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Global recurrent classifications in experimental and clinical pharmaco-toxicology*

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Premise

The Greeks were already aware of the fact that a *farmacon* could be both a drug and a toxic substance (*in cauda venenum*). However, current pharmaco-toxicology (PT) has not yet been able to establish definite risk / benefit ratios related to drug administration: this concerns both the recipients, including the population, individual subjects and organisms, complex analytical or kinetic structures distributed over time, and dynamic structures, and the time frame involved (simultaneous, mixed). Especially on these critical issues I have reserved to the Accademia a number of dense and original contributions, especially of methodological nature, some of them quite extensive[1-7].

These contributions have been published only in our Proceedings/Papers, the last three involved communications presented at least 12 years ago. Given the time elapsed, I feel a brief update, at least of some of them, is now in order, also in view of the possibility of their diffusion in print in the near future.

Even the continuously evolving PT sciences, whose evolution is affected by crises related to the ability of the models themselves, and of the experimental tests, to be falsified, cannot escape the repeated classification of their complex nature, albeit consistently dependent on their individual, even isolated concepts of individual and general knowledge; this presents indefinite aspects of debates of educational and professional responsibility that is first and foremost personal, making reference to ethics values that are only occasionally enforced in national and regional regulations. For instance, it is essential for professional training in biomedicine to collect consistently and preserve completely all available information from animal experiments – as in standardized multidimensional screening.

Though contrasted this is essential information, like that of clinical trials, that cannot be confined to traditionally controlled studies, but must be extended to all possible cases justified by the diagnostic, preventive, therapeutic and rehabilitative interventions applied. The IT revolution, together with the revolution related to the most advanced knowledge domains of the analytical chemical, physical and epidemiological theories, has enabled its dynamic structuring of feasibility. Also in this context the vocation of *grentzgebiete*, the need to delve deeper into shared borders, should not be neglected. Those interested can find the relevant bibliography also in the newer references reported here[8-15].

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Recent Contributions

Over the last few years all toxicology-related research avenues have been inexplicably and unjustifiably abandoned by this university and regional hospital (despite, but certainly not by, ourselves). The resulting damage has been severe and irreversible, affecting persons as well as the institution. Nonetheless in the framework of the experiments of the first substitutive Projects (Cf: Chancello n 8791, 1.4.2009) financed in the 2007-8 budgets, it has been possible to address only our own permanent research lines, objective autoclassification, based on the adverse reactions and effects database, an international network begun here and encompassing today 141 national reference centres of the current 137 participants.

In addition (and very much unlike the literature[16], where the issue has only exceptionally been addressed), thanks to the courtesy and generosity of the colleagues of the Uppsala International Collaborative Centre, our original software[20] – subsequently distributed to the 141 Centres, has enabled analysis of the 201,928 adverse events and reactions reports relating to the 73 contrast agents included in the conventional classes, sent to the WHO bank over the first 40 years of its foundation[20].

Their significant autoclassification profiles were examined according to the original standardized model, i.e. as divided into the **seven most frequently reported groups in the two 20-years periods**[17-18] **as well as grouped** into the chemico-pharmaceutical classes of 30 ionic and non-ionic iodinated agents (ATC V08A, subclasses –A, -B, -C and –D)[20], used as radiographic agents; 10 paramagnetic agents for MRI enhancement (subclass ATC V08C-A)[19], and their biosimilars[21]; finally, for the same products, the 4,436 reports sent from Italy were compared to the 181,744 sent by the other countries[22].

Current Conclusions

The diagnostic products employed in radiology should not give rise to direct dynamic benefits, but present risks of rare complex toxicities such as nephropathy (CIN) induced by iodinated agents and nephrogenic systemic fibrosis (NSF) associated with gadolinium-based contrast agents (GBCAs), which due to their specific clinical effects were not included in our analysis.

As regards the other adverse reactions, i.e. toxicity arising at the normal dosage, the reasons and/or criteria for their subdivision into classes and subclasses are principally related to physical and chemical similarity of chemical-pharmaceutical nature, or to the onset of (never sought) individual events and/or reactions even of a favourable nature, or else identification of local or systemic organic disorders (SOCDs), according to the ATC, the most widely accepted classification, approved by the WHO, which is based on anatomical, therapeutic and chemical criteria.

It must be noted that the significant projections detected in our analyses, significant in all cases[17-20], matched neither the known chemico-pharmaceutical criteria nor those adopted for the ubiquitous use of ATC classes. This suggests the urgent need for a review of their suitability and re-examination of the need to maintain them despite their lack of robustness, and consequent precariousness. Possibly another paradigm. Specific national trends have also been detected[22], as have highly significant distinct features among the reference products and their salts, which are still and erroneously considered as biosimilars and equivalent under all profiles[21].

Developments

The multi-author paper published in Science[23], preceded by a presentation in the Perspective in the same issue[24], regarding the new *MINE Statistics* has restored confidence in the ongoing exchange between the MIT, Harvard and Oxford groups[25], which is in line with the Anglo-Saxon tradition of letting researchers work after the local retirement age: to prevent teaching, honed and developed with passion and with new enthusiasm, from being

obliterated and allow it to continue to provide its contribution[26]. Besides this project dates from September 1, 1991, the date when the Italian Health Ministry Study Centre approved the outcome of the First Convention January 13, 1989 on *"Research addressing the development of a statistical-modelling program for the detection of consumption and the evaluation of benefits and resources of some groups of drug using data of the WHO cofounded Uppsala data bank "*, whereas the continuation, besides the evolution reported here, already financed with[27], has mythically been lost ... along the way: one is reminded of the citations of Tolstoj and Vonnegut in *E noi?* [28].

Citations

(1) Rossini L., Cingolani ML., Lo sviluppo delle scienze chimico-farmaceutiche nel '900, Memorie Istituto marchigiano Accademia di scienze lettere e arti Ancona, XXIV, 39-71, 1986.

(2) Rossini L., Bernardi M., Cavalieri L., Concettoni C., Galeazzi G., Gentili M., Moretti V., Moroni L., Pettinari F., Picchi L., Pigini P., Rossini P., Tonnini C., Violet C., Farmacovigilanza internazionale: uso ed abuso dei farmaci, Memorie Accademia Marchigiana Scienze Lettere ed Arti, Ancona, XXIX, 151-197, 1996.

(3) Rossini L., Bernardi M., Galeazzi G., Moroni L., Pettinari F., Pigini P., Rossini P., Tonnini C., Vagionis G., Violet C. Domini del tempo e di frequenza in Fenomeni Biomedici, II, Memorie Accademia Marchigiana Scienze, Lettere ed Arti, Ancona, XXXVIII, 211-256, 2005.

(4) Rossini L., Didattica vissuta e aggiornamento della "Nuova Tabella XVIII", Memorie Accademia Marchigiana Scienze Lettere ed Arti, Ancona, XXXVIII, 323-342, 2005.

(5) Rossini L., Regione Marche, Il Polo universitario – ospedaliero dorico, Il Servizio di Farmacologia e Tossicologia clinica, I., Memorie Accademia Marchigiana Scienze, Lettere ed Arti, Ancona, XXXIX, in print, 2012.

(6) Rossini L., Bernardi M., Galeazzi G, Gatti G, Moroni L., Pettinari F., Re L., Rossini P., Violet C., Regione Marche, Il Polo universitario - ospedaliero dorico, Il Servizio di Farmacologia e Tossicologia clinica, II., Sviluppi più recenti di aspetti del monitoraggio diagnostico e delle verifiche preventive, terapeutiche e riabilitative farmacotossicologiche. Memorie Accademia Marchigiana Scienze, Lettere ed Arti, Ancona, XXXIX, in print, 2012.

(7) Rossini L., Bernardi M., Galeazzi G., Gatti G., Moroni L., Pettinari F., Re L., Rossini P., Violet C., Mencarelli R., Regione Marche, II. Polo universitario - ospedaliero dorico,Il Servizio di Farmacologia e Tossicologia clinica, III., Altri sviluppi degli aspetti post-genomici del monitoraggio diagnostico e delle verifiche preventive, terapeutiche e riabilitative: coinvolgimenti farmacotossicologici analitici ed esplorativi proteomici-metabonomici strutturali. Memorie Accademia Marchigiana Scienze, Lettere ed Arti, Ancona, XXXIX, in print, 2012.

(8) Coulston F., D'Ambrosio V., Danieli G., De Martinis C., Foschi F., Magnani B, Orlandi F., Pocchiari F., Poggiolini D., Rossini L., Segre G., Silvestrini B., Tinti D., Volterra V., Documento conclusivo del Convegno di studi sulla sperimentazione dei farmaci sull' uomo, Ancona, 29 aprile 1974, La Clinica Terapeutica 73, 483-491, 1975.

(9) Giornate nazionali ed internazionali di Farmacologia, Ancona, 25-28 settembre 1978; XIX Congresso della Societa' italiana di Farmacologia, unitamente alla Societa' italiana di Farmacologia clinica, alla Societa' italiana di Farmacia ospedaliera, alla Societa' italiana di Scienze farmacologiche applicate, ed alla Societa' italiana di Tossicologia; First Joint Meeting of Yugoslav and Italian Pharmacological Societies; Second Portonovo Conference on Biomathematics, Organized by WHO-ITA/ITA-OMS WHO-National Center on Drug Monitoring: Section A) Clustering techniques in pharmaceutical chemistry and in experimental and clinical pharmacology- Section B) Epidemiological techniques applied in drug monitoring. Volume of the Abstracts, 1-589, Grafiche Bellomo, Ancona, 1978.

(10) Rossini L., Bastianelli P., Cingolani ML., Gamba G., Giannella M., Gualtieri F., Leone L., Martorana F., Melchiorre G., Moretti V., Periti P., Pigini M. & P., Re l., Roda G., Tuccella S., Pattern recognition in profiling pharmacological receptors, in Portonovo Conference on Biomathematics (De Martinis C, and Rossini L, eds), pp 257-290, Palermo, Cofese Ed, 1978 & Padova, Piccin Int Ed, 1980.

(11) 5th Annual Meeting of Representatives of National Centres participating in the WHO International Drug Monitoring Programme, Portonovo, Ancona, 5-7 October 1982, World Health Organization PHA/83.2, 1-20, 1982.

(12) Cingolani ML., Re L., Rossini L., The usefulness, in pharmacological classification, of complementary pattern-recognition techniques and structure modeling as afforded by the iterative collation of multiple-trial data in data banks, Pharmacol Res Commun 17, 1-22, 1985.

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

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

(15) Rossini L., Rossini P., After the new "Year of Darwin", Pharmacologyonline 1, 754-771, 2010.

(16) Campillos M., Kuhn M., Gavin AC., Jensen LJ., Bork P., Drug target identification using side-effect similarity. Science 321, 263-266, 2008; Bromberg KD., Mz'ayan A., Neves SR., Iyengar R., Design logic of a cannabinoid receptor signaling network that triggers neurite outgrowth., Science 320, 903-909, 2008; Lamb J., Crawford ED., Peck D., Modell JW., Blat IC., et al, The connettivity map: Using gene-expression signatures to connect small molecule, genes, and disease. Science 313, 1929-1935, 2006.

(17) Bernardi M., Bradu D., Di Sarra B., Galeazzi G., Marcucci M., Montecchiani G., Moretti V., Moroni L., Re L., Rossini L. & P., Tonnini C., Ionic and non-ionic contrast agents. A contribution by WHO-ITA and the Drug Documentation and Information Centre of Regione Marche, Pharmacologyonline Newsletter 2, 497-517, 2010.

(18) Bradu D., Rossini L., Contrast agents-Iodinated products. Second WHO-ITA / ITA- OMS 2010 contribution on aggregate WHO System-Organ class disorders and/or clustering based on reported adverse reactions/events, Pharmacologyonline Newsletter 2, 727-753, 2010.

(19) Bradu D., Rossini L., Contrast agents – paramagnetic gadolinium and manganese chelates and superparamagnetic iron-based products. Third WHO-ITA / ITA-OMS 2010 contribution using WHO System Organ Class Disorders (SOCDs) and Adverse Reaction and Event preferred names (ADRs), Pharmacologyonline Newsletter 3, 728-781, 2010.

(20) Bradu D., Rossini L., Contrast agents – full list of the 30 iodinated products for which reports have been sent over the first 40 years of the WHO Pharmacovigilance system, subdivided into two 20-year periods. Fourth WHO-ITA / ITA-OMS 2010-2011 contribution on the 30 basic aggregated WHO System-Organ Class Disorders (SOCDs) and Suspected Adverse Reactions and Event preferred names (SADRs). Pharmacologyonline Newsletter 2, 701-836, 2011.
(21) Bradu D., Rossini L., Biosimilar branded iodinated contrast agents related to the largest number of reports to the pharmacovigilance system over the first 40 years of the Programme. Fifth WHO-ITA / ITA-OMS 2010-2011 contribution. Pharmacologyonline Newsletter 2, 929-962, 2011.
(22) Bradu D., Rossini L., 4,436 reports from Italy, accepted in the WHO-UMP Collaborating Centre Thesaurus Vs 181,744 globally collected reports from other participating Countries of same 33 monitored contrast agent-products over the first 40 years of the Programme. Sixth WHO-ITA / ITA-OMS 2010-2011 contribution. Pharmacologyonline Newsletter 2, 1140-1160, 2011.
(23) Reshef DN., Reshef YA., Finucane HK., Grossman SR., McVean G., Tumbough PJ., Lander ES., Mitzenmacher M, et al, Detecting novel associations in large data sets, Science 334, 1518-1524, 2011.
(24) Speed T., A correlation for the 21st century, Science 334, 1502-1503, 2011.
(25) Reshef YA, yakirr@gmail.com 5 marzo 2012, 16.47: Dear Prof. Rossini, Thank you very much for reaching out to us, and for your kind words! We are both so excited to hear that you think our work may prove useful for your research. Your data look to us to be exceptionally rich and interesting, with a lot of potential. Unfortunately though, none of us is in a position right now to begin any collaborations. If this changes, we will certainly let you know. In the meantime, we'd be interested though to hear how it goes, and if you make any progress using MINE on your data. With best wishes for a fruitful research effort, Yakir.
(26) Cerati F., Piu' vicina la terapia su misura, Il Sole24 Ore, nòva24, 319, 45-46, 2012; Park A., Don't trash these genes. "Junk" DNA may lead to valuable cures. Time October 22, 13-14, 2012; Fantoni S., Professori a misura di Anvur, Il Sole24 Ore, 284, 37, 2012; Luzzatto L., Costa E., Spirale fuori controllo, Il Sole24 Ore 159, 35, 2012; Jarrel TA., Wang Y., Bloniarz AE., Brittin CA., Xu M., Thomson JN., Albertson DG., Hall DH., Emmons SW., The connectome of a decision-making neural network, Science 337, 437-444, 2012; Llera VA., Roldan JA., Postmarketing trials for rare disease, Science 337, 154, 2012; Valente ThW., Network Interventions, Science 337, 49-53, 2012; Sharp B., Accelerating drug discovery, Scientific Computing World, 123, 30-31, 2012; London AJ., Kimmelman J., Carlisle B., Rethinking Research ethics. The case of postmarketing trials, Science 336, 544-545, 2012; Bianco P., La bolla di Big Pharma, Il Sole24 Ore, 345, 33, 2011; Bodemer N., Ruggeri A., Finding a good research question, in theory, Science 335, 1439, 2012; Cowen T., When do incentives corrupt, Science 335, 541, 2012; Fedoroff NV., The global knowledge Society, Science 335, 503, 2012; Pariente A., Abou Chakrab CN., Pineta L., Nkeng L., Moorea N., Moride Y., Il valore delle casistiche nella valutazione delle reazioni indesiderate da farmaci, Adverse Drug Reaction Bulletin (Ed italiana, sotto l' egida del Centro nazionale collaborativo WHO-ITA / ITA-OMS, Ancona), 203, 815-818, 2011; Carome M, Wolfe S., Rethinking clinical trials: Phase 1 studies insufficient. Science 334, 1346, 2011; Grove A., Rethinking clinical trials, Science 333, 1679, 2011; Moss J., Addressing the ethical dimension, Science 332, 1382, 2011; Rossini L., Letter to the Editor, Pharmacologyonline Newsletter 3, 1055-1060, 2011; Bradu D., Rossini L., Letter to the Editor, Pharmacologyonline Newsletter 3, 991-992, 2011; De Martinis C, Rossini L., Some internal medicine and pharmacological clinical views and perspectives on global essentials, regionally protected, brand-name or unbranded equivalents, off-label and "me-too", neglected, repurposed, complementary, prescribed and/or distributed over-the-counter, differently marketed available or not counterfeit diagnostic, preventive, and therapeutic medicinal products. Pharmacologyonline Newsletter 2, 475-496, 2010; Leshner AI., Turekian V., Harmonizing global science, Science 326, 1459, 2009; Stins JF., Establishing consciousness in non-communicative patients: A modern-day version of the Turing test. Consciousness and Cognition (2008), doi:10.1016/j.concog.2007.12.005; Science Specialsection Clinical Trials and Tribulations, Marshall E., Introduction, Lemons, Oranges, and Complexity, Science 322, 209-223, 2008.
(27) Cf: CS/413/FARM/93/AG/1526 del 26.11.1993, Oggetto: "Ricerca di aggiornamento di studio di modalita' autoclassificative per il confronto di profili di reazioni avverse di gruppi di farmaci, come segnalate alla Banca internazionale O.M.S., Uppsala Ginevra", Responsabile lo scrivente, ove si comunica all' Universita' degli Studi di Ancona, Istituto di Medicina Sperimentale e Clinica, Via Ranieri, Monte d' Ago, 60131 Ancona "che in data 22 ottobre c.a. l' On Ministro, in conformita' al parere espresso dal Comitato di Coordinamento di questo Centro Studi, ha approvato la ricerca in oggetto, che sara' affidata in convenzione a codesto Istituto, per un compenso di lire 60 milioni".
(28) Nori P., E noi?, pagg 71-79, in Racconti d' Autore, I Libri della Domenica, Il Sole 24 Ore, novembre 2012.