UNIVERSITA' POLITECNICA DELLE MARCHE AND MARCHE REGION, ITALY: MEDICAL PHARMACOTOXICOLOGY TODAY

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Summary

After our presentation to the Marche *Accademia delle Scienze, Lettere ed Arti* on 19th May, we now discuss newer data—many of which have been published in *Science*—recalling the most prominent, either cited and non-cited, and explaining the reasons for the approaches that have enjoyed the greatest success and have been implemented most swiftly *online*, besides the experimental (analytical) and explorative (epidemiological) reference models for pharmacotoxicology—including those for human clinical pharmacotoxicology—that have been developed thanks to newly available resources from Università Politecnica delle Marche and the Marche Region. The authors provide an update on socially relevant outstanding issues in the field and stress the need for collecting all (global) protocols and all research data for the completion of the collaborative WHO database of adverse reactions and pharmacotoxicological effects, a global electronic network including not only the pre-marketing phases of current trials. The authors go on to highlight the critical unresolved deficiencies of the continuously updated (auto)classifications, which have been proposed and implemented for optimization in this field. They finally discuss some interpretive examples of the latest non-invasive methods for medical analysis and of the ongoing study of pre-cognitive decision-making or non-decision-making steps for the appropriate uses, as well as examples of the abuses of the current pharmaceutical medicalization.

Key Words: Pharmacotoxicology, Clinical Pharmacotoxicology, Analytical and explorative classifications, Complex biosystematization

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[+] Corresponding author. Completed 10th September 2008. References listed in inverse temporal order. As for all Seminars currently in press, the full papers of all cited References (including complete copies, summarized and annotated) are available from the Archives.

"Do your work, respecting the excellence of the work, not its acceptableness", 3. Richness; "One would say, the rule is, -- What a man is irresistibly urged to say, helps him and us", 5. Behavior. Ralph Waldo Emerson, The Conduct of Life, The Collected Works of R. W. Emerson; vol. 6 (J. Slater, D. Emory Wilson, B.L. Packer eds) Boomer Books, 2008; Norman, OK, USA.
"I am convinced that He does not throw dice". Albert Einstein, 1926 [1];
"Who after all is an aristocrat? It's a woman untouched by vulgarity even when she is surrounded by it". Muriel Barbery, The elegance of the hedgehog, Europa Editions, 2008.

Introduction

In this note related to the current last year we mainly intend to refer to the "*Perspective*" [2], which the present contribution extends and updates after [3], which focused on *Pre- and post-marketing pharmacovigilance*, including the myths of *Placebo effects and the off-label use* of diagnostic, preventive and therapeutic-rehabilitative drugs prescribed ethically or non-ethically and/or (self)administered. Unfortunately, *given the conspicuous neglect by the Università Politecnica delle Marche committee in charge of the allocation of research funds (Cf:* ***Note Ia****), of the appointed Members of the ministerial committees of "national interest" (Cf:* ***Note IIa****), and of the same Administrations, which are the first-line responsible at the local and interuniversity level (Cf:* ***Note IIIa****), after the joint Region-Hospital and local Health Service committees, which have never to date manifested the least interest, or become constructively involved, not even by complying with the minimum requirements of the regulations they contributed to adopt*, the present paper highlights both the original scientific contributions, either in terms of teaching and of healthcare provision, and those relating to the failed regeneration of effective institutional renewal, which has not even begun to be addressed despite being repeatedly brought to the attention of the highest competent authorities. The situation has caused the widespread conviction of the prevalence of de-qualification, incompetence, obtuseness and abuse, and may have even damaged the state coffers. Nonetheless, it should be stressed, besides the content of the five references [26] of the previous Note [3], that the committee members were not the required authoritative, long-serving professionals [4], as demonstrated by their ignoring the recommendation that "*it is the impact and importance of the work that matters, ..., not where the work is published*", etc [5], and by their neglect of the ongoing debate [6] on the sociological analysis, demonstrated by the attention of the contributors to *online* journals to crucial topics of the current debate. The drafters of inadequate opinions have thus halted the progress of original research works planned and developed for the first 30 years. Suffice it to recall here, besides the self-explaining content of the integrally attached **Notes** in the **Appendices**, the failed refinancing of the "*Modellistica biomedica, Farmacocinetica e Bioingegneria*" Doctorate despite the exceptional, topical interest in these issues by the international Community, also presented in *Science*, after ref [7] in [3], as documented below.

1. Understanding system complexity extended to (medical) Pharmacotoxicology

From 1933 to 2008, in practice over the last 75 years, as demonstrated by the papers published in the undisputedly first and foremost global scientific journal, we have not only witnessed but also contributed – as shown by the eight notes, the present one included, in the 1st *online*

Society Journal in the three years from its foundation - to Pharmacology considered as a part of "*Whole-istic Biology*", special issue 2002 [7], which has followed the 1999 issue [8] on *Complex systems*, beginning with the contributions of von Bertalanffy [9] and the same Noble [10], on whose model problems persist at various levels (Cf: [11]).

There is no doubt that the new *online* method will continue to be followed for Science Signaling [12], but to confine ourselves to the question at hand, it cannot be denied that Pharmacotoxicology, primarily medical Pharmacotoxicology, should appropriate the "border areas" (*Grentzgebiete*; Otto Loewe) also addressed in [13]; we should all be aware of the limited scope of approximation, which appears to be increasingly simplistic or conditioned by the heuristic requirements of the recognition of the fallibilities of the essential incompleteness of the statistical models and of the mathematical frustrations of the complexity highlighted in Paragraph 3 below, especially when applied to the study of cognitive functional integrations. Clearly, in Pharmaco(toxico)economy, which fully belongs to the complex, systemic social sciences, each and any regulatory policy is included in the evaluation of cost-benefit evaluations of game theory, which currently are even discussed in the daily press [14]. Nonetheless, the extraordinary and unexpectedly complex genome of *Trichoplax adhaerens*, the more complex genomic data and the same genetic traits of the more malignant neoplastic process suggest, like ref [12] and [3], the inadequacy of the reification denounced by Lewontin [15]. Megaenzyme adaptability to novel functions is by now an established fact, which makes them very similar to pharmacological receptors. This may be due to their modular architecture and to the presence of native "metamorphic" conformations [16]; the current enzymology research is working especially on their *in vitro* microdynamics and kinetics [17], which however often fail to correspond to those found *in vivo*, for instance the ratio of substrate to protein concentrations is very low, making the adoption of its revolution *in vivo* ever more urgent, *not excluding choices that are no longer merely complementary, but essential, like those of the measures of magnetization transfer, here too implemented for a long time* [18]. Analyses of protein "interactomes" [19] and deeper are increasingly applied as systemic reference bases for the control of biomedical concentrations at the levels supported by the ever more sophisticated integrated models, as also mentioned above. It is quite surprising that only today its has been communicated as something of the utmost necessity at the same levels of gene and protein feedback interactions not only negative but also positive, where constant, robust outputs that rapidly adapt to relatively broad ranges of sustainable frequencies are required (Cf: [20], [11-, 10]). Once again we point out that our times require *the rapid, global diffusion of protocols and data* [21], primarily *online*, not only for clinical pre- and post-marketing pharmacovigilance (Cf: [3]), but also for all experimental pharmacotoxicology work, supported by the implementation of the more robust, modular but integrable models. The current alternatives, which ostensibly still receive the greater consensus and are equally suitable for systematization, require simulations of pharmacotoxicological target identification at the (sub)atomic, (macro)molecular-(sub)cellular receptor levels, *given the defined deterministic and non-deterministic limitations* of the results of analytical trials (Cf: [1]; [4] in [3]), with aspects that also encompass increasingly complex explorative-epidemiological experimentation for the maximum potential reduction of the translation lag, which have prompted a number of initiatives and some preliminary local developments [22]. Several examples can be provided that the lack of effective planning, in our case especially the lack of effective upstream socio-economic planning at the peripheral or at the central level (**Notes Ia and IIa** cited, in **5. Appendices**), on which we all necessarily depend, are to be ascribed to what can derive from them and thus reproduce, as our main reference Journal has reported in a timely manner [23].

2. Other possible consequences associated with fragmentary research approaches and with those affected by loneliness and "impertinency" (in the words of R.W. Emerson) of adequate not consistently systematized modelling

3.

In parallel with the Editorial of the FDA member recommending a revision of intellectual property law to stimulate a more productive cooperation between drug industry and academia, the press offers to an increasingly wide and involved public of readers a number of considerations on the European primacy, for instance in the field of investment for physical research, but not for biomedical and pharmacotoxicological research, not even at the national level [24], whereas our academic researchers have always been aware that their findings were being offered to the drug industry, being legally excluded from any eventual profits. In our previous contribution [3] and in the Monographic course (Cf: [25]), in the text and in the Addenda, specifically in the References [4], [100], [157-158], [173], [175-176], [182-183] and [191], we discussed the topics that continue to be tackled by the international scientific press and have finally reached the national popular press [26]. Again, it is not surprising that in the absence of effective coordination of sustainable planning for the physicists, or in the face of the inadequacy of the European and national and even regional coordination of biomedical research both in the industrial and in the academic field mentioned above, we are still lacking minds capable of conceiving first of all the modelling premises, which must be able to be integrated in the global analysis of optimization of viable systems. It cannot be satisfactory to be spurred on by the surprises mentioned in [23], examples of disappointed revelations [27], by discovering susceptibilities possibly ascribable to lack of synchronization [28], by admitting intolerable delays, e.g. of bipolar disorder [29], by privileging classes of or individual cardiovascular drugs [30], by awaiting *sine qua non* replies [31], or by privileging not adequately and immediately substantiated suspicions that an intervention is required by investing in preventative medicine, e.g. for atherosclerosis and/or osteoporosis (Cf: [47]; [54] in [3]), by extending the prescription scope of zoledronic acid to stem metastases [32], while continuing to ignore their limitations, highlighted by not less authoritative and enthusiastic operators. In any case the recommendation of the FDA member is clear, given the persistent decline in the number of new registered molecules, 53 in 1996 and 17 in 2007; it is equally clear that the issues, especially the practical aspects related to the sustainability of "bioequivalent, bioavailable, biotechnological and biosimilar" drugs that may eventually become generics also in fragile subpopulations after registration after the expiry of the patent for the original drug, not only for new evaluations of pre- and post-marketing pharmacovigilance (Cf: [33], [3]), cannot monopolize European research. To return to the comparison with modern physics, the debate on the secondary role of the Large Hadron Collider (LHC), developed by CERN (Geneva) with the largest research investment in history, is untenable until the project of the International Linear Collider (ILC; Waxahachie) is restarted and the Super B (Frascati) and the KEKB (Tsukuba) have reached full capacity (Cf: [34]). We all know that WHO-ITA (Ancona) would have been preferable, also to the academic world, to the International Collaboration Centre in Uppsala, which the Swedish government actively pursued and Italy did not. The advocated implementation of the database of integrated models of standardized biomedical system data of Sector BIO 14 can equally be conducted in the European region that is the "mother of great science" and of "precision physics", as well as of biomedical pharmacotoxicology, and cannot but assume also a potentially universal value (Cf: [35], [3]).

3. (Auto)classification priorities and sensitive issues of updated non-invasive, restandardizable evaluations

According to Huxley, science is the classification of common knowledge [36], and it is undisputable that pharmacotoxicological classifications, like the earlier chemico-pharmaceutical and human clinical therapeutic, constitute essential orientative systems for the profession, having regulatory, ethical-prescriptive as well as practical applicative functions. We first addressed the, originally binary, classifications of cholinergic products and receptors [37] and subsequently contributed to the development of modelling and calculation procedures, generalizing the topic [38]. More recently we focused on mixed dynamics and kinetics and on the characterization of substance abuse-manias and of placebo effects, also encompassing the effects of the symmetric motivations of the off-label use and potential abuse of products [39], which reflects an avoidable lack of international structural definitions and normalizations. After considering the latest contributions to the issues of drug addiction and manias [40], and, for the placebo effects, the consistency of the significant contributions of the Turin physiological school, with special reference to Fabrizio Benedetti [41], it should be noted here that these advanced research fields, which are surely borderline and potentially on the frontline, like those of great cognitive neuro-psycho-physio-pathological interest, at least considering the latest confirmations of the best known publisher (Cf: [42]) and, as regards pharmacotoxicology, are not yet systematically and globally organized or structured according to their actual, also biomathematical, complexity, while the need for (auto)classification structuring, where it is not ignored, exists and is inevitable. From 1992, in the single issue cited [7], devoted to "Systems Biology", to 1994 non-invasive PET and fMRI imaging techniques [43] have demonstrated an overlapping of neuronal modulation networks of placebo and analgesic effects, something that today is broadly established for all higher sensory and neuropsychic motor modalities at all levels of the "interactoma-connectoma", as stressed in the References. With regard to the application of essential non-invasive investigation methods like fMRI, whose advances are always included in our contributions (we were the first in the university to support them, in the Programme that was eventually adopted) (Cf: [44]), some criticism and perplexity has been expressed in some quarters [45], considerations that have long ago been addressed in the approaches to the autoclassification models of analogue drugs and of the corresponding convergences, which can not be fully, definitively optimized, and of their iso-receptor specificity and selectivity [37]. The application of "statistical tools without direct averaging potentially heterogeneous voxels" will require profound revisions where spatial and temporal sensitivity has been strengthened with obsolete calculation tools, and will benefit from cardiovascular gated imaging [46]; nor will it be sufficient to address and resolve, for instance, the questions related to clinical fMRI not depending on the (micro)circulation [47], like those of the non-secondary glial contribution to the mixed dynamics and kinetics of the technologies [48] vs those of biological specimens, maybe also samples subjected to pharmacological treatment. It will be essential to observe in each cases the actual results that can be obtained using statistical models for the evaluation of the significance of the inhomogeneity of non-independent factors that can no longer be addressed by the rough, misleading, mean estimate of central values of distribution not defined in the models. The proposed approach necessarily requires outside confirmation where the analytical data acquired are no longer available for evaluation with the more sophisticated IT tools. At the same time, beside the precision and accuracy of the significance in each individual case, it will be necessary to review the diagnostic applicative clinical contributions and those from the verifications of pharmacological interventions, prescribed and administered. It is inadmissible, indeed unthinkable, that the application of the more advanced technologies should not involve the use of the potentially more refined IT tools, both as regards (micro)spatial resolution and the fastest observable kinetics.

Only in this way can the problems of discipline and autoclassification interactions be addressed and resolved, including those of complementary medicine, of substance abuse and dependence, of placebo effects however overlapping, of the off-label or regular use of drugs, up to those of the motivation of personal and/or professional decisions of "synthetic bioethics without borders", and of "moral sentimentalism", and of the same "sympathetic and emotional economy"[42], whose topical nature is however clear to all.

4. Current conclusions

It has now been communicated that funding has been made available for the enlargement of the Ancona branch of the National Institute for Geriatric Research (INRCA). After the request by the University to host and collaborate with us, each year since 1983 (Cf: **Note Ia**, **a)**, Faculty meeting of 11.5.85, item 6 on the agenda, we have been the only ones to be excluded from operating there, from participating in the Ph D, the Section of the Interuniversity Centre, the Specialization School, the WHO-ITA Collaboration Centre and the Clinical Pharmacology and Toxicology Service, given the lack of a hospital and the disparity of the working space granted on university premises. Ironically, or perhaps cynically, the Administration is now offering, though only for next year [49], a new cofinancing tool for "large and/or medium-sized equipment", which should have been reserved to upgrading the (micro)imaging tools and to strengthening the sensitivity of the MR digital spectrometer (HR-MAS), the first to be delivered in Italy, fully approved as planned according to our recently developed initiatives, also elsewhere [50], but remained incomplete, without reason ignored in the only two previous financing programmes, at a time when we read that the "University lacks authoritativeness, funds and projects" (Cf: [24]). Nonetheless, Elsevier publishes the *online* Physician's Journal (Giornale del Medico, GdM), whose first issue begins with an article on "Non-conventional medicine: four universities on the starting line". Our effort, here re-proposed and updated by citing the most authoritative literature, has been to establish the presence and the urgent, topical nature of projects focusing on the implementation of complex integrated systematic modelling, which elsewhere are successfully being developed. In effect this, our last contribution of notes and comments, here devoted to the current year issues of *Science* as well as to previous papers [2-3], [11], [18], [20], [22], [26], [35], [37-39], does not aim at exhaustiveness, but recalls the various threads of our work; this requires further development, modelling and organization into a biomedical-pharmacotoxicological database to extend and complete the WHO database, the first and still only such initiative. We thus hope that our contribution will inspire other researchers and sensitive colleagues and that they will be able to continue this work and contribute to implement its essential lines.

5. Appendices

Note Ia
a) Annual example of locally coordinated programme, the sole submitted for university funding (formerly 60%) since the foundation of the Sector and not financed again after document no. 1959 of, 7.5.2002, where the sum granted was 478 euros.
b) Observations made every successive year, all unanswered.

a)
UNIVERSITY RESEARCH PROJECT No 3987, Financing year 2008, Title: Innovative methods in general and special pharmacotoxicology (continuation).

Project description and principal aims

The total sum requested is 5,164 euros, for the five years in which the contribution was not granted. Over these five years my work has exclusively been devoted to the Projects approved by the board of the institute, to the inventory of existing equipment, including complex machines, and to appropriately trained personnel, with the MAIN CONSISTENT OBJECTIVE of the INNOVATIVE PROGRESS OF THE SECTOR founded for the University, according to the conditions listed here, for the relevant details of which the reader is referred to the description of the earlier attached Projects, including those of the partial contributions obtained, especially nos. 3161 (2007), 1881 (2006), 1849 (2005), 1345 (2004), 646 (2003) and 265 (2002). The President and Coordinator of the Faculty Committee, and through him the committee Members (e.g. the Chancellor, the Dean and the Department Head) were informed with registered mail, letter no. 12973361335-5 of 22.1.07, of the destruction of my research group through its forced transfer, decided against the will of three additional collaborators, two of whom were graduate researchers, besides the hospital staff. It has never even been possible to use half of the time of the remaining staff, as had been agreed. For each item listed (from a to i), as for the items relating to the present submission, not only the title and front page, but also the full text of papers published in indexed international journals (or in national journals where the interest of the data is local or regional), are available:
a) Assays and autoclassification techniques of iso-receptors and analogue drugs; b) Redox, nitrosative and phosphorylation potentials, and non-invasive in vivo/in vitro readout techniques, including magnetization transfer for the measurement of native iso-PCK and metabolo/nomic activities and for metabolic syndrome co-identification; c) Pharmacotoxicokinetic monitoring of more than 80 drugs and their metabolites, extended to the studies of the consumption of multiple substances-manias and of sport and leisure time doping in the Marche region; d) Pharmacotoxicoepidemiology (Development of the WHO-ITA Collaborative Centre approved by the World healthcare assembly, of "Pre- and post-marketing pharmacotoxicovigilance", corresponding to the clinical healthcare project approved by the Head of the Ancona Azienda Ospedali Riuniti on 1.1.2006); e) Pharmacotoxicokinetics of time series; f) Multiparameter studies of the peptidergic, puri/pyrimidinergic and nitrinergic, non-adrenergic, non-cholinergic systems (ongoing ITA-USA-Canada collaborative projects); g) Caspase modulations in apoptotic cycles; h) Joint research of the first jointly founded interuniversity centre, I.M.O., Section of "Human pharmacotoxicology", specifically of fluorescence spectrometry, near infrared and multinuclear MRI of organs/tissues, cells and intact subcellular preparations; i) Other topics, subjects and titles detailed in the volume of the First 20 Years of the University and Proposal of an agreement with INRCA (Ref. no. 6351, 9.2.83; Faculty meeting of 11.5.85, item 6 on the agenda, decision still postponed at the time of writing).

b)
Letter dated January 4, 1996; copy to: the Chancellor, the Dean and the University Research Project Evaluation Committee (formerly 60%) sent each year and gone consistently unanswered.

Dear Dean
Competent Committees
and Chancellor

Re: Funding applications for University Research Projects, ref no. 1339/95 the Dean's office, 20.12.1995.

I am grateful for the reception and the regulations recalled. In what I hope is the general interest I must however call again the attention of my colleagues sitting on the Committee on the fact that research published in indexed journals with an impact factor (IF) should not be valued more than other contributions. This practice has caused severe damage, also in some public competitive exams, leading on occasion to an unjustified award of public goods for research.
Italian (and European) research is not less authoritative than the Anglo-Saxon, which has unfortunately introduced the fad of the IF, which, I repeat, has resulted in no greater prestige but in unreasonable violence against researchers who have honoured first of all the science of their country and then of Europe and also of the world.
A radical rejection of this approach is urgently needed, for it prevents the detailed assessment of the merit and the substance of works which, besides the well-known utilitarian reasons, are often the expression of festering or actually scandalous scientific societies, of formalism rather than content, of overt inability to conduct in-depth analyses and especially, indeed crucially, of lack of original and serious individual contributions.
The IF, as it has unfortunately come to be conceived, calculated and applied, and already described as misleading, is the expression of banal, elementary arithmetic/algebraic criteria denoting merely a mastery of accounting skills, which neither qualify nor honour us. I wish to stress that they have nothing to see with the soundness, the originality, the genius of exceptional research, hopefully "occasional current trend". In fact, they are often a prize to fatuousness, when not to personal interest and to economic entrepreneurial groups that oppose the purity and essentially individual integrity of the scientific endeavour. To sum up, it can be concluded that to date the IF has characterized especially mutual aid clubs that side with or participate in activities of serial

killing of authentic, genuine researchers.
In this context and as reflected in the three enclosed letters (1-3), I hope that the committees will abandon these criteria, if they have ever shared them, thus privileging the scientific value of applicants.
I have listed below some alternative criteria that could be applied for the evaluation of the projects submitted for University financing, on which it may be useful to open a formal discussion in defence of the rights of those who assiduously continue to conduct their research work in their respective fields, characterizing the survival itself of our Medical School (and the University);
a – Original line of research also reflecting consistent, systematically pursued studies. The successful applicants should not address areas of research that are "normative" or "fashionable" and buoyed by the support of powerful publishing groups but, rather, "orphan" fields, or at least fields that are not very popular, maybe harder but capable of producing results that will never be ordinary or banal;
b – A better utilization of the goods, including equipment, that have accrued to the University through long-standing dedication and personal commitment, through consistent effort and full-time presence. It appears obvious that the lines of research to be privileged are those that have been approved by the central administrative bodies, which reflect the persistence of the rule of law of our autonomy. Outstanding issues to be resolved include unfortunate situations, where complex and costly pieces of equipment have remained under- and even unused for up to decades due to inconsistent funding, which has also extended to current expenses and maintenance. This is all the more troubling when such equipment is also mentioned in approved projects (e.g. interdisciplinary projects that are also of didactic, inter-multi-disciplinary, interfaculty and interuniversity interest). In addition, those lines of inquiry, that undertake to address local and regional deficiencies, should not be neglected a priori, despite their limited circulation.
c - Priority financing (never approved!) for the needs of the winners of post-doctoral scholarships and PhD students should also be envisaged, as they risk spending years at their desks precisely because of an inconsistent grant system (this is indeed a characteristic of the *bel Paese*). Lines of research that have proved productive and competitive also for teaching have substantially been abandoned without a clear justification and/or explicit reason of merit or lack thereof, and left to the vagaries of national policies for research funding, maybe according to the elusive principle of the "automatic, indiscriminate rotation of privileges", which has characterized our national institutions. A remedy to this needs to be found within our autonomous planning activity.
d –International cooperation projects with authoritative and prestigious institutions, approved and awaiting approval, should be sustained and pursued, especially since they are inadequately funded in our country. Here the focus is on the autonomous policies for scientific development of the Medical School (and the University);
e – We also need to defend, enhance and where necessary restore the principle of scientific coordination if it has been ignored and overruled by the same Faculty organs;
f – Finally, it is essential to restore the crucial institutional principle that assessments of scientific merit, which must always be explicitly motivated to be acceptable, be expressed by researchers in the same areas, at least those indicated in the current regulations, or else by individuals in charge of specific sectors.
The application of arithmetic calculations of normalized and normative IF, which are general as they are generic, must be indignantly rejected, especially if they regard specific areas, because it substantially tends to ignore the deeper problems, underestimating them, possibly due to an unconscious bias, and replacing specific technical figures with elected authorities, which have nothing in common with and do not derive from them.
The essential competence of the individuals, where defined and specified by higher regulations and divided into didactic-scientific areas in the medical School and in the University, should not be replaced by criteria that are not in the remit of the Faculty. Besides being patently and overtly misleading, they totally ignore the scientific debate, which has been exhaustive for those interested: the enclosed note suggests for instance a number of corrections, but other skills can be harnessed if pedagogic and scientific superficiality and inadequacy due to administrative decisions are to be avoided. The diagnostic potential of multivariate autoclassification criteria for χ_2 minimization, multiparameter criteria for holistic evaluation, also in fuzzy sets, should be fully studied to replace casual applications with guidelines that from the viewpoint of theoretical inquiry I consider as expressions of well-established stupidity.
As Karl Popper noted, the history of science is the history of its errors, but in the current preliminary phase of funding allocation that makes this possible previous errors should not be repeated.
In conclusion, as a member of the faculty and of the university, I therefore wish to dissociate from the adoption of practices that have exhausted their experimental impetus, acquiring a less noble significance: if their adoption were publicized beyond the local situation we could all be involved and covered with ridicule tomorrow.

Sincerely,
Luigi Rossini

Enclosed documents
1 - G Lewison, J Anderson, J Jack. Assessing track records. Nature 377; 671:1995;
2 - S Hansson. Impact Factor as a misleading tool in evaluation of medical journals. The Lancet 346; 906:1995;

3 - G Motta, NB Metcalfe. Joumal Impact Factors. Nature 376; 720:1995.

A full literature update has been provided every year and even more amplified and urgently requested topics have been included. Now see [5] and the Editorial: Simons K. The misused Impact Factor. Science 2008; 322:165.

Note IIa

Abstract of the reply sent after the failed financing of the project submitted to the internationally coordinated programme of national interest (former 40%) for the 8th consecutive year. The letter went unanswered.

27.7.08 Registered letter

TO THE MINISTER Dr Avv Mariastella GELMINI,
MINISTRY OF EDUCATION, UNIVERSITY AND SCIENTIFIC RESEARCH, ROME,

Copy to:
to the CHANCELLOR OF UNIVERSITA' POLITECNICA DELLE MARCHE, Prof Ing Marco PACETTI,
to the DIRECTOR FOR RESEARCH DEVELOPMENT AND COORDINATION, MIUR, Dr Luciano CRISCUOLI,
to the CHAIRMAN OF THE PRIN STEERING COMMITTEE, 2007, Dr Prof Clelia MORA, University of Pavia,
to the MEMBER OF THE PRIN STEERING COMMITTEE for Biological Sciences, Dr Prof Carlo RICCARDI, University of Perugia,
to the CUN MEMBER, Dr Prof Vincenzo CUOMO, University of ROME LA SAPIENZA,
to the WELFARE MINISTER, Dr Prof Maurizio SACCONI and his CABINET, ROME.

RE: Reply to the Communication Ref. no. no. 93, 23.7.08 by the Director "Co-funding of research projects of national interest – Year 2007".

Today, on my 75th birthday, in the last year of my prorogated tenure, I wish to make on the occasion of the delivery of the above communication a number of preliminary considerations as the senior member and co-founder of the University, as a Coordinator irreversibly and conclusively excluded from Programma di Ricerca Scientifica di Rilevante Interesse Nazionale funding.

I have noted that Decree no. 112, GU 25.6.08 has given rise to reactions and objections from various quarters, of which we know the miseries (Cf.: 1). Nonetheless, there has been no word as of today on the regulations concerning PRIN financing, including that for the year 2007, which has been re-issued on the 17th of this month without taking any observation into account and without amendments, despite detailed yearly suggestions (enclosed herein for the convenience). After raising the issue at the meeting of the UPM Board on 18.2.08, I have felt the need to prompt an administrative verification of the ministerial funds of Healthcare research-AIFA. I hope that my letter of 24.6.08 to the welfare Minister, following the one of 4.1.08 to the Health Minister, will command the same attention as the present one.

The issues (3) publicly raised in this forum—see the comment of the new Editor of *Science* (2)—have not yet been effectively addressed in either case by our new central organs. These issues continue to be not separated from lobbying and are therefore devoid of the consistent, real, necessary authoritativeness that can accrue only from being faithful supporters of the basic principles of the rule of law, which the serious commitment of Italy's researchers and lecturers intends to privilege and request, above all at the UPM, the University with the symmetric peacock logo, which promotes "the future as a value" and "merit as method"; again in line with *Science*, the ethical imperative of senator Charles Grassley (4). Undeniably, applying the philosophy of Robert Aumann (5), it may be needed to go back to Ralph Waldo Emerson (6) before sharing the *Posizioni e concetti* (7), which cannot but lead to the nihilist political and moral desperation of the prophecies of *Der Nomos der Erde* and of *Die Wendung zum diskriminierenden Kriegsbegriff*.

The long route towards Reform (Cf.: 8) can thus still be taken, by your Authority, if the observations that I have definitively summarized herein are not again dispersed and rejected.

I hope I can be of help and further assistance.
Sincerely.

Luigi Rossini

(1) S Livadiotti. L'altra casta. L' inchiesta sul sindacato. Bompiani 2008, pp 237;
(2) B Alberts, B Hanson, KL Kelheer. Reviewing peer review. Science 2008, 321: 15; M Raff, A Johnson, P Walter. Painful publishing, Id: 36;
(3) IR Marino. Working toward meritocracy in Italy. Science 2008, 320: 1289;
(4) J Kaiser. Senate inquiry on research conflicts shifts to grantee. Science 2008, 320: 708;
(5) S. Hart, ed. An interview with Robert Aumann, Microeconomic Dynamics, 2005, 9: 683-740;
(6) RW Emerson. The Conduct of Life, The Collected Works of R. W. Emerson; vol. 6 (J Slater, D Emory Wilson, BL Packer eds). Boomer Books, 2008.
(7) C Schmitt. Posizioni e concetti. Giuffre' 2007, pp 563; Id. Il concetto discriminatorio di guerra. Laterza 2008, pp 85;
(8) E Brezin, A Triller. Long road to reform in France. Science 2008, 320: 1695; M Enserink. Despite protest, CNRS moves toward major shakeup. Science 2008, 320: 1705.

Enclosures:

Documents, comments and queries of the PRIN-COFIN 2000-2008 assessment sheets made available, received as of the present day. Total: no 63 sheets.

Abstract. Comment on the PRIN-COFIN 2007 ASSESSMENT SHEET, the only one received as of the current date.

Awaiting other replies (Cf.: Letter to Consulenza/Caronte Desktop, High Priority, 26.7.08 9:33), it is crucial to highlight that SHEET 2007BJ8T4W denies all evaluations previously made available and is unreasonably and unjustifiably contradictory, since neither the arguments nor the scores in the 8 previous years envisaged the possibility of a reply.
In addition:

a) The project was drawn up by three researchers. One of them, Prof Joseph Larner, is chairman of the department where the undersigned, already with tenure, collaborated with 6 recent biology and medicine Nobel laureates. The third, Prof Roxanne Deslauriers, is the scientific director of the NRC Biodiagnostics Institute (Canada), a major North American centre for the study, design and testing of spectrometry and functional NMR, where the undersigned was "principal investigator". The updates in English of Forms A and B of this year's submission were approved by the same researchers, with whom the undersigned collaborates consistently on the topics in question (see Forms 2007 A and B). I will make no comment on the irrelevantly apodictic observations on the obscurity of the Italian text, but I must denounce the totally misleading score of 5/15;

b) The coordinator closed Forms A and B on 26.10.07 11:24 and 17.10.07 12:04, respectively. The biannual proposal (including the request for funding) of the previous years was halved because – as highlighted by the writer of the Sheet in c) – his retirement on 31.10.08 will prevent him from continuing the project in Italy. Nonetheless, the same was agreed on with Collaborators Prof Giorgio Roda (Un. ROMA Torvergata) and Dr Lamberto Re (Science Faculty, UPM), who are reading my copy, since no separate proposals were presented on this or on previous years. The totally unreasonable score of 1/10 is therefore even humanly unacceptable;

c) The experience denied and/or judged with sufficiency by the latter proved merely his superficial inability, overt partiality and scarce competence. The incredible words "...publications in obscure journals", are denied by the content of paragraphs 7 and 6 of Form A and B respectively (Cf.: See note (°)). It is true that on the issue of the 2007 update the undersigned is still the sole Italian researcher who published an Editorial in Trends in Pharmacological and Toxicological Sciences (TiPS, 1981, 2: I-V). Thus, the Chairman of the Steering Committee, formerly of the Guarantors, is formally invited here to perform the required rectification, offering formal and sincere excuses;

d) The score of 3/10, equally unacceptable as formulated, cannot but be rejected; the "scarce interest of the project and its objectives" pointedly ignore permanent international collaborations with authoritative researchers. The higher authorities are asked to intervene because the problems, also of economic nature, that have ensued contrast with the genuine, imperturbable consistency of the coordinator (Cf.: Riflessi condizionati da stimoli termici nella cavia. I, Effetti della narcosi, dell' ipotermia e di farmaci psicotropi. Arch Sci Biol XLVI, IV, 356-369, 1962) with regard to the very topical area of "peripheral memory". It is essential to use only non-invasive methods, including spectrometry and 31P functional NMR imaging, to avoid the terrible and confusing systematic approach of "mediated" estimations of metabolite (and drug) levels whenever absurd tissue (and obviously cell) fragmentation is performed. This method does not respect the native living integrity and does not estimate the respective distribution of (micro)volumes. These ways are erroneous and must at last be

officially abandoned. The definition of the evolution of the forgotten compartmented redox and (nitro-)phosphorylative parametrizations, adequately updated, is an undeniably original and necessary correction to the current incest of international biomedical research (°);

e) Score: 2/12. The Director for Research Coordination and Development of MIUR, after reading the enclosed e-mail of 18.6.08, also sent as a Letter to Caronte/Desktop, High Priority, 23.07.08 10:15, is asked to annul the Sheet given the several opposite statements and replies, including the enclosed assurance of the Department Head Dr Giovanni D' Addona, S.A.U.S. - Uff VIII, ref. no. 1004, 12.7.02, "... . It is barely the case to confirm that intra- and interuniversity programmes both receive equal attention from the Committee as well as the Reviewers";

f) Financial sustainability, which consistently passed the examination of the previous Reviewers, is considered "too high" this time. The colleague appointed for the last devastating round is probably unaware that functioning and maintenance expenses and those for the purchase of the cryogenic gases for the advanced superconducting digital Avance Bruker instrument, which lies quenched, as per the supply contract reported under paragraph 1.7 of Form B amounts to 22,680 euros, or more than one fifth of the yearly request reduced to 100,100 euros, whereas the use of the minimum number of 300 rats was subtracted from the previously conducted experiments, of which the colleague must have learnt from reading the two "preparative" notes reported for the purpose among the seven cited in the Note (°): "Rossini L, et al. Epicardial auto-fluorescence NAD(P)H kinetics in the ischemically preconditioned Langendorff rat heart. ... . Part 1, Pharmacologyonline 3, 125-176, 2005; Part 2, Id, 18-63 – Attachment: 18 pp (tables of Data)-, 2006 (ISSN: 1827-8620)". Therefore, unless the evaluator is competent in statistics, and the minimum number of animals depends on strain variability, he should avoid making inappropriate comments and express unfounded evaluations.

The sheet clearly and as usual fails to report the explanation for the impossibility of calculating a correct mean, unless it is weighted, merely giving a total (obviously false, another insult to minimum intelligence!) of 17, and repeating the abused, boring, unacceptable excuse "given the scarce scientific interest and its lack of organic approach ", which do not deserve even the endeavour of devising further comments. I am thus awaiting the REQUESTED SHEETS to complete the examination with a view to choosing a course of action, not only to protect the respect due to my own person and position, and that of the coordination group of this University in whose foundation I participated.

Luigi Rossini

(°) The Chancellor of UPM well knows that the continuity of production, prompt preparation of the first notes – seven in the last three years, in the jointly founded international society, albeit online, journal – preceding the possible final diffusion in more authoritative printed journals the undersigned, possibly the only person to do so with faith in the national Institutions, has not hesitated to spend in the same three years no less than 30,000 euros of his own money.

Note IIIa
Failed adoption of the Departmental decision of reactivating the Human Pharmacotoxicology section, the 1st Interuniversity centre to which the University of Ancona has been affiliated

4.7.08 Afternoon
Delivered by hand, by internal mail o by registered mail. Please let me know the relevant ref. no. at l.rossini@univpm.it

TO THE CHANCELLORS
Dr Prof Ing Marco Pacetti,
and through his office, to the Senate and the Administrative Board, UPM,
and Dr Prof Silvano Focardi,
University of Siena
Copy to Director, Department of Neuroscience, UPM,
Director of the Physics Department, formerly Director of I.M.O. Interuniversity Centre, University of Siena,
Dr Prof Mario Rigato, Physics Department, University of Siena.

Re: Today's meeting of the Neuroscience Dept, UPM (4.7.08); item 9 on the agenda – Adhesion to the I.M.O. Interuniversity Centre

I wish to thank first of all the Director of our Department, Dr Prof Guidalberto Fabris, for making available to the board the documents required for casting a reasoned vote (Cf.: my letter of 19.6.08, enclosed in "A", 139 pages) and for the final expression of the favourable unanimous vote, which has just been held.

To gain as much time as possible, here follows a summary of my relevant interventions in the faculty meetings. Those that have been addressed directly are enclosed in "A" ("B", 7 pages; "C", 27 pages, and "D", 17 pages, are already known to those who are sent copy, due to previous mailings), as is the full text of two notes of 23 February (26 pages), cited several times, which are the expression of the continuity of the collaboration, based on jointly founded and willed Programmes, not only with the Physics Department of the University of Siena since the beginning the first Interuniversity centre in which the University of Ancona, now UPM, has participated – a continuity that is still reflected in the letter of 28.4.08 by Prof Angelo Scribano (in "A") -, and later as Section of Human Pharmacotoxicology, of which I have long been head. Some Programmes, on which I have worked until the presentation of the second on 19.5.08 and which have already been sent to colleagues in Ancona and Siena, have also been developed abroad at other Institutions.

I am not sending this correspondence to the recently elected Director of I.M.O., whom unfortunately I have not yet met, not even after the missives whose full text is enclosed in "A", whereas I am sending it for the first time to the Chancellor of Siena University, Prof Silvano Focardi, co-founder of the contemporary Section of Ecotoxicology and first Secretary of the Scientific Board of the Centre, knowing that he will usefully and conclusively discuss it with the Director, Prof Claudio Leonzio as well as with Professors Angelo Scribano and Mario Rigato, witnesses of the steadfast, consistent contributions from the Ancona section.

During the discussion at the Department board meeting I reminded the members of the goods inventoried by myself, all of which have been acquired exclusively with public funds of national and regional scientific and healthcare bodies, according to joint interuniversity planning, and whose value is at least 1200 million former lira. These goods have been impossibile to use for at least the last 15 years, after the excellent direction of the former Dean Prof Andrea Corsi, and Faculty decisions by the former Dean Prof Alessandro Rappelli, a decimation of which I was never informed and that penalized the ad hoc trained technical and administrative staff. Researchers and lecturers previously affiliated to the founding sector moved to other Faculties of the University of Ancona, or were hired elsewhere – e.g. Prof Giorgio Roda, who won a position as an Associate Professor at Rome 2 – Tor Vergata – and were never replaced and/or made available for the formally adopted joint Programmes. Material and, alas, human resources were thus ignored and made redundant. This was later compounded by avoidable incompetence and lack of skill, when they were not disaggregated and anyway where they were partially used as an effect of organizations that never included, indeed unreasonably excluded us. These are examples of harsh, limitless irreducible prevarication, unless one makes reference to the cases cited by Matteo Motterlini in *Trappole mentali* (Rizzoli 2008).

All these facts were re-proposed in the same Department board meeting of 27.6.07 after the Chancellor's decree no. 643 of 25.5.07 (Cf.: "A"), and later, obviously, to the higher Authorities. Nonetheless I wish to summarize them again for a definitive elucidation of the issue, besides, clearly, to protect myself from any administrative liability, to which I am totally extraneous. In synthesis,

a) Enclosure "B" reproduces a draft of which if I am correct I heard about during the Faculty meeting, and which I have decided not to examine or enclose as proof of my TOTAL PERMANENT CONTINUING, UNINTERRUPTED SUBSTANTIAL DEDICATION of confirmed participation in the work of the INTERUNIVERSITY CENTRE, AT LEAST DURING MY PROROGATION OF TENURE despite the ostensible interruptions of the activity of the Section of Human Pharmacotoxicology, of which I was not informed. The draft recalls and reproduced without important changes the points jointly decided and adopted by the Chancellor Paolo Bruni in the agreement (Atto Convenzionato) examined today (Cf.: Ref. no. AA.GG. 18790, 9.8.88);

b) Knowing Art 10 of the agreement, at the end of the first six years, or at least since 9.8.94, each year and on each occasion and venue I have expressed in vain to the authorities my will and intention of continuing to pursue the project, not only concretely, by using the patrimony of investment in human resources and goods. The same occurred at the Neuroscience Dept, despite my formal requests ever since the first department board meeting (17.9.03);

c) Also knowing Art 6 a) of the agreement, and the enclosed Chancellor's designation (no. 67, of which AA.GG. 778, 9.11.89, at the time when lecturer Dr Lamberto Re transferred to another Faculty of our University to take the post of first pharmacologist), I have also continued to state formally, at Faculty meetings and subsequently on request in the notes sent to colleagues and finally in print, *my inability to indicate to the Chancellor* an

alternative candidate from the Ancona section of human Pharmacotoxicology (lecturer or researcher) *for the possible new appointment*.

To summarize, because all this really cannot be borne any longer, I have communicated the UNIQUE CASE described above to the higher authorities from a sense of duty and propriety but also for my further protection.
So I have had to reiterate the reason for my unfavourable vote on the *Inventory of mobile goods* (agenda items nos. 3 and 7 of the proceedings of the Board meeting of 28.3.08) which however did not prejudice the content of item 10, *Sundry*, on the agenda, on the issue of *Planning of lecturer needs, etc*, a topic that was addressed almost simultaneously with the one discussed in the parallel Faculty meeting of 27.3.08 and commented on in the cited enclosure "C", here again attached. I fully supported, upon request, the explicit stance of the Director on item 3 of today's meeting – *Organization of the Technical-administrative staff* -, recalling the recent surprise - 1.7.08 in front of the Provincial Occupation Office (Convening of the conciliation board as per art 66 DL 165/2001, Director of "Ospedali Riuniti di Ancona" ref. no. 18718, 10.4.08) -, while I was firmly against item 4 – *Distribution of funds for running expenses 2008* – since for at least 10 years I have been unable to use the funds allocated to the first lecturer, ordinary Professor, of the Pharmacology sector to conduct the same previously approved research work, duly extending my analysis to the case stated in item 12, *Sundry*, regarding the sum total of what I personally advanced to finance those activities, all documented, amounting to 30,000 euro.
I therefore trust in the rapid conclusion of the process involved by the vote on today's item 9, which I hope the Chancellor will coordinate personally. I am as ever ready to provide any additional clarification both in Siena and in Ancona. I hope that the TWO competent bodies will work to achieve a prompt solution after the adoption of the current decision.

I also thank again my readers and colleagues, men and lecturers of the best and proved faith and will, and return their kind wishes and regards.

The senior member,
Luigi Rossini

Documents cited: enclosures "A","B","C", "D".

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