Africa hominids, see [3]). In 2008 "Defining Species" was of course a promising section [4]. Nevertheless the same year—the "Year of Darwin"—a new AAAS Editorial, "Species uncertainties" [5], stated that "You cannot even begin to make sense of biodiversity until you have some systematic sense of what is actually there". In the same issue the special section, "Speciation", presented contrasting reviews and papers [6]. Therefore the 2008 "Global perspective on Science and Technology" [7], and the 2008 and 2009 Editorials "Making one world of Science", "A celebration and a challenge", "On incentives for innovation", and "Harmonizing global science" [8], continue to promote the development of a better approach, to be worked out effectively.

Our 2009 paper [9] made reference to the bicentennial of Charles R. Darwin's birth (12 February, 1809) and to the 150th anniversary of the publishing of his best known work [10] on 22 November 1859. It also offered some modest proposals that are updated herein. One of the most prolific and quoted scientists ever, Darwin would have been recognized as an outstanding researcher "even if he had never written a word about evolution" (Ernst Mayr and John Haldane, cited in [11], p 23), for instance for his contribution to experimental botany. Darwin has also been celebrated in Italy, sometimes causing public protests similar to those caused by Galileo Galilei, who has been considered by some authors as the most prominent Italian literary personality (Italo Calvino, cited in [12], XII, p 99, ff). Here we review at least some of Darwin's universal contributions, which will continue to inspire the scientific community, within the boundaries of our current critical knowledge, which albeit seemingly acquired, is however never certain to remain such in the course of the evolution of human populations and was certainly unknown to the great Charles R. Darwin. Finally, we intend to make some observations and general considerations, which we hope to be at least temporarily conclusive, on the research in biomedical neuropsychiatric pharmacology.

1. Charles R. Darwin, the Man and the "Origin of Species"

Charles R. Darwin started his voyage on the "Beagle" on 27 December 1831 aged 22 years, after failing to complete a medical degree in Edinburgh and taking a theology degree in Cambridge, to return on 2nd October 1836 with 5436 specimens. He began writing, besides the fabulous Notebooks, the numerous and seminal publications on which he worked until his death in 1882, in

his country house in Down (Kent), where he had moved in 1842 with his cousin Emma Wedgwood, married in 1839. They had 10 children, seven of whom survived adolescence. Already in September 1832, in Bahia Blanca, Monte Hermoso and Punta Aka (Northwest Argentina) he collected fossils and described armadillos, giant and otherwise (glyptodonts), ancients rodents and giant earthbound birds (of the genus *Rhea*, which he mistook for ostrich) in the *pampa* and, later, in Patagonia. These, as he wrote towards the end of his life in the private memoirs written for his family [13], he considered as facts among the most interesting for the foundation of his theory of evolution through natural selection, which was eventually confirmed in the 1940s through the advancement of genetics. He incessantly applied to these studies his "love of science, unbounded patience in long reflecting over any subject, industry in collecting and observing facts, and a fair share of invention as well as of common sense", intense curiosity, undoubted caution, exceptional observation and classification powers and intuitive instinct of all the connections that are possible in nature. His powers were aided and sustained by his knowledge of the Principles of Geology of Charles Lyell, a theorist of Actualism, and of his more expert botanical friends, like Joseph Dalton Hooker (Cf. [14]) and the same Reverend John Stevens Henslow (formerly his mentor in Cambridge), the anatomist Richard Owen and the ornithologist John Gould. He was certainly also helped in 1838, by Thomas Malthus' *An essay on the principle of population*, which was to be illuminating for his contemporary and antagonist Alfred R. Wallace. It was *On the Tendency of Varieties to Depart Indefinitely from the Original Type*, written by Wallace in February 1858, received by Darwin on 18 June 1858, and read at the London meeting of the Linnaean Society in July of the same year, that prompted Darwin to prepare a definitive, concise draft of The *Origin of Species*, initially entitled *An Abstract of an Essay on the Origin of Species and Varieties Through Natural Selection*, which at the time of the first edition of November 1859 the publisher convinced him to change into the title we know [10]. "The man who wasn't Darwin" [15] also arrived independently at the solution of adaptation, the third major ingredient of the theory of evolution after variation and selection, rediscovering Aristotle's intuition in the process (Cf. again [11], p 43). The theory of clustering in time and space, of relatedness and succession (subsequently transmutation) among closely allied species, interbreeding individuals, and populations that gradually change for exclusively natural reasons, was undoubtedly more economically inductive and persuasive than the fixed, unchanging scenario of contemporary creationists, who even rejected the notion of intelligent progress (which they later supported as an alternative). Darwin however kept his theory secret for at least 26 years, something that should never be forgotten, together with the standardization of the research method and its necessary control (Cf. [17]) by whoever accepts the consistently heavy responsibility of the judge and of the possibility of hampering its potential, also subjected to economic conditions.

With reference to the less lucky Wallace, it should also be noted that the title of his cited essay explicitly mentions the endless, gradual changes made possible by the adaptation of varieties to ever newer natural contexts. Darwin replied to him that he had reached the same conclusion considering (since 1830) the artificial selection effects exerted by domestication and rearing procedures of domesticated animals (besides his botanical experiments). Darwin was therefore an epidemiologist as well as an experimenter and analyst, whereas Wallace was merely an epidemiologist, explorer and bio-geographer, who eventually distanced himself from Darwin. The overwhelming evidence for [17] and originality of Darwin's theory, accepted today without any residual criticism [18], was incompatible with the neo-Lamarckism of phyletic senility of Edward Drinker Cope and Alphaeus

Hyatt, who followed the creationist theory of the parallel lines of descent expounded in Robert Chamber's *Vestiges of the Natural History of Creation* (1844) and shared Ernst Haeckel's belief that ontogenesis is a brief recapitulation of phylogenesis. Their stances were also incompatible with Spenser's "social Darwinism" and later with the eugenetic programmes studied by Francis Galton, risks of political implications and moral abuses that cannot be separated or avoided in any scientific development, not only where ultra-Darwinism may appear to have overridden the same "Year of Darwin" (Cf. "Darwin is dead-long live evolution" [19]).

After stating the respective qualities of the two authors, it is useful to note the common but distorted interpretation of Darwin's' *Transmutation Notebook D* of 1830 advanced independently by Wallace in 1855, where the tree of life is read in both directions, or towards a single point of origin, like towards irregular indefinite, indeterminate branches, never predetermined or predictable. Significantly, Darwin seems to have never interrupted his friendship with Hooker, nor did they ever lose their mutual respect. Hooker, to give an order (see again [14]) to the ideas of the dean's appreciated cultural revolution, which he shared, achieved the firm conviction that no interference in the scientific tests of the research under way should be accepted. According to this notion, both would therefore, for instance, be enthusiastic of and grateful for the possibilities—offered first of all by the mathematical techniques and the current technologies of IT biosystematics—to extend and further detail the dynamic classification, random or otherwise, of variants and new speciation events beyond the original conception, then necessarily raw and schematic and certainly unsatisfactory, of the theory of evolution, unravelling a scroll of the open-ended struggle for existence by a selfish nature depicted by the divergent transmutation tree. In fact, the celebrated narrator and pioneer spoke since then to the broadest audience, disclosing by guesswork a number of mechanisms and processes without being aware of how changes took place, i.e. without knowing genetics. Also at the primitive epidemiological and analytical level of his investigations, he certainly could not make use of the model theories of the connections of the networks in the same social and economic conditions, which are capable of detecting both individual patterns and group behaviours (Cf. [20]), even when the physics of infinity is reduced by the possible transformation of variables (Cf. [21]), where the same RNA computing in a living cell may program cell behaviour [22]. Spatial cell biology, Special Section [23] up to the studies of microcompartmentalization functions in bacteria [24] stress the current difficulties met with in defining intracellular spatial locations, which are as significant as the geographic and ecological locations with regard to the temporal adaptations of variants, races and species of living populations. These issues have so far been addressed only partially and have not been satisfactorily resolved in the same pharmaco-toxicological kinetics and dynamics [25], at a time when we have just become aware of the flow velocities of evolution in action at the level of gene mutations, spontaneous and typically induced (in complete genome sequences of *Arabidopsis thaliana*), which have been found to exhibit a different spatial concentration and to be related to equally differentiated polymorphisms [26]. It is well known that the degree of variability is artificially enhanced by artificial domestication. However part of the variation in wild selection in nature is indirect, apparently purposeless, with a variability that to some extent is indefinite, maybe equivalent, as applied in the same ongoing classification of speciation by adaptive radiation. Well, here, too, there are recognized disagreements regarding the genesis of the same varieties, related to ecological and genetic factors that are also morphologically and functionally developmentally contingent. Therefore, in most cases, more data are needed [6,

27], and species uncertainties persists, since the way we classify is ultimately a product of why we classify (See again [14]). Also, more data are needed since the integration of Mendelian genetics into evolutionary biology. Most of the work appears to be still to be done; since genes appear unequal in evolution, evolutionarily relevant mutations tend to accumulate in hotspots in specific positions, and conserved sequences are not sufficiently explicative at the level of species, individuals, and tissue cells. Therefore imperfect understanding of gene functions, the structure of genetic networks, and population biology complexities still make genetic evolution largely unpredictable [6, 28]. Speciation often involves the evolution of incompatible gene interactions that cause sterility or lethality in hybrids [29]; completely regulatory variant repertoires can only be uncovered in the context of cell-type specificity [30]; apparent evolutionary steps can come about because of several little mutations in the enhancers upstream—as for *ebony* gene in *Drosophila melanogaster* and *Pitx1* gene in multiple populations of freshwater sticklebacks, *Gasterosteus aculeatus*—so that even these adaptive mutations can exist unnoticed in a population [31]. Differences in regulatory DNA sequences drive species-specific gene expression; nevertheless the universal regulatory code under the same ENCODE model study may be the sole hope to achieve a full clarification [27, 32]. Reik's epigenetic epimutations may challenge Mendel and Darwin beyond the book of life [33], and eventually reach a final frontier [34], the case of the midwife toad, and Paul Kammerer's suicide may be only the last to day clarification as histone methylation, acetylation, etc, and the regulation turnovers and cross-talks [27, 35] finally discovered: A stochastic single-molecule event can after all determine a cell's phenotype [36].

Given these premises it is important to stress the recent contribution of natural science philosophy, which can make it more effective also in the classification aspects of evolutionary interest, not simply borderline, alternative to the current paradigm of current hypotheses and/or theoretical models and based on IT and decision games, directed at refining them by increasing their precision and/or accuracy, thus improving their predictive value [37]. Exactly the line supported for pre- and post-marketing pharmacovigilance [38]: application of the principles of systems analysis, planning and implementing first of all an exhaustive data collection to analyse in view of maximum density the (automatic) generation of the most significant optimized potential conclusions. With reference to evolution and development ("evo-devo") genomics, data exhaustiveness is no longer sufficient to identify a list of candidate genes for evolutionary adaptation. Each study needs integration with a functional approach, namely to achieve advances in genomic ecology by integrating the "omics" techniques and traditional environmental and climatic ecology investigations, to define adequately adaptation events and potential speciation mechanisms [39]. This is what has immediately appeared necessary, first of all in optimizing research financing procedures, no longer ignoring the same poor significance and misleading concept of the impact factors [33, 40].

2. Science Magazine's Tribute to the "Origin of Species"

Science's twelfth Newsfocus monthly series in the year of Darwin, with more on evolutionary roots at **blogs.sciencemag.org/origins** and **www.sciencemag.org/multimedia/podcast**, starts with (I, [41]) the few words devoted by Darwin to the origin of life on earth as it was conceived then, which do not explicitly comment on the possibilities of its replication also at different times and in

different places, as some would like, from prebiotic precursors such as N_2, CO_2, RNA, amino acids, etc (Stanley Miller, 1953; Henderson James Cleaves, 2008). While DNA-based microbes have been found alive after more than 3.5 billion years, Tracey Lincoln and Gerald Joyce described double-strand RNA (in beakers), and Jack Szostak and colleagues described autosynthestic membranes in trapped vesicles obtained by repeated application of heat treatment cycles (2009). In addition, it seems possible to produce proto-cells artificially, and even more complex self-generating and self-organizing structures are being developed [42]. At first photosynthesis does not generate oxygen, later it becomes oxygenic and is considered among the earliest evolutionary milestones, arisen from 3.8 to 2.7 billion years ago (III, [43]). Gymnosperms dating from 200 million years ago (mya), and rapidly diffusing angiosperms between 120 and 70 mya have been studied by the Floral Genome Project (IV, [44]). Their flowering (in *Arabidopsis* the major repressor flowering locus gene *FLC* [45]) is, among other factors, epigenetically backwards regulated by antisense RNA transcripts, and histone demethylation. More recent and even more controversial is Darwin's theory of the gradual selective advantage, multiple and variously co-opted by the adaptive immune system (V, [46, 47]), at least until the definition of clonal selection according to Frank Macfarland Burnet (where antibody selection is predated by an enormous accumulation of mutations) and the identification of transposon and toll-like receptors systems. The recent proteomics and transcriptomics reports on the functional relations of *Mycoplasma pneumoniae*, from the complete genome, also regulatory reduced to 816 kb, are surprising for the complexity of the metabolic control, considered as already acquired and required for the survival of the more evolved bacteria, if not for the eukaryotes dating back to 3, 4 or 5 billion years ago, endosymbionts of mitosomes and of the same mitochondria, already endowed with ribosomes shared by the domain of *Archeae*, exchanges that occurred up to 2.5 billion years ago. The history of eukaryotes is consistent with the fusion of species by mosaic acquisition of the same nuclear genes from bacteria, *Eocytes* and *Archeae*, which makes the reconstruction of their gene exchange events—one of the 10 greatest inventions of evolution, since it obviated competition with ecological nutrients through simply feeding off the opponents—at the basis of the current evo-devo scientific knowledge extremely difficult and elusive, if at all possible ([48]; VIII, [49]). The aggregation of eukaryotic cells has led to the selection of the nervous system, first diffuse and later central, distinctly different in modern animal. Darwin began the description of its functional evolution over the last 600 m years as new methods that allowed its analysis were introduced. It remains controversial when and where the tree of life, once arisen, subsequently branched, since the theory did not adhere also for this trait/system to a random fractal onto-phylogenetic model, or otherwise, which has been mentioned in the previous Section. In any case, it is significant that here, too, genomics has already in 2007 led to the identification in the sea sponge *Amphimedon queenslandica* of genes of sets of proteins typical of the neuronal synaptic membrane and of neurotransmitter receptors, while electron microscopy and other neurochemical techniques have failed to identify them, confirming the continuing inadequacy of functional recognition, which is typical of the traditional concept of adaptive struggle. A number of other findings at the end of the report lend support to a range of possibilities, overlapping or parallel, found in the morphological and functional history of the radiation of the nervous system in the various Darwinian populations (VII, [50]).

An issue that elicits consistent interest, not only Darwin's, is sexual reproduction, whose "how" is well known but whose "why" is still unclear. Gender, which arose in a common eukaryote ancestor

2 billion years ago as duplication of the female haploid genome, seems to have been preceded in certain asexual forms, which can contain activated sex genes, as demonstrated in yeast and in plants, that are expressed only at times of distress or of natural selection pressure. The hypothesis, named The Red Queen after Lewis Carroll' *Through the looking-glass*, envisages for sexual and asexual forms prolonged cycles of advantage, disadvantage and stasis typical of host-parasite co-evolution, models of laws according to Lotka and Volterra. Darwin, who considered speciation, i.e. the arising of populations of individuals capable of producing viable offspring, the deepest of mysteries never knew that the natural, not causal, selective adaptive model of isolation in niches or ecological barriers, leading with time to genetic incompatibility, in some cases exists together with the sexual model, although this has been abandoned by Ernst Mayr and Theodosius Dobzhansky (VI, [51]; [52]). Only in 1900 did Hugo de Vries, Carl Correns and Erich von Tschermak rediscover the laws of heredity described by Gregor Mendel in a Moravian journal in 1866—snubbed by scientists to whom he had sent his studies and unknown to Darwin—where he identified the genes as the discrete units composing the essential reproductive evolutionary heritage, thus focusing the analysis of heredity on the basic structural and later molecular mechanisms identified in 1953 by the 1962 Nobel prize winners, Francis Crick, James Watson and Maurice Wilkins, not to mention Rosalind Franklin. Successive cycles of predation and competition among species and of stress exerted by ecological and sexual factors, as well as by immigration and emigration, which on a sufficiently large scale result in imbalances that go against the laws of genetics according to Godfrey Hardy and Wilhelm Weinberg (1908), which are respected when mitotic couplings are no longer equally probable. In turn, observation of the physical underpinnings of the species dynamics described by Alexander Humboldt in 1802 for the plants growing on the Andes on Monte Chimborazo, on Monte Bianco and on the Sulitelma mountain range have preceded the experiments conducted by Darwin in the gardens of Down House a half-century later, up to the synthesis proposed by Stephen Hubbell (1997), who encompasses random and not mutually exclusive speciation, interactions, extinction and dispersion into the unified neutral theory of biodiversity, the more general definition of current ecological structure dynamics (X, [53]). Nevertheless, the large number of variables involved, ranging from the transient niches of stem cells (intestinal, in *Drosophila*) to the stepwise modification of a modular population (*ebony* locus, again in *Drosophila*), the bacterial community variations making sense of genetic and ecological diversities, also in human body habitats, the mapping of human genetic diversity in Asia, the study of the molecular bases of size differences, the evidence for sequential sympatric construction of new niche cascades throughout trophic levels move, mutational- and ecological-order speciations, make predicting what will happen difficult [53, 54]. *Surprising results come from enough long-term experiments* [55], *needs for larger, more detailed data sets and more refined models than previously available, even in response to climate changes combined with habitat fragmentations, particularly avoiding the problems often encountered in trying to scale up results from small local-scale studies* [56]*, and highly variable spread rates in replicated biological invasions as classic screening approaches providing parts lists of the essential components of signaling networks, not indeed providing complete insights into the hierarchical and functional existing interrelations* [57]*, still pose fundamental limitations to predictability* [58], *imposing renewed caution in drawing conclusions that however are merely potential.*

A new, though quite ancient factor having significant implications for humans (clearly also for statesmen [59]?), co-operation (IX, [60]) is an apparently contradictory "adaptation" (Cf. p 3) encompassing every trait of the evolution of plants, insects and bacteria [61] as well as the personal and socio-economic traits of humans [62], including those of the systematic review of the contributions on cognitive neuroscience 2009, presented in [9]. Significantly "so pervasive as to be considered as the third major principle of evolution after mutation (variation) and natural selection, it achieves sociality, like multicellularity, multiple times at different times, in various ramifications (taxa) and reaches several different levels of integration [60]. Especially for man, to whom the second best known work of 1871 is dedicated [63]; the third, published in 1872, is a chapter from the same work (all these publications are available on Darwin Digital Library, http://darwinlibrary.amnh-org), a final complex of symbolic factors of co-operative promotion, still inextricable, undergoing an accelerated process of increasingly broad adaptation, of predispositions found in the same early phases of our individual development, from communication (languages, etc) to paleo-artistic creative activities and of religious beliefs, whose earliest traces date to 500,000 to 50,000 years ago, in the remaining discussions of the Origin of Species of the evolutionary principles (II and XI, [64]), to which the reader is also referred.

3. "Tomorrow", Especially for Human Medical Neuropsycho-pharmacology

In *On the Origin of Tomorrow* (XII, [65]) Science Magazine's News Focus finally repeats that Darwin certainly did not consider forecasting evolution possible, but he insisted that man, besides the triumphs of domestication and intensive breeding, would have contributed to species extinction by influencing their evolution more deeply than any massive physical event, also changing our species, eventually strengthening our own virtuous habits [63], also consciously, through cultural evolution. The majority of mutations (ca. 130 in each newborn), neutral, i.e. without detectable effects observed at the time, are destined to spread randomly through our population, while natural selection for survival and reproduction proceeds, conditioned by changing filters, stressors and favorable or adverse ecological environmental pressures, variably fast-acting and far-ranging, attributable to the same civilization (as documented for instance in the subjects of the Framingham heart study, also related to medications) and certainly more and intensely significant after birth control and the introduction of biotech engineering, developed up to the most complex biological syntheses, sustained on a vast economic scale. All human evolutionary traits change with our growing evo-devo knowledge, also thanks to their effective distribution and their mass media coverage (Cf. for instance [66]).

Much emphasis has been placed on the hope for greater success of functional genetic studies [67], whose insights have been likened to the certainties acquired with regard to the demonstrated, rapid adaptive radiation documented in cell cultured prions [68], in human saprophytic intestinal bacteria (Cf. again in [11], XII and XIII, pp 91-105), and, by Rosemarie and Peter Grant (1973), in the finch population of Daphne Major (Galapagos), seasonal over annual cycles of a small number of years, where the genetic mechanisms ascribed by Arhat Abzhanov and Cliff Tabin to BMP4 protein, expressed by *Geospizas magnirostris* genes (whose deeper and wider beak is adapted to crack open seeds and nuts), and calmodulin (long and thin beaks, used by *Geospizas conirostris* to probe for

seeds in cactus fruit): "a finch with a smaller beak is not a new species of finch, but it may take only a few such episodes before a new species is established that would not choose to reproduce with its parent species". Even more significantly, Simon Fisher, Constance Scharff and their colleagues (2001) found *FOXP2* gene in mouse, zebra finch, and in human children, where it is associated with learning rapid sequences of song and language. Neil Shubin and his group (2004) found that in the Tiktaalik—a 375 million year old fossil that fits neatly in the gap between fish and land-living animals—and in a primitive bony fish called paddlefish, the same pattern of gene expression which builds the bones in fins is much the same as the one that assembles the limbs in the embryo of birds, mammals, or any other land-living animal. So it is not merely the individual genes, but also their order and sequences, and especially their active or inactive state, also the state of those that have been passed down from ancient biogeological eras that count: evolution operates not only by mutating genes, but also by changing their state of activation over different time periods; so "Primary fuel for the evolution of anatomy and function turns out not to be the gene changes, but changes in their regulations that control development. The difference is only that it is switched on for a shorter time in fish"(Cf. again [66]). Darwin never could hypothesize a redeployment of an old reproductive recipes in new ways! Nevertheless, today robust and resilient interactoma systematic network system analyses can identify links between metabolome and genome for Claude Bernard' internal milieu regulations [69], apt to be applied to forging better shared speciation transmutation mechanisms in the external world.

As regards more specific evolutionary advances in human neuro-psychopharmacology that are thought to be able to become potentially effective in the very near future, they are of course predominantly related to those biological adaptive evolutionary histories of the nervous system and other Origins presented above, and depend on misinterpretations and mistakes (Cf. [70]). The 4 "P"s of future medicine, i.e. Predictive, Personalized, Preventive and Participatory (Cf. [71]), are too important for psychiatric research and practice, as any principle of evolutionary medicine [72] and any advanced neuroscience method (Cf. [73]). As can be noted in the complete list reported in [9], the papers regarding cognitive neuroscience published in Science Magazine in the "year of Darwin" do not however go beyond traditional topics —save for very few exceptions indeed— and most of them are characterized by incomplete data; in particular they fail to address, even in complementary simultaneity, at least the models cited here, too [20, 21]. Hence also the first contributions of the new period, on which we now comment [74]: *the neuro-psychopharmacological topics, when related to epigenetics, affirm its advantages for the use of new diagnostic and therapeutic drugs, which are nonetheless aimed at molecular receptor targets that are single, or little more than binary/ternary, often defined as secondary, without evaluating their advantages (and risks!), since they lack systematic omic planning, especially genic nucleoproteic targeted at DNA and RNA, at least sectorial and partial in addition to effectorial proteic central – histones, etc – and peripheral, extended potentially to all tissue cells and organs. In addition, scant resources are invested, with patent waste of material and especially intellectual Energy, with insufficient and ethically never crystalline respect for the same subjects undergoing experimentation, designing and conducting simultaneous analyses of relational networks to achieve a classification of sensitive critical meanings to the more frequent interactions, fusing as discussed kinetic and mechanisms modelling* [25, 75]. *Similarly, the myth of selective medicine, encompassing the verifications of the effectiveness and profiles (always multidimensional) of adverse reactions,*

including addictions, vs the off label use of drugs–40% of "big pharma" revenues—and complementary/alternative, also presented in [76], *has not been resolved. Transactional research itself, which has recently grown the most, also in terms of financing and destined to an increasing development also in applicative terms for the activities of the central and peripheral nervous system, has been unable to take advantage of it.* Therefore in the majority of reviews and of research articles, where it is stated that the hopes of individually tailored medicine based on genetic discoveries have largely been disappointed over the first two decades, it is concluded that "It will be very interesting to see where the field will be at in 2018".

4. Little Italy recent mostly political issues

An award for Science may be an obsolete notion [77] at a time when Stephen Jay Gould's self-critical view of science, including evolutionary Darwinian science, is making a comeback (Cf. [19]). According to this view science is constitutively filled with inextricable sociopolitical, historical and cultural prejudice, which makes it unsuitable to draw permanent, definitive conclusions. Researchers need to be extremely cautious, but also brave (not like Galileo! see again [12], IX, p. 74-80) and authority must clearly and without exception refrain from meddling and thus, if it is authority indeed, not merely tolerate scientific activities, but also promote them and favour their development, leave researchers free to conceive philosophies or mathematical theories, life histories and individual progress, and struggles for rights, first and foremost human rights, which have also come to involve nature. Politics, though an indissoluble component of science, must therefore be high politics, not a negative element, even temporarily! The Darwinism of the *Origin of Species*, like the Hegel of the *Encyclopaedia*, of the *Philosophy of Spirit* and of the *Logics* will have pointed the route to wisdom, but wisdom will be achieved only after, and if, the historical and human process has really been achieved, as Alexander Kojève wrote in his introduction to *Sophie: Philosophie et Phénoménologie* (1940-1941), which he never completed (Cf. in [78], p. 227, ff). After all, there is really no reason to feel proud about the same priorities, because also the consequences of the above discussed facts indicate that evolution goes on anyway, and that each present contribution will be an acquired and accepted fact tomorrow. Certainly the same personal evolution of the dialectic dualism of the "Hegelian post-Heideggerian" Russian anthropologist does not escape the admission, according to the *République des Lettres*, that the life of reason is nothing but a collective and indefinite advance towards an unknown, never achieved goal (Cf. again [78], p. 219; on p. 181 the reader is reminded that Paul Valery considered science as a system of problems that always remain unsolved), like his thinking religiously of overcoming religion, and "in brief, I have sought a route towards God (p. 188 and p. 80, [78]), recalled as propaganda and myth in Gaston Fessard's reply, because necessary specifications are still to be provided, and are not being found ([78], p. 203).

Nobility of senses that are not shared in the polemic arising in Italy in the same year [79]. This polemic is in fact often merely conformist, it does not lead to or offer constructive developments to the extent to which the general frame work of the debate among the scholars of evolution does not address for instance the practicalities of the necessary actions, which today are possible, where according to Edgar Morin ([78], p. 183) the idea of permanent laws guiding all things in nature, has

been replaced by the idea of laws of interactions, namely depending on interactions among physical bodies that depend on such laws. … The order means that there are no "laws", but rather constrictions, invariances, constants, regularities in our universe, and the systematic analysis of connections and linkages, throughout complex network connectome/interactome research, repeatedly mentioned above, is therefore warranted (and needed) if one accepts, again with Alexander Kojève, that modern physical science, quantum and undulatory mechanics, lead to the indeterminist, or even statistic-probabilistic view of reality: there is a structure enabling verifiable statistical hypotheses to be advanced, but it is no longer possible to understand and verify exactly, without experimental sensitivity limitations, the behaviours of particular phenomena, which can never be viewed singly (again [78], p. 185, ff). This conflicts with the idea of the Laplace equation of the universal omniscient observer, and opens nonetheless the field, today maybe the most appropriate to interpret and describe the history and the development of the evolutionary processes, judged as immanent according to Kant. On this issue, pope Urban VIII, Andreas Osiander and Cardinal Roberto Bellarmino, but also Pierre Duhem and Willard Quine ([12], p. 76 ff) have commented that scientific theories cannot hope to explain how the world is really made, because they are merely possible and not necessary interpretations of phenomena. And it may be not superfluous to stress, with Karl Popper, that any scientific hypothesis must be able to undergo testing for verification whereas "the characteristics of the verification of the basic hypothesis of natural science only possible subject to an infinite number of verifications, to which corresponds an infinity of theories, whose verification subject to an endless historical process of infinite approximation, is associated with an unexplained premise" ([80], p. 71, ff). Finally, "fundamental principle of contemporary epistemology, which undermines any attempt at defining a univocal model of rationality, the same historical event can be the object of a conceptualization process in different directions"([81], p. 73, ff). An additional example, recalling the "tree of life" proposed by Darwin (1830) and Wallace (1855), read at the time in the direction of a single point of origin as discussed above, is the "rhizome of life" proposed by Didier Raoult [82], which can be considered fascinating, brilliant and equally sustainable until proved otherwise.

Therefore, after the completion of a revamp plan [83], all we have to do is to unify the standardization of ICT research places, of information and communication technology [84], and to begin to work on the basis of "merit", accurately avoiding provocations from non experts. Of course, after MB Yaffe's Editorial Guide [70], to the effects that "Articles should be judged on their own merit, not the impact factor of the journal in which they are published" - fully confirming our own proposals, and consistent, practical lifestyle [9, 33, 40] -, any serious researcher will not care if, in Italy, a superior incapacity to finally clarify the offensive but widespread market habits of selection is confirmed, against any simply honest, long-needed expectation, as by para. 4, art 3, possibly merely politically correct, nevertheless scientifically fundamentally offensive of the ministerial Decree of July 28 2009, no 89/2009, not certainly a tribute to Darwin's effective evolution for years to come.

References

1. Vogel G. Reprogramming cells. Science 2008;322:1766-1767.

2. Gibbons A. *Ardipithecus ramidus*. Science 2009;326:1598-1599; Alberts B. Science Editorial The breakthroughs of 2009. Science 2009;326:1589.

3. Stone R. Signs of early Homo sapiens in China? Science 2009;326:655; Balter M. New work may complicate history of Neanderthals and H. sapiens. Science 2009;326:224-225.

4. Rating last year's areas to watch: Defining species. Science 2009;326:1602.

5. May RM, Harvey PH. Science Editorial Species uncertainties. Science 2009;323:687.

6. Sugden A, Ash C, Hanson B, Zahn L. Special Section Speciation Introduction Happy birthday Mr. Darwin, and Rewiews. Science 2009;323:727-751.

7. Baltimore D. A global perspective on science and technology. Science 2008;322:544-551.

8. Leshner AI, Tureikan V. Harmonizing global science. Science 2009;326:1459; Alberts B. On incentives for innovation. Science 2009;326:1163; Sugden A, Hanson B, Pennisi E, Culotta E. A celebration and a challenge. Science 2009;323:185; Hassan MHA. Making one world of science. Science 2008;322:505.

9. Rossini P, Rossini L. Experimental and clinical pharmacotoxicology 2009. Narrative update prevalently related to cognitive neurosciences. Pharmacologyonline Newsletter 2009;3:443-457.

10. Darwin C. On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. John Murray, London 1859; Id. The origin of species. Simon & Schuster, Inc. New York 2008.

11. Odifreddi P. In principio era Darwin. Longanesi, Milano 2009.

12. Odifreddi P. Hai vinto Galileo!. Mondatori, Milano 2009.

13. Quammen D. The Darwin bicentennial part one. Darwin's first clues. National Geographic February 2009;44-53.

14. Endersby J. Lumpers and splitters: Darwin, Hooker, and the search for order. Science 2009;326:1496-1499.

15. Quammen D. The man who wasn't Darwin. National Geographic December 2008;106-133.

16. Alberts B. Promoting scientific standards. Science Editorial 2010;327:12; Sim I, Chute CG, Lehmann H, Nagarajan R, Nahm M, Scheuermann. Keeping raw data in context. Science Letters 2009;323:713.

17. Pigliucci M. The overwhelming evidence. Science 2009;323:716-717; The year in evolutionary biology 2008. CD Schlichting, TA Mousseau Edts. Ann New York Ac Sci 1133:VII-X, 1-203 Blackwell Malden, MA 2008; Quammen D, Clark R. Was Darwin' wrong?- No. The evidence for evolution is overwhelming. National Geographic November 2004;2-35.

18. Bowler PJ. Darwin's originality. Science 2009;323:223-226.

19. Smocovitis VB. Darwin is dead-Long live evolution. Science 2009;326:800-801.

20. Grossman SR, Shylakhter I, Karlsson EK, Byrne EH, Morales S., et al. A composite of multiple signals distinguishes causal variants in regions of positive selection. Science 2010;327:883-886; Davidoff F. Heterogeneity is not always noise. Lessons from improvement.

JAMA 2009;302:2580-2586; Odenbaugh J. A fresh theoretical frame work. Science 2009;326:368-369; Krackhardt D. A plunge into network. Science 2009;326:47-48; Jasny BR, Zahn LM, Marshall E. Introduction Connections, Science Special Section Complex systems and networks. Pushing networks to the limits, Reviews and Perspectives. Science 2009;325:405-432; Achlioptas D, D'Souza RM, Spencer J. Explosive percolation in random networks. Science 2009;323:1453-1455; Lazer D, Pentland A, Adamic L, Aral S, Barabàsi A-L, et al. Computational social science. Science 2009;323:721-723; Bohman T. Emergence of connectivity in networks. Science 2009;323;438-439.

21. Cheianov VV. When infinity does not count. Science 2009;323:213-214.

22. Shapiro E, Gil B. RNA computing in a living cell. Science 2009;322:387-388.

23. Hurtley S. Introduction Location, location, location to Special Section Spatial Cell Biology Reviews. Science 2009;326:1205-1228.

24. Tamaka S, Sawaya MR, Yeates TO. Structure and mechanisms of a protein-based organelle in *Escherichia coli*. Science 2010;327:81-84.

25. Rossini L, Rossini P. Requirements for the assessment of pharmacokinetic, pharmacodynamic and mixed population models and some topical considerations: A seminar. Pharmacologyonline Newsletter 2007;2:48-72.

26. Ossowski S, Schneeberger K, Lucas-Lledò JI, Warthmann N, Clark RM, et al. The rate and molecular spectrum of spontaneous mutations in *Arabidopsis thaliana*. Science 2010;327:92-97.

27. Dermitzakis' ET, Clark AG. Life after GWA studies. Science 2009;326:239-240; Monroe D. Genomic clues to DNA treasure sometimes lead nowhere. Science 2009;325:142-143; Gavrilets S, Losos JB. Adaptive radiation: Contrasting theory with data. Science 2009;323:732-736; Turanov AA, Lobanov AV, Fomenko DE, Morrison HG, Sogin ML, et al. Genetic code supports targeted insertion of two amino acids by one codon. Science 2009;323:259-261.

28. Myers S, Bowden R, Tumian A, Bontrop RE, Freeman C, et al. Drive against hotspot motifs in primates implicates the *PRDM9* gene in meiotic recombination. Science 2010;327:876-879; Baudat F, Buard J, Grey C, Fleder-Alon A, Ober M, et al. PRDM9 is a major determinant of meiotic recombination hotspots in human and mice. Science 2010;327:836-840; Parvanov ED, Petkov PM, Paigen K. *Prdm9 controls activation of mammalian recombination hotspots. Science 2010;327:*835; Cheung VG, Sherman SL, Feingold E. Genetic control of hotspots. Science 2010;327:791-792; Stern DL, Orgogozo V. Is genetic evolution predictable?. Science 2009;323:747-751.

29. Tang S, Presgraves DC. Evolution of the *Drosophila* nuclear pore complex results in multiple hybrid incompatibilities. Science 2009;323:779-782.

30. Dimas AS, Deytsch S, Stranger BE, Montgomery SB, Borel C, et al. Common regulatory variation impacts gene expression in a cell type-dependent manner. Science 2009;325:1246-1250.

31. Pennisi E. Spineless fish and dark flies prove gene regulation crucial. Science 2009;326:1612.

32. Coller HA, Kruglyak L. It's the sequence, stupid!. Science 2008;322:380-381.

33. Hall SS. Beyond the book of life. Newsweek 2009; July 6/ July 13:38-41.

34. Dove A. Science' Life science technologies Epigenetics. Science 2009;326:303-306.

35. Pennisi E. The case of the midwife toad: Fraud or epigenetics? Science 2009;325:1194-1195; Hait NC, Allegood J, Maceyka M, Strub GM, Harikumar KB, et al. Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. Science 2009;325.1254-1257; Smith E, Shilatifard A. Histone cross-talk in stem cells. Science 2009;323:221-222.

36. Choi PJ, Cai L, Frieda K, Xie XS. A stochastic single-molecule event triggers phenotype switching of a bacterial cell. Science 2008;322:442-4.

37. Nabel GJ. The coordinates of truth. Science 2009;326:53-54.

38. Liang BA, Mackey T. Reforming off-label promotion to enhance orphan disease treatment. Science 2010;327:273-274; Gardner A, Kaplan BJ, Rucklidge JJ, Jonsson BH, Humble MB. The potential of nutritional therapy. Science 2010;327:268; Rossini L. Pre- and post-marketing pharmacovigilance: The myths of the placebo effects and of the off-label use of drug. Pharmacologyonline Newsletter 2008;2:80-94.

39. Pennisi E. Ecological genomics gets down to genes and function. Science 2009;326:1620-1621.

40. Rossini L, Rossini P. Universita' Politecnica delle Marche and Marche Region, Italy: Medical pharmacotoxicology today. Pharmacologyonline Newsletter 2008;3:85-108.

41. Zimmer C. On the Origin of life on earth. Science 2009;323:198-199;

42. Lingwood D, Simons K. Lipid rafts as a membrane-organizing principle. Science 2010;327:46-50; Balazs AC, Epstein IR. Emergent of just complex?. Science 2009;325:1632-1633; Kauffman S. Two deep issues in evolutionary theory. In Darwin's descendants. The New York Academy of Sciences Magazine Winter 2009:17-18.

43. Leslie M. On the origin of photosynthesis. Science 2009;323:1286-1287.

44. Pennisi E. On the origin of flowering plants. Science 2009;324:28-31.

45. Liu F, Marquardt S, Lister C, Swiezewski S, Dean C. Targeted 3' processing of antisense transcripts triggers *Arabidopsis FLC* chromatin silencing. Science 2010;327:94-97.

46. Mueller K. Introduction First responders. Science Special Section Innate immunity Perspective and Reviews. Science 2010;327:283-300; Travis J. On the origin of the immune system. Science 2009;324:580-582.

47. Horwath P, Barrangou R. CRISPR/Cas, the immune system of bacteria and *Archaea.* Science 2010;327:167-170.

48. Güell M, van Noort V, Yus E, Chen W-H, Leigh-Bell J, et al. Transcriptome complexity in a genome-reduced bacterium. Science 2009;326:1268-1271; Yus E, Maier T, Michalodimitrakis K, van Noort V, Yamada T, et al. Impact of genome reduction on bacterial metabolism and its regulation. Science 2009;326:1263-1268; Kühner S, van Noort V, Betts MJ, Leo-Macias A, Batisse C, et al. Proteome organization in a genome-reduced bacterium. Science 2009;326:1235-1240; Ochman H, Raghavan R. Excavating the functional landscape of bacterial cells. Science 2009;326:1200-1201.

49. Zimmer C. On the origin of eukaryotes. Science 2009;325:666-668.

50. Miller G. On the origin of the nervous system. Science 2009;325:24-26.

51. Zimmer C. On the origin of sexual reproduction. Science 2009;324:1254-1256.

52. van Doorn GS, Edelaar P, Weissingn FJ. On the origin of species by natural and sexual selection. Science 2009;326:1704-1707; Mank JE. Sexual selection and Darwin's mystery of mysteries. Science 2009;326:1639-1640.

53. Clark JS. Individuals and the variation needed for high species diversity in forest trees. Science 2010;327:1129-1132; Stolstad E. On the origin of ecological structure. Science 2009;326:33-35.

54. Chan YF, Marks ME, Jones FC, Villareal Jr G, Shapiro MD, et al. Adaptive evolution of pelvic reduction in Sticklebacks by recurrent deletion of a *Pitx1* enhancer. Science 2010;327:302-305; Mathur D, Bost A, Driver I, Ohlstein B. A transient niche regulates the specification of *Drosophila* intestinal cells. Science 2010;327:210-213; Costello EK, Lauber CL, Hamady M, Fierer N, et al. Bacterial community variation in human body habitats across space and time. Science 2009;326:1694-1697; Rebeitz M, Pool JE, Kassner VA, Aquadro CF, Carrollo SB. Stepwise modification of a modular enhancer underlies adaptation in a *Drosophila* population. Science 2009;326:1663-1667; The HUGO Pan-Asian Consortium. Mapping human genetic diversity in Asia. Science 2009;326:1541-1545; Crickmore MA. The molecular basis of size differences. Science 2009;326:1360-1361; Forbes AA, Powell THQ, Stelinski LL, Smith JJU, Feder JL. Sequential sympatric speciation across trophic levels. Science 2009;323:776-779; Schluter D. Evidence for ecological speciation and its alternative. Science 2009;323:737-741; Frazer C, Alm EJ, Polz MF, Spratt BG, Hanage WP. The bacteria species challenge: Making sense of genetic and ecological diversity. Science 2009,323:741-746.

55. Reich PB. Elevated CO_2 reduces losses of plant diversity caused by nitrogen deposition. Science 2009;326:1399-1402; Collins SL. Biodiversity under global change. Science 2009;326:1353-1354.

56. Willis KJ, Bhagwat SA. Biodiversity and climate change. Science 2009;326:806-807.

57. Bakal C, Linding R, lliense F, Heffern E, Martin-Blanco E, et al. Phosphorylation networks regulating JNK activity in diverse genetic backgrounds. Science 2008;322:453-456.

58. Melbourne BA, Hastings A. Highly variable spread rates in replicated biological invasions: Fundamental limits to predictability. Science 2009;325:1536-1539.

59. May R. Cooperation among nations: A crowded & changing world. The New York Academy of Sciences Magazine Winter 2009. Darwin's descendants:18-19.

60. Pennisi E. On the origin of cooperation. Science 2009;325:1196-1199.

61. Carnaval AC, Hickerson MJ, Haddad CFB, Rodriguez MT, Moritz C. Stability predicts genetic diversity in the Brazilian Atlantic forest hotspot. Science 2009;323:785-789; Chuang JS, Rivoire O, Leibler S. Simpson's paradox in a synthetic microbial system. Science 2009;323:272-275; Pennisi E. Agreeing to disagree. Science 2009;323.706-708.

62. Ule A, Schram A, Riedi A, Cason TN. Indirect punishment and generosity toward strangers. Science 2009;326:1701-1704; Sood GDS. Asking about origins. Science 326:1190-1191; Acemoglu D, Robinson J. Foundations of social inequality. Science 2009;326:678-679; Krajbich I, Camerer C, Ledyard J, Rangel A. Using neural measures of economic value to solve the public goods free-rider problem. Science 2009;326:596-599; Malmgren RD, Stouffer DB, Campanharo ASLO, Amaral LAN. On universality in human correspondence activity. Science 2009;325:1696-1700; Rand DG,

Dreber A, Ellingsen T, Fudenberg D, Nowak MA. Positive interactions promote public cooperation. Science 2009;325:1272-1275; Kawakami K, Dunn E, Karmali F, Dovidio JF. Mispredicting affective and behavioral responses to racism. Science 2009;323:276-278; Smith ER, Mackie DM. Surprising emotions. Science 2009;323:215-216; Sundaram JK, von Armin R. Trade liberalization and economic development. Science 2009;323:211-212.

63. Harrison T. Apes among the tangled branches of human origins. Science 2010;327:532-534; Darwin C. L' espressione delle emozioni nell' uomo e negli animali. Bollati Boringhieri, Torino 2006; Darwin C. L' origine dell' uomo e la selezione sessuale. Newton Compton, Roma 2007 (The descent of man. Appleton and Co. New York 1871).

64 Culotta E. On the origin of religion. Science 2009;326:784-787; Balter M. On the origin of art and symbolism. Science 2009;323:709-711.

65. Zimmer C. The origin of tomorrow. Science 2009;326:1334-1336.

66. Ridley M. Modern Darwins National Geographic February 2009:56-73; Stromswold K. The genetic of speech and language impairments. New Eng J Med 2008;359:2381-2383; Milano G. Gli OGM sono tra noi. Panorama Dossier 20.12.2007:150-162.

67. Harris T. Reading your genes. Science 2010; 327:782-783; Costanzo M, Baryshnikovas A, Bellay J, Kim Y, Spear ED, et al. The genetic landscape of a cell. Science 2010;327:425-431; Drmanac R, Sparks AB, Callow MJ, Halpern AL, Burns NL, et al. Human genome sequencing using unchained base reads on self-assembling DNA nanoarrays. Science 2010;327:78-81; Gore MA, Chia J-M, Elshire RJ, Sun Q, Ersoz ES, et al. A first-generation haplo type map of maize. Science 2009;326:1115-1117; Schnable Ps, Ware D, Fulton RS, Stein JC, Wei F, et al. The B73 maize genome: Complexity, diversity, and dynamics. Science 2009;326:1112-1115; Swanson-Wagner RA, DeCook R, Bancroft YJ, Zhao X, Nettleton D, et al. Paternal dominance of trans-eQTL influences gene expression patterns in maize hybrids. Science 2009;326:1118-1120; Feuillet C, Eversole K. Solving the maze. Science 2009;326:1071-1072; Xia Q, Guo Y, Zhang Z, Li D, Xuan Z, et al. Complete resequencing of 40 genomes reveals domestication events and genes in silkworm (*Bombyx*). Science 2009;326:433-437; Chain PSG, Grafham DV, Fulton RS, FitzGerald MG, Hostetler J, et al. Genome Project standards in a new era of sequencing. Science 2009;326:236-237; Huang L. Biology's odd couple. Newsweek July 7/ July 13, 2009:34-37.

68. Wang F, Wang X, Yuan C-G, Ma J. Generating a prion with bacterially expressed recombinant prion protein. Science 2010;327:1129-1132; Li J, Browning S, Mahal SP, Oelschlegel AM, Weissman C. Darwinian evolution of prions in cell culture. Science 2010:327:869-872.

69. Rihel J, Prober DA, Arvanites A, Lam K, Zimmerman S, et al. Zebrafish behavioral profiling links drugs to biological targets and rest/wake regulation. Science 2010;327:348-351; Nechaev S, Fargo DC, dos Santos G, Liu L, Gao Y, Adelman K. Global analysis of short RNAs reveals widespread promoter-proximal stalling and arrest of Pol II in *Drosophila*. Science 2010;327:335-337; Amieux PS, McKnight GS. Perspective: Cyclic nucleotides converge on brown adipose tissue differentiation. Scienceonline, www-sciencesignaling-org, www.sciencemag.org 2010;327:245; Bailor MH, Sun X, Al-Hashimi HM. Topology links RNA secondary structure with global conformation, dynamics, and adaptation. Science 2010;327:202-206; Haas B, et al. Protein kinase G controls brown far cell differentiation and mitochondrial biogenesis. Scienceonline, www-sciencesignaling.org, www-sciencemag.org. Science 2009;326:1313; Lieberman-Aiden E, van Berkum NL, Williams L, Imakaev M, Ragoczy T, et al. Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science 2009;326:289-294; Beloqui A, Guazzaroni MG, Pazos F, Vieites JM, Godoy M, et al. Reactome array: forging a link between

metabolome and genome. Science 2009;326:252-257; Collins MO. Evolving cell signals. Science 2009;325:1635-1636; Vander Heiden MG, Cantley LC, Thompspon CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 2009;324:1029-1033; Rathmell JC, Newgatrd CB. A glucose-to-gene link. Science 2009;324:1021-1022; Vinson VJ. Introduction Proteins in motion. Science Special Section Protein Dynamics Reviews and Perspective. Science 2009;324:197-215; King RD, Rowland J, Oliver SG, Young M, Aubrey W, et al. The automation of science. Science 2009;324:85-88; Schmidt M, Lipson H. Distilling free-form natural laws from experimental data. Science 2009;324:81-85; Waltz D, Buchanan BG. Automating science. Science 2009; 324:43-44; Stice E, Spoor S, Bohon C, Small DM. Science 2008;322:449-452; Matthew-Fenn RS, Das R., Harbury PAB. Remeasuring the double helix. Science 2008;322: 446-449; Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, et al. The connectivity map: using gene-expression signatures to connect small molecules, genes, and disease. Science 2006;313.1929-1935.

70. Gabaglio L. Farmaci da buttare. L' espresso 2.4.2010:130-133; Koscielny S. Perspective: Why most gene expression signatures of tumors have not been useful in the clinic. Scienceonline, www.sciencecareers.org, vwww.sciencemag.org. Science 2010;327:245; Krane DE, Bahn V, Balding D, Barlow B, Cash H, et al. Time for DNA disclosure. Science 2009;326:1631-1632; Yaffe MB. Editorial guide: Living by the numbers. Scienceonline, www.sciencesignaling.org, www-sciencemag.org.science 2009;326:1313; Marshall E. Medicine under the microscope. Science 2009;326:1183-1185; Field D, Sansone S-A, Collis A, Booth T, Dukes P, et al. 'Omics data sharing. Science 2009;326:234-235; Enserink M. Some neglected diseases are more neglected than others. Science 2009;323:700; Taubes G. Paradoxical effects of tightly controlled blood sugars. Science 2008;322:365-367; Vogel G. Falsification charge highlights image-manipulation standards. Science 2008;322:356; Marshall E. Lemons, oranges, and complexity. Introduction to SpecialSection Clinical trials. Science 2008;322:209-223; Francalacci N. Truffa globale sui medicinali. Panorama 11.13.2008:109-112.

71. Hood L. A doctor's vision of the future of medicine. Newsweek July 6/ July 13, 2009:46-47; Rosenberg RN, Stűve O, Eagar T. 200 years after Darwin. JAMA 2009;301:660-662 (republished from the Archives of Neurology 2009;66:153-155).

72. Ellison PT. Evolutionary biology for doctors. Science 2009;325:1207; Evans JP. The voyage continues. Darwin and medicine at 200 years. JAMA 2009;301:663-665.

73. To T-L, Maheshi N. Noise can induce bimodality in positive transcriptional feedback loops without bistability. Science 2010;327:1142-1145; Levens D, Gupta A. Reliable noise. Science 2010;327:1088-1089; Tero A, Takagi S, Saisgusa T, Ito K, Bebber DP, et al. Rules for biologically inspired adaptive network design. Science 2010;327:439-442; Marwan W. Amoeba-inspired network design. Science 2010;327:419-420; Mesirov JP. Accessible reproducible research. Science 2010;327:415-416; Stern P. So you want to learn how to network?. Introduction to Neuroscience methods Special Section. Science 2009;326:385-403.

74. Barker R. A flexible blueprint for the future of drug development. The Lancet 2010;375:357-359; Maze I, Covington Ill HE, Dietz DM, LaPlant Q, Renthal W, et al. Essential role of the histone methyltransferase G9a in cocaine-induced plasticity. Science 2010;327.213-216; Friedrich MJ. Epigenetic therapies offer new approach to fighting cancer at the genetic level. JAMA 2010;303:213-214; Edwards MJ, Flatman RH, Mitchenall LA, Stevenson CEM, Le TBK. A crystal structure of the bifunctional antibiotic simocyclinone D8, bound to DNA gyrase. Science 2009;326:1415-1418; Dickman DK, Davis GW. The schizophrenia susceptibility gene *dysbindin* controls synaptic homeostasis. Science 2009;326:1127-1130; Kaiser J. Looking for a target on every tumor. Science 2009;326:218-220; Freedman DH. Brain boosters. Newsweek July 6/ July 13,

2009:48-51; Kandel B. A biology of mental disorders. Newsweek July 6/ July 13:54; Lane E, Becky H. Personalized medicine: Successes tempered by significant challenges. Science 2009;324:1658; Zhao S, Lin Y, Xu W, Jiang W, Zha W, et al. Glioma-derived mutations in *IDH1* dominantly inhibit IDH1 catalytic activity and induce HIF-1α. Science 2009;324:261-265; Poliard PJ, Ratcliffe PJ. Puzzling patterns of predisposition. Science 2009;324:192-194; Cahoon L. A new view on-and hope for-an old disease. Science 2009;323:203-205.

75. Rossini L. Drugs and the future. Pharmacologyonline 2005;1:12-44.

76. Rossini L, Rossini P. Pharmacotherapeutic receptor specificities and selectivity classes, and placebo effects: A perspective. Pharmacologyonline 2006;2:206-235.

77. Gozum M. An award for science is an obsolete notion. Science 2009;323:207.

78. Filoni M. Il filosofo della domenica. Bollati Boringhieri, Torino 2008.

79. Searchinger TD, Hamburg SP, Melillo JU, Chamedeis W, Havlik W, et al. Carbon calculations to consider-Response. Science 2010;327:781; Sørensen B. Carbon calculations to consider. Science 2010;327:780-781; Friedland AJ, Gillingham KT. Carbon accounting a tricky business. Science 2010;327:411-412; Lovejoy CO, Suwa G, White TD. Studying extant species to model our past-Response. Science 2010;327:410; Whiten A, McGregw WC, Aiello LC, Boesch C, Boyd R, et al. Studying extant species to model our past. Science 2010;327:410; Roberts RG, Brook BW. And then there were none? Science 2010;327:420-422; Evoluzionismo: Il tramonto di una ipotesi. A cura De Mattei R. Atti del Workshop promosso a Roma il 23 febbraio 2009 dalla Vice-Presidenza del Consiglio Nazionale delle Ricerche per offrire un contributo scientifico al dibattito in corso nell'anno darwiniano. Edizioni Cantagalli, Siena, 2009; Holden C. Creationism at Italian science agency. Science 2009;326:1597; Battista P. I conformisti. RCS Libri, Milano 2009:167, 169, 211-213; MicroMega Almanacco di scienze. Darwin, 1809-2009:1-210; Pievani T. Dove sono finiti quei milioni di anni? MicroMega 2009;6:109-117; Gnocchi A. Zittite il creazionista. La libertà d'opinione non è eguale per tutti. Il Giornale 12.23.2009:28-29; Carioti F. Evoluzionismo - Il disegno poco intelligente dei fan di Darwin. Libero 12.2.2009:41; De Mattei R. Vietato discutere. Per i fan di Darwin tutto si evolve. Tranne la scienza. Il Giornale 11.28.2009:32; Carioti F. Evoluzione. L' outing degli scienziati contro Darwin. Libero 11.3.2009:34.

80. Husserl H. La crisi delle scienze europee e la fenomenologia trascendentale. EST, Milano 1997.

81. Rossi P. Avventure e disavventure della filosofia. Il Mulino Saggi, Bologna 2009.

82. Raoult D. The post-Darwinist rhizome of life. The Lancet 2010;375:104-105, Id. Creationism-remember the principle of falsifiability. The Lancet 2008;372:2095-2096.

83. Garattini S. Il Programma nazionale. Ricerca, cosa manca al piano di rilancio. Il Messaggero 1.25.2010:1, 15.

84. Mancini U. Innovazione e sviluppo. Informatica, a Roma il centro d' eccellenza. Il Messaggero 1.3.2010:2; von Herrmann B. The systems biology dilemma. Scientific Computing World. October/November 2008:62.