

**EXPERIMENTAL AND CLINICAL PHARMACOTOXICOLOGY 2009. NARRATIVE
UPDATE PREVALENTLY RELATED TO COGNITIVE NEUROSCIENCES**

Paola Rossini[°] and Luigi Rossini^{*^}

[°]Psichiatria, Ospedale S. Giacomo, ASL 22, 15067 Novi Ligure, ^{*}Farmacologia Neuroscienze, Servizio di Farmacologia e Tossicologia Clinica, UPM and Azienda Ospedali Riuniti di Ancona and Sezione di Farmacotossicologia Umana, Centro Interuniversitario I.M.O. Retired October 31, 2008

Summary

Weekly perusal of the leading scientific journal, especially the contributions of the previous year in the field of neuroscience after those received as a retired Professor, easily demonstrates the same inobservances by the local and national administrations. Lack of discussion of items on the agendas and inattentions that hamper the necessary equitable distribution of resources, leading to a class action by those researchers who are keen on their work and are aware of their essential duties, including those related to teaching and healthcare. The authors' previous papers and the research avenues currently pursued at the international level are briefly mentioned. The small number of local and regional contributions by the members of the Committees that are in charge of their assessment is noted, something that does not overestimate their discrimination abilities and competence.

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“The passion of the mind [had a wonderful and powerful influence] upon the state and disorder of the body”. J. Haygarth, 1801 [1].

“Après tout, le réel n’est qu’un cas particulier”. P. Valery, Mauvaises pensées et autres, 1841. From a note by F. Lucentini to J.L. Borges; Ficciones, 1941.

“E’ bello raccontare i guai passati”. P. Levi (1919-1987), Il Sistema Periodico. G. Einaudi Ed. 1975 (The Periodic Table, 1984).

Another year has passed since our previous contribution, submitted to our society’s online international journal [2] before the retirement of the elder author (LR). In the course of this year the local and national ad hoc Committees have not even discussed the documented communications, including the 2008 Editorial of Science [3]. This confirms once again, were it needed, the irremediable, serious, irresponsible and overpowering determination of its civil servant members. It has merely been possible to continue to carry out one’s voluntary work—in the face of the neglect of the dean’s and founder’s unique competence, experience and sensitivity toward the right and duty to defend one’s teaching guidelines, research avenues and healthcare commitments, in line with the relevant regulations—using one’s personal resources, aware of the damage to oneself, but also of the collective damage that has derived, including the loss of potential funds. This regards not only the national and local funds, formerly “40%” and “60%”, which *have not been granted for the tenth consecutive year* as is undeniably documented, for the purchase of consumables, but also the funds that served to complete the *central extraordinary investment for large and medium-sized equipment*, denied at least three times previously and inexplicably. This decision that clearly does not even affect recipients by rotation. This stop has been imposed without justification not only to the group, technicians, internal collaborators, grant holders and volunteers, researchers and PhD holders already involved over the previous 10 years in training in the use of the equipment also through tiring and costly courses at prestigious foreign institutions. Individuals who are maybe still using this training abroad, or are waiting to be appropriately employed even though too much time has elapsed for such course of action to be deemed correct. The same publisher, while lamenting the delay in the attribution of the Impact Factor (I.F.) to the sole *online* journal of a society, hopes that this will finally happen next year [4]. Nonetheless the Committee members are neither reading nor assessing the applications, except for the basic criterion of continuity, but exclusively rely on the I.F. when granting the yearly funds, cynically ignoring the communication that attribution of the I.F. takes at least three years and even 10 years, as has been noted, for new international journals. However, the total funds to be assigned appear to shrink further and further, but those who have no civic sense have arbitrarily continued to defend their prerogatives, preserving their majorities as customary and ignoring the rights of minorities, indeed boycotting them acidly, pursuing dishonourable behaviours and failing some deserving projects without qualms, certain of impunity. They have done nothing worse. But there is nothing worse than strengthening those who are above the possibility of being touched.

And yet, already in the late 1960s we were among the first to perform biochemical kinetic investigations (especially point kinetics according to Wollenberger), to study tissue, cell, and even subcellular (mitochondrial, cytosolic, etc) metabolic equilibria *in vivo*, finding *new integration interaction parameters* (Cf: [5]) such as the redox and nitro-phosphorylation potentials of the

relevant spaces, *multivariate (stepwise)* analysis, by identifying the multidimension classification profiles of the fractionated amount of the covariances of samples vs controls and samples treated in parallel with single doses, and/or fractionated, subsequently administered continuously or by steps (Cf: [6]). Besides the assessment of free and bound metabolic and pharmacotoxicological levels respectively, we also addressed the measurement of fluxes of the same central energy-related metabolic pathways by means of multinuclear spectrometry (e.g. ^1H , ^{31}P , ^{13}C)[7], and then non-invasive enzymological studies *in vivo* (e.g. iso creatine phosphokinase, by magnetization transfer, both in heterotherms – *Rana*, *Xenopus*, and in mammals (rat, *mx* mouse)[8]. We subsequently continued our investigations at national and foreign associated interuniversity institutions, addressing *adaptation and/or peripheral memory* of rat and mouse preparations according to Langendorff (Cf: hypoxic/anoxic-ischemic preconditioning) in standardized conditions, studying metabolic kinetics by optical spectrophotometry and fluorescence associated with measurement techniques of more significant complexes of conventional physiological parameters [9].

There are nonetheless some satisfactory, albeit bitter, truths if one can think beyond the local miseries, that are continuously confirmed by the more prestigious international studies, as indicated below.

1. The Large Hadron Collider adventure

Any experiment reserves surprises, or it would be useless. After the stop of last September, the reactivation of the CERN's Large Hadron Collider (LHC) might be postponed to November or even later due to some leaks in the cryogenic system and some more bad electrical connections around half of the maximum theoretical power of 12 teraelectron volts (TeV). This might give the Fermilab in Batavia, Illinois, which fires protons into antiprotons at 2 TeV, the opportunity to detect the Higgs boson first, after its success with the Top Quark (Cf: [10]¹). That which may count also in this situation is the fact that theoretical physicists have already modelled and operatively structured a distributed universal calculation and memory system (Cf: "Wlcg-Grid" (Cf: [11]) that is without any doubt superior to those of the interuniversity I.M.O. and also to the WHO's pharmacovigilance system—in whose foundation one of the authors (LR) participated-. In the global view of Science and Technology and of the aim to achieve a single science world [12], also experimental, clinical, and pharmacotoxicological [13], the latter system must clearly not be confined in biomedicine to analytical applications, as envisaged by the Italian grid infrastructure (igi) and the Progetto MAGIC-5, like studying for the same spectrometric neuroimages and functional magnetic resonance imaging (fMRI) data also inverse single shot, aiming to identify a perceptual representation, activation or cognitive state on the basis of single voxel regional signals, albeit localized in predefined areas of interest (ROIs) unless subjecting the whole structure to multivariate identification of ROIs which from the standpoint of IT analysis entail specific information autoclassification types of which for instance our experience with the adoption of wavelets according to Gabor, entails, if the difficulties of replication are to be avoided, no less than the modelling identification given 60,000 voxels and $60,000 \times 300 = 18$ million time points per sec in only 5 min single volumetric scans, which is still widely considered computationally prohibitive (Cf: [14]).

In this context it is fairly clear, for instance for Pharmacotoxicogenomics (Cf: [15]), that it is no longer acceptable to invest manpower, time, technologies, etc in single isolated analyses, commercial or otherwise, unless they are included into a global project, for which the only hope of progress must reside in the continuing prestige of the WHO, while any different effort should be ignored, never rewarded. A contribution of the quoted second volume of great and not only local

¹ In his email of August 6 2009 to the CERN personnel, re: LHC News, Rolf Heuer wrote that "for the first part of 2009-2010 a run at 3.5 TeV per beam had been selected because it allows the LHC operators to gain experience in running the machine safely while opening up a new discovery region for the experiments" and subsequently raising the energy to 5 and 7 TeV. "No more repairs are necessary for safe running this year and the next".

interest is however the upgrading of neuroimaging methodologies [14], where, summarized the advantages, merits and risks/drawbacks of the individual procedures {Multinuclear magnetic resonance spectroscopy (MNMRS), fMRI, voxel based morphometry (VBM), diffusion tensor imaging (DTI), diffusion spectrum imaging (DSI), magnetoencephalography (MEG), electroencephalography (theta 2-9 Hz EEG), optical imaging (OI), diffusion optical tomography (DOT), positron emission tomography (PET), unic/multibarrel stimulation and recording electrophysiology, fast-scan cyclical voltammetry (with 0.1 sec cyclical repetitions (Cf: [16])), the year 2009 ends with what has been reported as undertaken, organized-implemented and proposed in the 1960s, i.e. not only the advisability but the need for proceeding always associating a multiparametric aim in each specimen, something that still here and now recall the hope, where the parochial distribution of peripheral articulations of our university is by now incontrovertible, which at least for superior cognitive Neuroscience achieves centralization of complex machines, of statistics-epidemiology and analytical correlated to the same centralized acquisition of reference data, training/learning control sets and hyperspecialized experts really working full-time, also in the context of a first extended “grid”, as always believed and proposed (Cf: again [2], I, § 3, 4) and where possible practiced thanks to the extensive use of the IT storage space and abilities of the peripheral branches global, experimental and clinical. This is the bicentennial of the birth of the genius Charles Darwin (February 12) and the 150th anniversary of the publication of *On the origin of species* (November 24). His observations and surmises will finally ripen in the context of universal science when the pro and contrary data finally and automatically evaluated in proven generalized models, even though subjected to a possible internal evolution (Cf: [17]).

2. fNMR/EEG/MEG/PET/multiparametric neuroimaging interpretation and applications

For the same recent and faster evolutions of fMRI, whose standards of operativity have been proposed [18], the study of spontaneous fluctuations (at ≤ 0.1 Hz) compared with the baseline, besides those of cardiorespiratory parameters and those dependent on CO₂, pH, redox and nitro-phosphorylation, which we have studied too [19], technology can express neuronal and glial phase-coherent flows in the form of tests by means of the motor cortex, and of cognitive somatosensory perceptions, where necessary using a contrast agent, by superimposing low or high spatial resolution time sequences (from 10 to 60 Hz). Nonetheless the identification of activated areas can offer an association with the tasks performed, but not yet cognitive mechanisms and indications of principles of brain organization, or a distinction between excitatory and inhibitory actions [14]. We make reference to the operative computational model developed by Cohen JD, McClure SM, Montague PR and Associates, indicated and discussed in § 4, 8 of R. L and P (2008 [2], 2006 [16]). We agree with Oliver Sacks on the merits of the work of Jonah Lehrer [20], whose bibliographic references are not however usable, at least as regards the Italian edition²: there is a variety of volumes and reviews on similar topics, but for the Italian authors we refer the reader to the clear and concise writings, extending to the implicit application of the *Voci* by Paolo Legrenzi and Carlo Umiltà' [21], which allow going back to the essential contributions of the consequences of the separation of the analysis of nature in general, comprising all its creatures (*zoè*) compared with specific, personal forms (*bios*), conducted and updated with incomparable mastery by our Giorgio Agamben [22], something which recalls both the non-causality of correlations and the impossibility to separate the individual cases, unless by preparing and applying experimental designs and observation models that address the various components of inter/intrasubject covariates separately.

² The Committee members, too, would have found considerable advantages in making reference to Robert H Frank, *The Economic Naturalist* (2007), who provides complete references at the end of each chapter.

The paragraph reports a selection of the contributions on our main subject that have appeared in Science in the interval since our last contribution [23], presented in the usual inverted temporal order. This is a veritable global encyclopedia of superior advanced innovative knowledge in neurology, with very rare contributions from Italian researchers. In addition, only another paper is cited, published in the course of the last 12 months and also mentioned by Newsweek's well-known scientific writer, Sharon Beegly, denouncing the practice of interpreting higher nervous function in analogy with those of the puppets of Voodoo rites (Cf: [24]). This has led the Editor of the Journal of the Association for Psychological Sciences to open an uncommon procedure of "prepublication dissemination", open, public prediscussion by the reviewers, an inspiring example that could usefully be followed by any peer-reviewed journal. The ensuing discussion, available at http://www-psychologicalscience.org/journals/pps/4_3.cfm has enriched not only scientific psychology, but also the debate on the statistical analysis of fMRI images (and others too), which clearly must make all the data acquired available, so that they can be confirmed not only in meta-analyses and "data fusion"(1984) of possible initiatives by the publishers, but also as the most rapid reorientation of researchers' approach, in this case beyond any form not only in the fashion of Offray de La Mettrie (*L'homme machine*, 1748), of Mesmerism (F.A. Mesmer, 1734-1815), and maybe "Marinism" [after the Neapolitan Marino (1569-1625) "wonder is the poet's goal"], to avoid learning of some critical interventions or comments from the New York Times or our disposable Gazettes, like the intervention by Iacoboni et al {Cf: [21], (2007; II:53-99)}, by giving an exaggerated importance to any prediction of prejudice, angst, anxiety, fear, pain and happiness, importance/cognitive surmises of personal and social ethics, which today are frankly more transient than the fast pace of the possible acquisitions, of significance data that are "too good to be true", in fact incredible. "Neuroethics" which is proposed as an essential teaching subject, but could first share the same 1/k rankings among the co-authors [25], to avoid mentioning it in the next paragraph.

3. Symple ethical issues

Our civilization proves to be rooted, rather than in Plato's dialogues, in the writings not made for publication, esoteric, of Aristotle's morning discussions to the initiates. Although everyone tends to the supreme good, *eudaimonia*, they do not all share the same concept, even though the ethical virtues, which derive from experience and habit, differ from the dianoetic or rational ones, and concern feelings and passions, require a fair measure, thus leaving wide margins for action [26]. Such borders may be too ample to represent a satisfactory, believable philosophy for modern man, who shies away from the drive to perfection of Plato's (and Pythagoras') lessons, needing constant mediation between practical (wisdom, *phronesis*) and theoretical reason (knowledge, *sophia*). Maybe someone has nonetheless wanted to live by regenerating the *ethical* conscience all by himself, and one cannot avoid thinking, even today, of the example of Wittgenstein's life [27], of how much seminal material he has left, especially in the second phase of his meditations and consistent activity. Clearly, with him it is the study of the internal cognitive processes preceding language, and that which can be thought but not said or written. In particular *ethics* to him is a transcendent mystique that is communicated through doomed attempts to show the inexpressible given the need to be silent, whereas thought is a sort of spatial and temporal representation or image of possible logical form, that may or may not exist, or be true or false. *Ethics*, like logic, esthetics and religious belief, belonging to the ineffable transcendent, has no sense but is not senseless. Significantly, in 1929/30, in a lecture to the Heretics' Society in Cambridge (published in 1965), he exceptionally read a short text following first Moore's definition of ethics (1903) ("ethics is the general search of the good") or, to him, has value, or is the meaning of life, or is the right way of living: these expressions were all used in the arbitrary, predefined *current or relative sense*, as a statement of fact devoid of a value judgement, and a really *absolute ethical sense* that can never entail a value judgement and, if it is anything, it is supernatural, and cannot be seen in

terms of any situation which, as such, would exert the coercion of an absolute judgement. He adds that in ethical and religious languages we always use similitude (without facts) or allegory, which however depend on something that, if it were removed, would make them senseless paradoxes. He concludes, echoing Voltaire, albeit in a different context, “Ethics is a document of a tendency in the human mind which I personally cannot help respecting deeply and I would not for my life ridicule”.

The Argentine Jew and great artist, Daniel Barenboim [28], has a Palestinian passport. He writes that, despite the extensive travelling required by his work, he never abandons the ethics of that great solitary, the Baruch who was expelled from the synagogue, who died at 35 years and left a heredity that has not been mined to the full [29]. Others, including some of our lay *maitres à penser*, express an interest even in centuries-old ethics systems [30]. Are there any alternatives? Not many; maybe the only serious ones are those followed for instance by Primo Levi, and, after the invocation on the last page “I write: have mercy. And then?” [31], by Cesare Pavese³. Moreover, how can one forget that suicide is the first cause of death among the young, who maybe are not sufficiently prepared? Current authors present as a form of precarious livelihood [32] the power of authority, albeit fictitious, experienced, here too as operating within the long-standing diatribe of the application of DL 517 to the clinical staff and, more in general, ominously attributing institutional goods, undeniable examples of discontinuity or better, warnings of intolerable states of emergency.

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³ Just two more examples: Walter Benjamin, cited in a recent paper of ours and, by inference, Meursault, the protagonist of Camus' *The Stranger*.

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