

SINCERELY, ... I CAN'T GIVE UP

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SUMMARY

A narration diary of some key periods in my life.

**“Multitudo non est sequenda”
(Augustine of Hippo)**

Dedicated to Prof. Lorenzo Maniscalco, MD, PhD, a world renowned surgeon with Doctors Without Borders.

Keywords: Life artifacts, Basic decisions, Education and first steps in competition, Home anectodes and “in the new world”: US and Canada, Back to Italy, Multiple joint foundations in biomathematics, chemical physiology, and in vitro, in situ, in vivo physio-pharmacotoxicological non-invasive read-outs, World pharmacotoxicological epidemiology and monitoring. Final plea to the Authorities.

Introduction

Obligations toward family, students, and friends

(Thursday 29th October, 2015)

Yes, I feel the need to write down some of my memories. Now 83, it is quite clear that I don't know whether I'll have or want to stop.

This endeavor stems from the suggestion, or better the reiterated request in favor of students, by a group that was undoubtedly a community of excellence, teaching and research at the time when its name was Università di Ancona. It is now Università Politecnica delle Marche, because nobody then felt up to opposing the name change - in favor of technology and engineering - advocated by Marco Pacetti, who has been Chancellor for many years.

I have taken up this invitation to honor the last, great friend I had the luck to make in Ancona, Lorenzo Maniscalco, a surgeon 11 years my junior, who retired early from his hospital job. Well, at least over the last 3-4 years, after I retired as late as was allowed in Italy, and after suffering severe humiliation during the time I was doyen, I met Lorenzo on October 31th, 2008 at the Passetto public swimming pool in Ancona. I was swimming to recover from a bad fall. During one of her short and increasingly rare week end visits, my daughter Paola, a psychiatrist living and working away from home in Novi Ligure (Piedmont), brought her dog. Silvy saw a rat at the bottom of our swimming pool, which was empty and undergoing repair, and jumped in, breaking a leg. I climbed down as Paola held the ladder, but when I climbed back up the last time, I did not realize that she was tending to her dog and was no longer holding it. I thus fell back from a height of 2.5 m like a sack. A cry and then unconsciousness. When I came to, a short while later, I had to find the strength to climb back up. Two days later I was examined at the ED by a team of internal medicine doctors, orthopedic surgeons, neurologists and radiologists, at a time when the CT machine was not yet available. After at least 5 hours of tests and consultations, feeling increasing and spreading pain, I was told that there was nothing the matter with me, that I could go back to playing tennis, and that I could take tramadol as needed. But in fact I had to self-inject morphine for a week - all of this without ever neglecting my work. Then one day, as I was walking like a monkey along a corridor of Torrette hospital, I accidentally met Maurizio Ricci, who then headed the rehabilitation service. He was so alarmed that he examined me then and there. He took my shirt out of the trousers and as I leaned against the wall he prodded the

protruding spinous processes. "Get yourself wheeled to the Radiology department at once" he said "because I'm sure you've broken some vertebrae. In the mean time I'll call GianMarco Giuseppetti, a very experienced radiologist from the hospital". The latter said that he could not carry out the imaging studies required, which would have to be done at the Neurosurgery department, then coordinated by Prof. Ugo Salvolini, but sent me to the Gynecological and Maternity Hospital, where a resident was waiting for me. She attentively followed my CT scan and eventually based her dissertation thesis on my case, where I was of course anonymized. The diagnosis was "full, oblique comminuted fracture of L3 and L5 vertebral bodies, with large free fragments". The scans were terrifying. I risked being confined to a wheelchair for life. There are unfortunately more of these stories that have come to my knowledge, and which may be instructive to tell, maybe later.

Back to Lorenzo Maniscalco. While I swam my 14-16 daily laps (each 33 m), he did exercises to counter the late sequelae of a fall down the hospital stairs, made slippery by a wash with a common rag. He suffered a fracture requiring cervical laminectomy.

What are two pensioners to do in Italy if they have not nurtured other professional or different interests ? We had both been completely absorbed in our work, which in his case included night shifts. As for myself, in the seven North-American universities where I had worked (5 in the US and 2 in Canada), retired researchers can no longer apply for grants, but are given an office, sometimes the services of a secretary, and access to labs and other services. However, I had left North America to become a Professor in Ancona. It is really an inexcusable waste of free teaching and research experience. I went back to my philately; if I took care not to be too loud - and before my osteoarthritis, I could also practice on the Steinway baby grand I had bought with all my savings when I was at Siena (before it was attacked by moths). After the oxidized chords had been replaced, I could finally follow Barenboim in all the sonatas of my beloved Schubert, performed by twos, at the Piccola Scala. I also read, commented in the margin, and annotated the major works of the 38 greatest philosophers of all times and of the 15 greatest universal poets. In turn, Lorenzo offered his help to Doctors Without Frontiers, and participated in several three-month stages in countries such as Yemen, Somaliland and, repeatedly, Haiti. Then, as I wrote to the Director of the Ancona local paper:

October 3rd, 2015:

"Doctors Without Frontiers are deeply saddened by the sudden death of colleague and friend, Prof. Lorenzo Maniscalco, surgeon and aid worker, at their Bikenge hospital, Democratic Republic of the Congo. After a long career in Italy as a surgeon and university professor, in 2012 he'd placed his experience at the service of DWF and their beneficiaries in conflict areas such as Yemen, Central African Republic, Somaliland, Haiti, and the Democratic Republic of the Congo, where he had been only three weeks. The DWF family, the humanitarian workers, the staff, and the voluntary workers are all deeply affected by Lorenzo's demise and their thoughts are with his loved ones", said Gabriele Eminente, general director of DWF.

Lorenzo had a heart attack at our Bikenge hospital while tending to his patients as usual. We'll remember him with affection and will always be grateful for the passionate, enthusiastic and dedicated work he donated to us in these valuable years together. DWF began working in Bikenge hospital in March 2015. Bikenge is a remote mining village in the eastern province of Maniana, where people live in extreme health conditions and DWF are the sole possibility of access to care". It is especially for Lorenzo, to remember his exceptionally lucid and accepting character, that I must follow him here, in telling some facts of our existence and our often obscure battles, sometimes because of shyness or fear, when one tries to keep high the spirit of research and service without even thinking of asking for remuneration".

1.

Disbandment of an internationally competitive research group, with a waste of millions of Euros of public money, while the competent control Authorities turn a blind eye

(Still Thursday 29th October, 2015)

Yesterday I read at 12:33 (updated at 12:51): **Ancona, mass flight of ward directors from Torrette hospital.** This is the other side of the budget balance achieved by the regional health service. The President of the regional government, Ceriscioli, replies to the question of councilors Zaffiri, Malaigia, and Zura Puntaroni (Northern League) on the exodus of high-profile physicians from Torrette Regional Hospital. Budgetary constraints and a reduction of activities, aimed at cost containment, have resulted in the mass departure of valuable professionals, including Torraca and Cascinu. (Not to mention Muzzonigro and Salvolini, who have retired in recent and less recent times). This is what Ceriscioli said to the

assembly: "Budgetary constraints have involved sacrifices from personnel, and production has slowed down, which for Torrette is the worst thing that could be done. This " added Ceriscioli " has generated passive mobility. We thus need a strategic plan, focusing on the structures that can operate at full capacity and reduce passive mobility". I can read between the lines the willingness to make changes at the top of the hospital management, to restore Torrette to its place as a regional excellence. But really, also Muzzonigro, my former Director, who has mounted an exhibition of old urological instruments in my former study! His Director followed the Dean, Prof. Corsi, who was always accurate, impeccable, really unique and admirable with everybody and a stickler to form. He suggested entrusting the multinuclear spectrometer, which enabled 13-C, 19-F, and, initially 31-P analyses, exclusively to his young, brilliant pathologist, a great fan of motorcycle world championship races. I agreed that he would manage the future of that lab, unique in Italy, which hosted optical, surface fluorescence, and mass spectrometry apparatuses (He divorced his beautiful wife, who was later diagnosed with breast cancer at a very young age; I have no idea where either has ended up). Then came Polito, who began by appropriating my sole radiology technician, who was forced to become an operating room x-ray technician overnight, whereas he was an excellent NMR spectroscopist and an expert cardio-coronary physio-pharmacological technician, at least for Langendorff preparations. The Dean ad interim approved the abuse - really a Far West story of arrogance and high handedness - in the teeth of national regulations. In the meantime Lamberto Re, a medical assistant, had refused a collaboration with the hospital to devote himself to electrophysiology, including unicellular electrophysiology, honed with the group of the Heidelberg Nobel laureate. He also worked with the trailblazer Vittorio Erspamer, but ended up dealing mostly with ozone therapy, ignoring the stimuli coming from Ferid Murad's physiological chemistry and working also with Camerano and Dubai, besides our Science faculty. The excellent graduate technician Cecilia Tonnini did not accept the unanimous decision of the Consiglio di Istituto, who had assigned her to the ongoing NMR spectrometry research, and opted for a position in the Hematology clinic. Should I really write my memoirs, as Lorenzo suggested? But then who would publish them? What about making them a free instant book? No, they will be published as a Note in the online journal of our Italian Society of Pharmacology.

During my latest ED visit, last month, they missed my

left rib fracture as they concentrated on the right scapular fracture. The injuries are due to a fall, facilitated by my chronic lower limb polyneuritis. I have radiculopathy and a beginning of axonotmesis, late complications of the fall into the empty pool I have mentioned above. What can one do if he has to spend the night in an armchair? How can one help remember, during one's sleepless hours, that Portonovo faculty meeting not so many years ago, when Ancona Medical School offered a post to this new, extraordinary pharmacologist? He was foisted on us, against my strenuous opposition, by the Dean (later Chancellor) of Napoli University, with the blessing of our long-time Dean. The move was related to the earlier offer of a post, in Naples, to a colleague from our University. Our faculty then had no choice but to accept this person, who had been waiting for a position for years, and whose state of academic eligibility was close to expiry, since no other university had offered one. However, very soon the then department head Muzzonigro and the newly arrived pharmacologist fell out, and Muzzonigro lost to the wily fighter of university battles. He had also appropriated my secretary, a relative of the elusive Re. The latter did not however pay her the compliment of ignoring her faults, and honestly acknowledged her scarce professional value, a feature that she shared with most of the people hired at the time of the institution of the new Medical School. And if I did not fall sick then, it was because I was relentlessly teaching and doing exams. (Oral examinations have since been replaced by tables of numbers and signs that are to be completed in less than an hour, every trimester, by all students. The answers are partially consistent with being arranged in advance with the students. These examinations replace the discussions of at least one and a half/two hours that I had adopted, asking random and exclusively oral questions.) This was the time when the lab hosting the mass, optical, and UV fluorescence spectrometers, and especially the multinuclear NMR apparatus, became a storing place for the bikes of the new occupants. To this day, its photographic records have apparently been ignored by the internal and external, local and national control bodies, which had formally been notified. This at the very least negligent course could not but lead to the scrapping of equipment that had cost several millions to acquire, some of which was original and had been built over years of hard, dedicated application by different inventors. Another apparatus was the fully accessorized Brüker spectrometer, still featuring in the current

product list: our residents traveled to Munich, all expense paid, to learn its basic functioning; as for the group of technicians, whose voluntary experience with it had been excellent, it was disbanded and assigned elsewhere to banal administrative tasks, for which they were not trained. And today we learn that a regional and possibly even national or international excellence - at least according to the President of the Marche government - has stopped being so and that the top dogs are fleeing en masse. But I'd like to stress another question of topical interest. Today some arithmologists have published a note (1) describing the successful application, and the safety of any side effects, of their antitachycardia protocol in patients with ventricular tachycardia and fast ventricular tachycardia. Well, it is widely accepted that clinical risks would have been reduced if the trial had been preceded by preclinical experimentation in animal models, for instance with Langendorff preparations of common rodents such as rat, Guinea pig, and mouse. Indeed, there are 499 published papers on the subject, one of which I have co-authored in 2006 (2). Application of non-invasive continuous monitoring - or monitoring through collection, according to Wollenberger - of PCr, creatine, ATP, ADP, AMP, adenosine, inosine, Pi, NO/CO/O₂/CO₂, HbO₂/Hb, and possibly the components of the central glycolytic and oxidative pathways (Krebs and G6P cycles) and of coenzyme redox levels in different compartments, at least NAD(P) (as in our experiments involving Cyto b and selective flavoproteins (3)), would definitely have contributed useful data to be correlated to the increase and decrease of amplitudes and frequencies, as well as to the time of application of the antitachycardia protocol, thus enabling optimization of the correlations obtained. Maybe - and this is critical for us - to define the mechanism of (metabolic) activation in a diagnostic and therapeutic model - through detection, for instance, of metabolic and electric uncoupling in the relevant pacemakers, and of conduction syncytia capable of being isolated, not to mention any interference with the models of preconditioned hypoxia/ischemia adaptation, whether related or unrelated, which today are among the best explored (again 2, 4).

References:

1. Landolina M, Lunati M, Boriani G, Ricci RP, Proclemer A, Facchin D, Rordorf G, Maines M, Gasparini G, Molon G, Turrini P, Gasparini M, ClinicalService cardiological centres. Ventricular Antitachycardia Pacing Therapy in Heart Failure Patients with Cardiac Resynchronisation Therapy Defibrillators: Efficacy, safety and impact on mortality. Heart Rhythm 2015 Oct 15. Pii 51547-5271(15)013^o3X.

2. Luigi Rossini, Bozena Kuzio, Roxanne Deslauriers, Craig W Johnson, Epicardial autofluorescence NAD(P)H kinetics in the ischemically preconditioned Langendorff rat heart. Effects of capsaicin, Part 1. *Pharmacologyonline* 3: 125-176 (2005); Luigi Rossini, Carlo Violet, Paola Rossini, Craig W Johnson. Epicardial autofluorescence and NAD(P)H kinetics in the ischemically preconditioned Langendorff rat heart. Effects of Capsaicin, Part 2. *Pharmacologyonline* 3: 18-63 (2006);
3. Luigi Rossini, Paola Rossini, Britton Chance, Continuous read-out of cytochrome b, flavin and pyridine nucleotide oxido-reduction processes in the perfused frog heart and contracting skeletal muscle. *Pharmacol Res* 23, 4: 349-365 (1991);
4. Rajesh K Kharbanda, Torsten Toftgard Nielsen, Andrew N Redington, Translation of remote ischaemic preconditioning into clinical practice. Review, *Lancet* 374: 1557-65 (2009).

2.

When a chronic protocol does not envisage the necessary follow-up monitoring

(Friday 30th October, 2015)

It has become accepted that genetics does not exert a decisive influence by itself, and that a much larger role is played by the epigenetics of selectively involved histones and of simple and complex, methylated, acetylated, phosphorylated, nitrous and nitrated, glycosylated, formylated and other proteins, directly and through modifications of the conformational traits that are most prone to selection and change by the "thousand forms" of the nucleic acids of double helix DNA with a thymine nucleobase, or of single helix RNA with a uracil, not thymine, nucleobase. According to the wobble base pair hypothesis, the latter constitute the guanyl-uracil, hypoxanthine-adenine and hypoxanthine-cytosine RNA pairs, hypoxanthine being the nucleobase of inosine (5). Notably, besides adenine, thymine, cytosine and guanine, DNA can stably be constituted at least of 5-formylcytosine (6). This affects with growing intensity the development of individuals and ethnic groups and increasingly large populations. We have recently addressed the placebo effects - either stable and acquired through adaptation and/or dependence - in the framework of physiological chemistry and molecular pharmacology. Despite the new insights into the functional details obtained for the latter (7), it has not sufficiently been realized that - besides the dynamics of the mechanisms that are in mass equilibrium in ranges of concentrations that can be linearized exponentially as S functions (which can be defined by the slope of min-max effect relationships according to general theories, chiefly based on the central doses and their relationships) - the construct does not in fact

include the different and never uniform effects of ionic and/or radical molecules, characterized by irreversible kinetics of their active interacting residues, which are consumed down to the last component... . A typical case that has largely eluded description in selectivity experiments, including my own, and the general statistical analyses carried out in clinical trials, including phase IV post-marketing trials, are the useful relatively stable block of platelet prostaglandin endoperoxide synthase, cyclooxygenase (COX-1), which is non selectively inhibited by chronic aspirin, even at low dose. This results in a greater amount of COX-1, thromboxane A₂, which by inhibiting platelet aggregation has been found to be highly effective in secondary prevention of myocardial infarction and ischemic stroke, having contributed to detect the selective inhibition of multiple proteases by the same salicylate, as noted in my first work in *Hoppe-Seiler Zeitschrift für Physiologische Chemie* of 1969 (8), a line so original that it has given origin to a rich, enduring school (9). Yes Lorenzo, I remember that long long ago, on the edge of the swimming pool, you did mention the dangers of aspirin, also in connection with surgery. I didn't know then that the daily dose of 100 mg (Cardioaspirin), which I've taken as CV prevention for many years, since well before I retired, was capable of causing the severe damage it did to me. We didn't elaborate then, it's my fault! However, I've always had some doubt about its chronic preventive administration, albeit at low dose. Clinical trials were carried out first of all by the Chieti pharmacologist, who obtained international consensus, and subsequently by numerous papers in journals such as the *New England Journal of Medicine*, which I have always followed and cited during my lectures. I have always been concerned with the use of "irreversible binders", which prevent establishing clearly how necessary are the equilibria of the key mass law for any pharmaco-toxicological interaction. In fact, each aspirin molecule does not react in equilibrium, albeit not always in an irreversible way, making it impossible to study in detail the pharmaco-toxicokinetic fate of each molecule, although this is absolutely necessary. It is clearly impossible to apply to it the linear theory, the theoretical reference base of pharmaco-toxicokinetics. I have investigated in depth the in vitro interactions of human (and bovine and rodent) serum albumin, isolated in the native state hence unfortunately in the impure state in which the molecule survives in the circulation, from which it is isolated by methods that are not per se denaturing. In contrast, I have done much less work on in vivo interactions, and then only in

rodents, since this requires ad hoc labeled molecules. Albumin of human serum from adult donors, of bovine serum from abattoirs, and of adult, genetically standardized lab rodent, hence of "mixed" blood, contains several molecules variously and stably bound also to all the other residues of irreversible binders to which it is exposed in its half-life, "native" molecules that are pure only in terms of their crystallization, which can be verified, but are in fact always different, like the other molecules on which aspirin (including isotope-labeled aspirin), and respectively non acetylated salicylate for controls, were made to interact (clearly by acetylating irreversibly, "artificially" in the lab in a controlled fashion) with the sole aspirin the residues of the various amino acid chains that were still free. In this way I have defined the various "specifically denaturated" forms. These are differently digested – see "younger" molecules - and also easier to acetylate on even freer residues, all determined to be free or not free in controls, amines of arginine and lysine at positions numbered on the basis of known sequences, made less digestible because further acetylation (which in the lab is even greater) blocks to a greater extent the selective pepsin binding sites. This is different from what is observed in chymotrypsin (which for instance recognizes them only if they are close to a tyrosine residue), papain, etc, toward "older" molecules that are more "denaturated in vivo", of digestion for controls already more inhibited, and anyway still more inhibitable in percentage with the further irreversible block of the less numerous free residues that have remained so when subjected in control experiments to additional, less selective in vitro acetylation. Digestion is therefore more inhibited in percent terms, but lower in absolute terms Clearly, in vitro digestion is applied as a model of in vivo turnover, of pool renewal In short, since my earliest work in Hoppe-Seyler's Zeitschrift für Physiologische Chemie, I have tried to assess the risk of its utilization ... in a personal way that has remained confined to biology, and to the best of my knowledge this has never again been explored in depth in human medicine. This is all. I could add, with hindsight (acquired in Ferid Murad's lab at Houston Medical Center) that the arginine free groups, when acetylated, can no longer be used for NO synthesis and other purposes. How will this apply to degenerative conditions such as Alzheimer's disease, and how will it affect the etiopathogenesis of the so-called "excess (which?) senile oxidation ...?". I remember that much more recently my contemporary, Silvio Garattini, said in a

TV interview that he had become opposed to the chronic administration of many drugs, also because it does not envisage close monitoring, but just checks "when it occurs to one". Below I report the confirmation by the Maestro, who also said, I remember it well, that he too took very aspirin at the lowest doses, but...

"Dear Rossini,

Thanks for the information you kindly sent.

I myself have not taken preventive aspirin for many years exactly for the reasons you mention.

Kind regards and best wishes.

Silvio Garattini

From: "Rossini Luigi" <rossiniluigi@hotmail.it>

To: "silvio garattini" <silvio.garattini@marionegri.it>

Sent: Tuesday 13th January 2015, 18:45:05

Re: A short report of the effect of chronic aspirin on CV prevention.

Dear Professor Garattini,

I'm writing to report information, that I deem useful, with regard to the clinical course of a condition from which I have suffered, that has now ostensibly resolved. In brief, in January 2014 I began to experience respiratory problems both during exercise and at rest (even while speaking). My blood Hb was down from 14 to 7.5, and the hematologist prescribed Fe²⁺ (Niferex UCB, 100 mg, 3 capsules/day), which I did not take ex juvantibus. A complete colonoscopy and gastroduodenoscopy prescribed by the surgeon I consulted, performed in June, gave the following results: the former was normal, whereas the latter demonstrated hemorrhagic gastroduodenitis. The condition was ascribed to the chronic use, for many years, of the sole drug I had been taking: aspirin 100 mg/day (Bayer's Cardioaspirin) for CV prevention. However, there had never been any adverse effects, esophageal or GI tract symptoms, or occult fecal blood. I was immediately placed on Tiklid Sanofi's Cardioaspirin 2 tablets/day (250 mg of ticlopidine chlorhydrate). Oral iron supplements restored Hb to 14 and my respiratory insufficiency resolved. Clearly, I'm well aware of the risks associated with aspirin, salicylates, and anti-inflammatories, on gastric mucosa. These effects are mostly seen in the elderly, but I trusted that the doses recommended by the CV prevention protocols and guidelines would not be so harmful as to lead to the condition I mentioned. The most surprising thing was that all the endoscopists I have consulted since then are well aware of the high frequency of gastro-duodenal hemorrhage in

subjects taking "preventive" aspirin (even at low doses), while the CV prevention specialists largely fail to mention the risks, or the need for the workup I eventually required, and prescribe chronic treatment without gastroprotective agents (eg prostaglandins), and symptomatic treatments for conditions they do not consider as side effects without prescribing a workup. Do you think I've been a fool in this case? I remember that in a TV debate you stated that, luckily, you did not take drugs, except low-dose preventive aspirin, "whenever I happen to remember".

Kind regards,

Luigi Rossini

Dear Lorenzo, the surgeon who prescribed me the endoscopic examination before the unwarranted administration of drugs ex-juvantibus was indeed you, and I will acknowledge it forever!

Warmest regards,

Luigi Rossini

References

5. Sarah Harris, The structural diversity of supercoiled DNA, Pressoffice@leeds.ac.uk Science News, 12 October 2015, Supercomputer DNA simulations at the UK University of Leeds, and Researchers at the Baylor College of Medicine in the US; Francis Crick, Codon-anticodon pairing: the wobble hypothesis. *J Mol Biol* 19 (2): 548-555 (1955);
6. Martin Bachman, Nature Chemical Biology, Science News, University of Cambridge, 27 October 2015; Richard Lewontin, Il sogno del genoma umano e altre illusioni della scienza, Traduzione di Michel Sampaolo, Editori Laterza (2004) 1- 288;
7. Luigi Rossini and Paola Rossini, Requirements for the assessment of pharmacokinetic, pharmacodynamic and mixed population models and some topical considerations; A seminar, *Pharmacologyonline Newsletter* 2:48-72(2007); Id, Id, Pharmacotherapeutic receptor specificities and selectivity classes, and placebo effects; A perspective: *Pharmacologyonline* 2: 206-235 (2006);
8. Luigi Rossini, Hemmung der tryptischen albumin spaltung durch 2,4-Dinitrophenol, *Hoppe-Seyler' Zeitschrift für physiologische Chemie* 33, S: 1-4 (1963).
9. George Bonewell, Luigi Rossini, Kinetics of 2,4-Dinitrophenol inhibition of tryptic, chymotryptic, and pronase digestion of native bovine serum albumin. *The It J Biochem* 19: 457-486 (1969).

3.

Collaboration with my friends, physicists at Siena university

(Friday 30th October, 2015)

Lorenzo: "But how did it come about that, at the age you had then, you set up a radiopharmacology lab (!) for non-invasive imaging including

multinuclear NMR spectrometry, which elsewhere is exclusively managed by specialists? What an unforgivable mistake!"

The most interesting period of my life after my stay in the US and Canada was the time I spent with the Sieneese physicists, Pier Giorgio Bergamini, Francesco Piantelli, and our director, Mario Rigato.

The Pharmacology Institute, like the Physics Institute, which became departments, and together with the hospital were moved out of town, occupied the top floor of a building just uphill of the Palio square, in the historical town center, and had a unique ambiance conferred by the view and the atmosphere of that fascinating medieval city. Moreover, as my family remained in Turin, I was free to enjoy the very personal luxury of a devoting my time wholeheartedly to my professional interests: pharmacology, which has been defined by the Nobel prize winner Otto Loewe as "Grentzgebiete" - between medicine and biology - and basic mathematics, chemistry, and physics.

In the company of my incomparable, cool friend Francesco Periti, we clean forgot the hour of the day (and night) as we did in Camerino, and worked furiously with the computer center at our full disposal. Oh, those moonlit nights spent behind the tall hedge listening, in complete absorption, to the already unrivaled beauty of Martha Argerich! She practised for hours on end in a villa in the country, the windows open, while we devised theories of algorithms... . In Camerino the center had been founded and developed for him alone, and dealt with models of genetic information reversibility to the complex protein receptor. I was bothered by problems that had followed me from Turin to the US and the Canadian universities, from physiological chemistry to neurophysiopharmacology. I could now undertake, with critical help from the new friends, the physicists, the design and construction of prototypes for the observation of macromolecules, cells and increasingly complex organisms, trying to go beyond the absurd generalizations of irrationally standardized preclinical in vitro and ex vivo research, and conduct human translational studies, which I later performed at the new Ancona Medical School. It was an exceptional period of free and wide-ranging research, with findings that evolved continuously. We heavily relied on Franco's exceptional abilities, engineering and manual skills, and attitude for lab and even DIY work, which made it possible to make apparatuses that, especially, today, I wonder why they were not patented and marketed by Siena university, which was heavily affected by the

economic collapse of Monte dei Paschi. In this sad story, wily politicians received double salaries and had access to financing that was out of the reach even of the Directors of Institutes and Departments. And here I'd like to add a recent record of an exceptionally objective, lucid, irreprehensible and incorruptible colleague, friend, and poet:

Paradigms

#1, PHYSICS DEPT. - Merged with two other departments and grown into a hypertrophic structure in different, scattered buildings, it is now paralyzed. The Director is ignored and far away, the teaching staff are absent, the frustrated technicians would prefer working to doing nothing. In sum, immobility, rage, and salaries paid without work being done.

#2, COURTHOUSE - I go there with my solicitor, to deposit a petition. The clerk of the court hands us the dossier. We go downstairs and photocopy it. Back up to the clerk, he takes the petition and declares it accepted. "But it's incredible, we could have changed all the documents, and the judge has not even see our petition". Explanation: the judge comes to sign documents every 20 days. The one who considers and decides is the clerk of the court.

#3, Siena PHILOSOPHY DEPT. - I go there to seek an interview with a Professor and ask for her office hours. I'm told: "There are no office hours". "I'll meet her after class then, when will she be teaching next?". "Classes have not resumed yet". "In mid-January?!". "You can call her on the phone ". "Well then, thank you. Can you please call her for me?". The usher gives me the Professor's telephone number and warns me: "Not from here, from an outside phone". It is a Rome number, the practice and residence of her physician husband. The Professoressa gets paid her salary and lives at home".

A poem by Mario Rigato:

"OSCURAMENTO"

C'ERA UNA VOLTA UN PICCOL SOGNATORE
CHE NEL VEDER TANTO DISTORTO IL MONDO
CONCLUDE CHE IL RIFARLO GIUSTO E TONDO
FOSSE UN'IMPRESA DEGNA DEL SUO ARDORE.

SI MISE DUNQUE ALL'OPERA CON LENA
MA PRESTO PICCHIÒ IL NASO CONTRO UN MURO
CHE I GENI GLI OPPONEVAN TANTO DURO
DA TRADURRE IL SUO ARDORE IN VANA PENA.

DOVETTE ALLOR AMMETTERE DELUSO
CHE I GENI IN GRUPPO RIESCON SPROVVEDUTI
COSÌ COME ASSOMMANDO ANGOLI ACUTI
SI VA A COMPORRE UN RISULTANTE OTTUSO.

IL MURO COLLEGIAL DUNQUE PROTEGGE
TANTE CAZZATE CHE NESSUNO PAGA
MENTRE IL PIGRO BUONISMO CHE DILAGA
LE CONFONDE CON OBBLIGHI DI LEGGE.

I'll make no further comments and additions, which could certainly be numerous, mine included.

In vitro and in vivo stability, which I've mentioned above when discussing the controlled digestion of albumin prototypes, has become significant also for plasma volume expanders (Hetastarch), and has been generalized with ad hoc apparatuses (10, 11) at the time when a new technique for the determination of ionizing radiation microdoses was being developed (12). It was especially my experience with the exceptional Britton Chance (13) while a Fulbright scholar (and with my now three-some family), in the neurophysiology lab of the bulky, hyperenergizing visionary, Carlo Terzuolo in Minnesota (14), who had sent me to Chance (15), that I undertook a new project, still unique in the world, that was carried out, moved, and sadly destroyed during the Ancona earthquake (16). It was an apparatus whose acquisition had involved the whole Siena Physics Institute, and also funds acquired thanks to the farsightedness of CNR, from the eclectic Rita Levi Montalcini, and from Fondazione Fidia. Such equipment should be developed in any biophysics, physiological chemistry, and pharmaco-toxicology lab, including private (industrial) ones, best in association with optical, UV surface and near infrared, and multinuclear NMR, contrast-enhanced imaging with radioisotopes, and molecular imaging also in vivo, in human and veterinary clinical practice ... In Ancona, I also addressed muscle evoked potentials and the, similarly non-invasive, study of pacemaker frequency in vitro and in vivo (17). But Franco again helped me in establishing the way, which had never been evidence with ³¹P-NMR spectrometry, to resolve an original topic that had obsessed me even before my degrees: the observation of the activation by low ouabain doses of its receptor in vitro as well as in vivo, which could be accompanied (or not) by the clinical activity of digoxin, commonly detected in chronic heart congestion and insufficiency: in brief, in the metabolic flow (oscillating? Definitely yes, to the extent that this has been ascertained, one of the most extraordinary and fascinating topics I've addressed, I still shiver at the thought), some labeled elements were activated, within a general framework, where others were clearly inhibited at higher, clearly toxic doses (18). These observations were fully in line with the general physiopharmacological theory of hormesis, where it is not excluded that at low threshold values also the antagonists give rise to agonist power spectra and vice versa: this is the my main, initial contribution to pharmacology (19). Well, with my forced move to Ancona, the collaboration with the Siense colleagues suffered, even though I did maintain my

commitments toward the development of the shared Center (20). Moreover, Franco had become entangled in cold fusion, at least according to the well-known chemistry researchers from my wife's Waldense valley, M Fleishmann and S Pons. I had already reported to him my meeting with them, which had taken place at the research center they had set up in Utah, after a paper in Nature which he considered not devoid of mistakes, and his model of hydrogen (and helium) saturation activation also magneto-constrictive where the central nickel electrode worked uninterruptedly, producing extra heat for years, as, stunned, we observed it together (the interested reader is referred to (21) for a study of the issue by other researchers). Our friendship did not suffer, since I cut short by saying: "Dear Franco I, unlike you, am not competent. Only you are capable of studying the theory. I thus invite you to do so and to write a timely report, by yourself, because it is clear to me that you can't deal with other topics, which albeit less demanding, would be a waste of time for you".

And then I abruptly left to go to the Canadian NRC in Ottawa, then to Winnipeg (Manitoba), at the new Biodiagnostics Institute, a short distance from Minneapolis (Minnesota), where my daughter Paola had been born. I still hoped to be able to live with my family. I went to learn, there too, non-invasive NMR, where the best physicists, mathematicians and engineers of the Country were gathering. They were directed by a Hungarian physicist, a former assistant of Einstein's in Princeton, who had been called expressly, and adequately financed, to coordinate and develop diagnostic and spectroscopic and imaging techniques for all Canadian hospital and university facilities, competitive techniques that should rival those by Brücker, UK-Oxford Ltd and, especially, General Electric-US. He later married the Quebec biologist Roxanne Deslauriers, who had invited me to the capital. Finally, I'd like to mention the latest report by the incredible Francesco Piantelli and to make a comment: he says that, over the 25 years or so since he began to study the topics I've summarized above, he's achieved a description of the phenomenon that has become his main interest that is neither complete nor satisfactory, but he's already identified 22 parameters. In my opinion, at least according to Jordan Ellenberg's "How not to be wrong" (pages 35-136 of the Italian translation published by Ponte delle Grazie, 2015), this means that he has reached a very good point if we accept from Kepler - for the 12 plane face-polyhedrons of pomegranate seeds - the evolution provided by

John Leech's odd reticulum lattice (1960) of 24-dimension spheres, where each interferes 196,560 times with the adjacent spheres. According to Henry Cohn and Abhinav Kumar (2003), the further measurement precision that can be achieved - should a denser reticulum exist - is merely 1.165×10^{-32} .

"Letter by Franco Piantelli to Mario Rigato (which Mario forwarded to me) 3. 9. 2015.

Dear Gigi, I'm enclosing ample (very ample) information. Be sure to read the P.S. (!).
Ciao ciao. Mario

From: Francesco Piantelli <piantelli@unisi.it>
Date: 03 September 2015 17:10:36 GMT+02:00
To: Mario Rigato <rigatoma@gmail.com>
RE: i casini

My dear Mario,

My life is down to a whisper and I don't know if I'll be able to complete this complex research work. Just think that the parameters identified have now become 22, and they may not even be all those that are required. I apologize for my wordiness below, but given the interest in the question I've tried to summarize, although I've not really condensed it, the abnormal phenomenon that I'm trying to understand and test experimentally.

Best regards

Franco

P.S.: Try to comfort our good Luigi, who has suffered great injustice at the hands of those he had helped most. The ungrateful are legion.

References

10. A. Al Savair, F. Bonsignore, V. Moretti, F. Piantelli, L. Re, L. Rossini, A spectrometric analysis of thermal stability of Hetastarch, ventennale dell' Università degli studi di Ancona, Nuovo Boll. Farmacol. Clinica 12: 123-129 (1989);
11. P.G. Bergamini, G. Palmas, F. Piantelli, L. Rossini, Una strumentazione e una metodologia per la determinazione dei limiti di stabilità di molecole sottoposte a gradienti di temperatura o radiazioni UV-VIS e IR. Atti Accad. Fisiocritici Siena XV, Tomo X: 267-374 (1991);
12. P.G. Bergamini, M. Mengoni, G. Palmas, F. Piantelli, L. Rossini, G. Tonnini, Una nuova tecnica per la determinazione di microdosi di radiazioni ionizzanti. Atti Accad. Fisiocritici Siena, XV, Tomo VIII: 119-127 (1989);
13. Britton Chance (1913-2010), Retrospective in Perspectives, Science 330: 1642 (2010);
14. C.A. Terzuolo, E.J. Handelman, L. Rossini, An isolated crustacean neuron preparation for metabolic and pharmacological studies. In: Invertebrate Neuron System, C. A. G. Wiersma, Ed., USA: 55-64 (1967); L. Rossini, H.P. Cohen, E. Handelman, S. Lin, C.A. Terzuolo, Measurements in oxido-reduction processes and ATP levels in an isolated crustacean neuron, Ann. N.Y. Acad. Sci. 137: 864-876 (1966);
15. C.A. Terzuolo, B. Chance, E. Handelman, L. Rossini, P. Schmelzer. Measurements of reduced pyridine nucleotides in a single neuron, Biochimica Biophysica Acta 126: 361-372 (1966); Chance B. Mayer D. Rossini L. A time sharing

- instrument for direct read-out of oxidation-reduction states in intracellular compartments of cardiac tissue. *Rev Sci Instr* 41: 11-114 (1970); L. Rossini, J. Lerner, Conformational transitions of glycogen synthase forms studied with fluorescent probes, *Atti Accad Fisiocritici Siena Serie XIV*, Vol 9: 53-75 (1977); Luigi Rossini, Paola Rossini, Britton Chance, Continuous read-out of cytochrome b, flavin and pyridine nucleotide oxidation-reduction processes in the perfused frog heart and contracting skeletal muscle. *Pharmacological Research* 23, n 4: 349-365 (1991); L. Rossini, Cinetica dei processi di ossido-riduzione delle codeidrogenasi in vivo, *Progressi in Biochimica III*, Minerva Medica, Torino: 1-24 (1965-66);
16. P.G. Bergamini, G. Palmas, F. Piantelli, M. Sani, and M.L. Cingolani, L. Leone, L. Re, G. Roda, L. Rossini, A multi- λ device for bioluminescence measurements in vivo. *Chem. Biomed. and Environ. Instrumentation* 10 (3): 289-309 (1980);
 17. L. Re, V. Moretti, L. Rossini, P. Giusti, Sodium-activated potassium current in mouse diaphragm, *FEBS Letters* 270, 1-2: 195-197 (1990); L. Rossini, Domini del tempo e di frequenza in fenomeni biomedici, I°, *Lettere dalla Facolta'*, Parte 2, 6: 21-25 (1999); Parte 2, 9: 23-26 (1999); Luigi Rossini, Marina Bernardi, Gerardo Galeazzi, Luca Moroni, Franco Pettinari, Paola Pignini, Paola Rossini, Cecilia Tonnini, Giorgio Vagionis, Carlo Violet. Domini del tempo e di frequenza in fenomeni biomedici, II, *Proc. Acc. March. Scienze, Lettere ed Arti, Ancona, XXXVIII*: 187-232 (2006);
 18. M. Bernardi, G. Galeazzi, E. Lamura, F. Piantelli, J. Rendell, L. Rossini, P. Rossini. (Ecto)nucleotidase kinetics observed by ³¹P-NMR spectroscopy: Resolutions of signals. *Pharmacological Research* 36, 5: 1997, 353-361 (1997); P. Dal Pra, P. Periti, L. Rossini, Ouabain effects on the levels of nucleotide phosphates in frog heart perfusate. *Pharmacol Res Commun* 4, 4: 287-304 (1973); P. Dal Pra, L. Rossini, G. Segre, The kinetics of ouabain uptake in frog heart in relation to the kinetics of inotropic effect and to the activation of transport ATP-ases, *Pharmacol Res Commun* 2, 3: 177-191 (1970);
 19. L. Rossini, Antagonismo della isoprenalina verso alcune sostanze ad azioni adrenergiche e colinergiche. *Archivio Italiano Scienze Farmacologiche III, XIV*, 2: 3-24 (Aprile 1964);
 20. Bernardino Di Sarra, Franco Piantelli, Vincenzo Moretti, Lamberto Re, Luigi Rossini, Cecilia Tonnini. Physio-pharmacological in vivo read-out: an interuniversity integrated analytical center. Issues, results and prospectives. *Quaderni Marchigiani Medicina, Special Issue 20th Anniversary of Ancona University* 5: 183-185 (1989).
 21. Roberto Germano, *Fusione fredda*, Bibliopolis (2003) 1-198;
 22. J. W. K. Lee, L. Rossini, J. K. Sanders, R. Deslauriers, Seasonal variation in isolated perfused *Xenopus laevis* heart as characterized by ³¹-P and ¹³-C MR Spectroscopy. A new digitalis effect. Vol V, *Proceedings Int Soc Magn Res /European Soc Magn Res*, Nice: 19.25: 82 (August, 1995).

4.

This part tells some facts and things that have happened to me, my family, acquaintances, colleagues, and friends at different times and places: at GassinoTorinese (Italy); during primary school, high school, and university in Turin (Italy); at the Institutes and/or Departments of Human

and General Physiology, Biological Chemistry, General Pathology, Pharmacology and Pharmacognosy in Turin; in Minnesota and at the Johnson Research Foundation (Philadelphia, Pennsylvania); in Camerino and Macerata (Italy); in Virginia and Utah; in Ottawa and Winnipeg (Canada), in Houston (Texas), Siena and Ancona (Italy); at Turin San Giovanni Battista hospital (the old hospital) as an intern while I was a voluntary assistant in Physiology; as a patient at San Giovanni Battista / Molinette hospital, or on holiday in Valtourneche (Italy)

(From Monday 2nd to Tuesday 4th November 2015)

Last summer, Lorenzo told me once again: "In our usual cultural meetings by the Passetto swimming pool, we have discussed some initial propedeutic topics, but the narration of our personal stories may also be of some interest, based as they are on our lives, which have centered on investigation and professional research. They involve widely different fields from surgery, and these will perhaps require my telling them. But the readers may find other anecdotes from your long life amusing, and learn from them..."

1.

Home

.....We lived in GassinoTorinese, where I was born. My mother was Lucia Ozella – a housewife from San Francesco al Campo whose family owned a cotton mill that made them rich during the Great War thanks to the patent of a filter that enabled using unrefined fuels; her brother, an engineer, founded FIAT's Centro Studi. My father was ordered to run away from the hydroelectric power station on the river Toce and narrowly escaped being struck by lightning outside it. He went on to become the technical manager of a stocking factory, Calzificio Sobrero, built on ground donated by the municipality. The factory grew hugely at first, then collapsed when, at the dawning of democracy in our country, the five brothers who owned it went into politics with the Italian Communist Party (PCI). Our two-floor house stood close to the factory. Under a cherry tree there was a large woodshed, where the partisans hid, and rooms at the back, where chickens, rabbits and a goat were reared by my grandfather, together with a pig, when we had one. The house was surrounded by lawns and by a garden and a large vegetable garden, which were fenced. When I was at primary school, I used to collect stamps, and remember quite well being fiercely beaten by the brutal petty boss of the opposed side. Soon I had to learn to go about nearly always alone.

On Friday nights, my mother would prepare the Piedmontese cakes for which our guest Father Piovano had a weakness. He was a great connoisseur of Saint Paul and used to talk to me about him. I started playing the piano with Mrs. Prelle. We had an upright piano in the sitting room. For the rest of my life I essentially taught myself, attending concerts, and setting up a huge music library of vinyl recordings, ultrasensitive tapes, and up-to-date CDs from all over the world, mainly performances of solo piano or its precursor, the harpsichord. My passion, which had always been overriding, reached its climax when in Siena I used all my savings to buy a Steinway baby grand. My knowledge of music was so extensive, since I used to listen to music throughout the day and also at work, that I was able to recognize a piece, and often even the performer, from the very first notes. However, last year I had to give up the concerts of "Amici della Musica" due to bilateral hypoacusia. I have now entrusted my piano to the specialist, master Roberto Valli - who has tended to it for years, replacing the chords oxidized by the sea air with new original ones every 15 or 20 years - to kill off moths by saturation with pure CO₂.

My parents started a stocking factory of their own in Corso Casale, Turin. My only, dearest brother, Dario, and his family also worked there, while I tried, unasked, to contribute by promoting our products abroad, always with poor financial results. My father was an excellent technician. The only factory producing vertical circular machines for knitting seamless men's stockings, in Chemnitz, had been destroyed by Allied bombs. My father succeeded in engineering and building faster and safer machines for the cams of the thousand rotating needles, at the "Monterosa" FIAT workshop, by changing the steel-cam, heat-sensitive adjustment mechanism of the needles, into an oleo-pneumatic coordination. Like me, though, he was no businessman.

Each day, traveling from Gassino on a SATTI train, I arrived in Turin at 11:30 a.m., often clinging to the carriage doors outside. The cars were so crowded that I preferred to cycle whenever the weather permitted. Classes in high school started at 1:30 p.m., so I had time to stroll under the arcades of Via Po and Piazza Vittorio, discussing all kinds of subjects with my friends. I even met a very knowledgeable theologian in the church in front of the street where the high school, Liceo Scientifico Galileo Ferraris, was located. Exhaustive discussions with him sometimes went on through the afternoon, meaning that I skipped class. During all

five high school years I shared a desk with the heir of the Cirio family of goldsmiths, who had worked for the Savoy. They owned at least two floors of the skyscraper in Piazza San Carlo, one of which housed their collection of works by the most renowned contemporary painters and sculptors. He farmed pearls (black ones too) on an island in the East, and every year traveled to South America and India to buy emeralds and rubies. I've always admired such arts. My friend even asked my daughter, already a psychiatrist in Novi Ligure (Piedmont), to work full time in his workshop, but she didn't accept. At my school where, regrettably, Latin was not taught well and Greek not at all (not to mention the main modern languages!), I luckily met an excellent history and philosophy teacher, whose advice was "never be happy with just reading Lisier's and Lamanna's textbooks: study the original texts in depth!". Thus I became aware of the way British, French, and German historians narrated the Italian independence wars and our Risorgimento!

After I passed my school-leaving examination, my parents presented me with a Frejus racing bicycle, the bike of the winners of the latest tours, including the Giro d'Italia. Sometimes I was also allowed to use my father's Lambretta. Since my very first years in graduate school, I had been accepted at the night ED of hospital San Giovanni Battista (the old one), where I had a bedroom all to myself. Beside classes, I regularly attended the Physiology labs, and the swimming pool too, where I became infatuated with a beautiful, dark-haired fellow student, a champion. We used to study together at her place and one day she actually assaulted and undressed me. As we were chatting during a class of the course of Chemistry and Biology, which was still taught by the Director of the Physiology Institute, Anna Maria Di Giorgio accused us of irresponsible inattention and threw us out of the lecture hall, threatening vengeance on the upcoming examination. She didn't forget, and she grilled me for the whole morning. Then she gave me full marks cum laude and invited me to attend the Institute as an intern to prepare my graduation thesis. We worked together for the next four years, and my dissertation on conditioned and unconditioned, spinal and thermal reflexes (Cf: 23, 24) earned me a first-class honors degree. My thesis was published and won the International Pfizer Prize as best graduation thesis of the year. Those were extraordinary, critical years and I still regret that I couldn't specialize as a chemist-physiologist due to a lack of places. Later, again at the swimming pool, I met attractive Maria, who immediately after graduation was hired as an assistant at the clinical

hospital of Ophthalmology, while Anna Maria advised me to continue my voluntary work at the Physiology institute, but to specialize as an occupational physician, in hopes of being assigned a paid hour as a health insurance doctor. However, the doctor in charge wanted me to spend half of the time with him at the clinic. This saved me from another thesis in physiology. This I was supposed to develop by breathing through the mask and cylinders associated with the Benedict apparatus, comparing the "typically women's" job of cleaning the Institute with a men's job, since the Anna Maria, a constitutional feminist, was persuaded that the energy metabolism was differently influenced and more easily sustainable. Then Rittenberg's pupil (in the UK) talked me into administering to myself a mass of unstable emitting isotopes, to evaluate the hemoglobin metabolism, in the presence of controlled, early-stage lead poisoning. This was another excellent, highly successful pioneering thesis. However, after I recovered from an eye condition treated by Maria, who was by then my fiancée, only my cousin Cornelio Valetto, the President of Turin's Federation of Industrialists, offered me a job as a specialist in one of his factories (in Ciriè). We realized that the remuneration there amounted to less than half the one of Prof. Scansetti, Rubino's assistant, who had won the post by an open competition. So I moved to biochemistry and to Prof. Camillo Lenti, who asked me to take a chemistry degree. This turned out to be a very tiring endeavor, also because Saini, the Chemical Physics professor - whom I later met in his hometown Camerino - maintained that a physician could not hope to enter into the required mindset. Anyway, I qualified for teaching Biochemistry, then Pharmacology and Pharmacognosy, and lastly General Physiology. Since I had no chances of paid employment in Turin, I tried Human Genetics with Director CPELLINI (who later gave me a teaching job at Siena School of Medicine), and then I tried again with Di Macco, the General Pathology Director. Of the latter I remember that he had elaborated a curious image of sexuality, including human sexuality, which he saw as being distributed on the two sides of a right-angled triangle: this could evolve from an isosceles into its opposite, the obtuse-angled triangle, and into the geometric squaring of the Pythagorean circle and the inscribed (or non-inscribed) squares. In the meantime, I spent my nights as a first aid physician of the Red Cross, visiting patients in their homes. I wasn't paid: it was the surviving patients who were supposed to do so. The experience was

extremely interesting anyway, and I tried to qualify it by identifying at least the patients I had sent to hospital, to make sure that the diagnoses and treatments applied wouldn't make me the only culprit. Finally, we managed to get myself hired by Farmitalia Monte-Edison in Milan, Via Gracchi, in the laboratory of Prof. Vittorio Erspamer, who then taught in Parma (or was it Bari?), in the cardiovascular section directed by Glässer. Each week I would go back, also to see my girlfriend, after sleeping in a nearby slummy guesthouse... At the end of this leg of my journey, Prof. Emilio Beccari, of the Bologna school, accepted me as an assistant through the introduction of a junior doctor I had met in the Biochemistry, General Pathology, and Medical Institute (Prof. Bastai, Rubino's colleague in charge of Occupational Medicine). When I resigned from the Milan factory I had to sign a document stating that I could not be hired again there. However, over the next two years I worked hard and published many absolutely original articles (Cf. 19, 25). Yet no open competition was in sight. Finally, without breaking with Prof. Beccari, but with his permission, I dashed to the US and the Neurophysiology Department of Carlo Terzuolo, who was from Turin but already collaborated with the physiologist Moruzzi in Pisa. ...

A final non-professional parenthesis: one night I went home exhausted after one hour of intense physical activity that was excessive for a student of the last year of high school. I fainted at the gate and was immediately admitted to the new San Giovanni Molinette hospital, in the ward of Moracchini and Volterra, with the rupture of a subpleural bulla and consequent right pneumothorax. I never ran a temperature and was given the newly-developed streptomycin without any bacteriological tests. Its protracted administration eventually caused vertigo attacks (and hearing impairment...). In the cinema, located in the hospital basement, with a collapsed lung, I developed left pneumothorax and had a narrow escape... Then, as soon as the lung had expanded again, I survived a make it or break it climb to the peak of Mont Blanc, where a friend drove me right after my discharge. (While ascending, I pierced my left hand with the ice ax I was holding in my right hand, which resulted in copious bleeding). Then there were the races as a sprinter on my Frejus, and the climbing, enjoyed for several summers, to the hut of Laboratorio Angelo Mosso on Mount Olen, to the Gnifetti refuge, the Dufour peak, and the north face of Liskamm, from the Capanna Margherita hut on the top of Mount Rosa or via the Signal crest. Always well, maybe God wanted it this way, but that hospital stay in the last year of high school persuaded

me that **I should try to become a physician, not an engineer**. Also, awesome skiing all over the Alps, even going to Sestrière and back the same day, after skiing down the most difficult slopes for hours on end, the two of us riding a Lambretta with the skis fastened upright, on roads where the ice hadn't always been removed. **So we made the second big decision, that is moving to the US**. I left by myself, as a Fulbright scholar, then I was joined by my wife who was on pregnancy leave.

2.

First stays in the US and Canada

I used to spend the whole day in the lab, in the cold room, dissecting under the microscope slow adapting neurons and comparing them with fast adapting neurons, placing them in the gas microchamber, monitoring them, isolating the motor plate nerve fibers, the accessory (GABAergic) inhibitory fibers where the neurons go back into the muscle, and centripetal ventral ganglia afferents, testing them through the quartz base of the chamber by electrophysiological and pharmacological approaches as well as using cell microfluorescence in optical chemistry and microphysiopharmacology tests (14, 15). It was really totally absorbing and exciting, but it prevented me from following what happened in the rest of the lab, where the Director kept losing his temper with colleagues Edwards and Ajala. The latter was the son of the Director of the Rome Opera House, whose American wife, married in Italy, eventually went back to the States with their children and two containers full of paintings by Guttuso and antique Palermitan furniture. Edwards was thrown out, whereas Ajala was admitted to a psychiatric clinic and became a clinical neurologist. He had published a paper in Science on epilepsy induced by penicillin filtered through the meninges, in rodents and humans. When the family decided to live in Italy for good their containers, even fuller than the first time, disappeared somewhere between Rome and Palermo. As for myself, good old Carlo (Terzuolo) made me write papers several times and then tore them up. Most nights I didn't sleep at the lab but was, instead, a guest at his villa and worked with him. There, too, I began to seek an independent role by associating with Lowry's pupil, Nelson Goldberg, a microanalysis specialist (for Pharmacology), and then making friends with two biochemists who were there at the time: Carlos Villar Palasi, the brother of Spain's Minister of Education, and, especially, Joseph Larner. The latter was a Czechoslovakian pupil of the two Nobels Cori,

who had been a high official of the secret central US chemistry and biological war labs during the war. He went on to become the undisputed master in that field and the teacher, as a pharmacologist in Virginia, of five Nobel laureates including Alfred Goodman Gilman Junior and Ferid Murad. During the summer, Carlo went back to Italy with his family, and asked me to mow the lawn in the garden and in front of the house. I didn't, and when he came back he couldn't go in because the weeds had grown waist high...Conditions were worse at Christmas, when my wife arrived. She was seven months pregnant and suffered from severe gestosis. Temperatures fell as low as -35°C , and our beautiful cottage on the edges of the golf course, on the Mississippi River bank, was covered in meters of snow, just like my VW, and the windows had turned into ice sheets. The colleague living on the upper floor, a remarkable architect, used to spend his weekends getting drunk and ended up shooting himself. The police broke down the door of our apartment, where Maria lived with Paola, because they hadn't opened since they couldn't understand the order; clearly they were terrified. Besides, whenever those half-Swedes from the North spotted them at the supermarket, they would say words like "mafia" out loud. On January 8th (1965), we celebrated Paola's happy birth with the typical local cakes looking all alike. We received the congratulations of Emilio Beccari, who also took the occasion to write that he had decided to retire and therefore, if I wished to go back to Italy, I should turn to Giorgio Segre, who had won the chair in Camerino. After risking to rent an airplane instead of buying a TV set, which I had ordered on the phone as a stroller, one terrible day my old Wols with myself at the wheel, Giovanni Ajala on the passenger seat, and Paola in a baby basket on the back seat, was run into by a big Cadillac at an icy crossroads. The car was crushed as flat as a cookie. Ajala's ribs and right clavicle were fractured, but the lesions were missed at Minnesota Hospital ED and he was discharged and had to go right back to work. Luckily, my daughter just took a fright. By then we had made our decision: after about three months, mother and daughter fled to Italy. I stayed on a few more months, but in Philadelphia, at the Johnson Research Foundation for Biomedical Physics, as an assistant to its extraordinary founder, the engineer Britton Chance (again (13)). He used to cycle by around 4:30 a.m. to check the diagrams lying on the desks, and to write in detail the tasks to be carried out the next day. Then he cycled away to go training on a boat on the Delaware river – at the time he was already an Olympic sailing champion.

Before closing, I'd like to tell an anecdote about Britton Chance, who was very rich. I had removed the ventral ganglia from a mountain of freshwater *decapod* crustaceans. We needed the ganglia to extract cytochrome b5, which contributes to respiration also in the presence of carbon oxide and cyanide, and is needed in considerable amounts to be studied by liquid nitrogen spectrometry. I was about to throw away the remaining tissues when he arrived and said: "Hey, no! Please, have them collected and cooked" (for the weekly dinner to which at least 150 members of the staff used to be invited on his model farm). A unique man (13, 3, 15)! Each time, his guests, gathered around the table in the salon, were expected to present "spontaneously", in turn, their best contributions. Similarly, during my last, long training periods at Houston Medical Center, Integrated Department of Biology, Physiology and Pharmacology, the recent Albanian Nobel laureate and former junior clinical pharmacologist of Joseph Lerner, Ferid Murad, wanted (with me by his side) all researchers of his lab to write a report and discuss it in depth: every Monday morning of every week, as he returned from a weekend spent on the greens of the Grenadines or in one of his other institutes, maybe in Hong Kong.

References

23. L. Rossini, riflessi condizionati da stimoli termici nella cavia. I. Effetti della narcosi, dell' ipotermia e di farmaci psicotropi. *Archivio scienze Biologiche* 46: 356-369 (1962);
24. A. M. Di Giorgio, L. Rossini, Fenomeni di disinibizione nell' animale spinale, *Boll Soc It Biol Sper* 20: 128-129 (1958); L. Rossini, Tasso catecol-enteraminico e reazioni di disinibizione d' indole termica, *Boll Soc It Biol Sper* 40: 673-676 (1964);
25. G. Rolla, L. Rossini, Fenomeni di rimbalzo farmacologico osservati nel dotto deferente isolato di cavia con certe sostanze anti- β . *Boll Soc It Biol Sper* XL, 12: 676-679 (1964).

3.

Back to Italy, south of the deep South (in the words of the S.I.F. President), then Siena

While in the North no door opened for me, my family was in Turin. My wife rushed from the eye clinic to the various health insurances, including FIAT's, once risking to be tipped over in her car by violent strikers as she broke the strike. Paola was being taken care of by grandpa Giovanni, owner of a big Norton motorcycle. He was an apparently grumpy man who had been an extraordinary master builder of roads, bridges, and railroads in the Belgian Congo and subsequently in Val d'Aosta

and Sicily where, in his words, "I met the most debauched workers, so dangerous even for my life that I had to give up the job". I decided to make a new start as a graduated technician at the School of Pharmacy in Camerino, where I was welcomed at the door by first assistant Giorgio Giorgi: "You're warned that I am the professor here, and you have arrived after me". My only answer was a shove with my shoulder as I took in my two giant suitcases full of books. Life as a single was egoistically better than the "nothing of indifference" described by Moravia. Director Giorgio Segre showed up very rarely, often driven in a Ferrari to the meetings of national drug committees, the ISS (Istituto Superiore di Sanità), and the ministries in Rome by the former Perugia gastroenterologist Francesco Orlandi, who later participated in the foundation of the new university and School of Medicine in Ancona. From my desk in front of the window – all I had been equipped with – overlooking the marvelous wooded valley, we used to peer at him with powerful binoculars, as he moved in and out of the tent with lively Franca, who had taken her Pharmacy degree in Turin. The third comer, a physician and highly knowledgeable mathematician from Piacenza, Francesco Periti, kept up with him: he would interrupt a lunch for a quickie just because he had played footsie with the student sitting in front of him. I drove down from Turin every week in my OSCA Pininfarina, then in the VW 914, or in a Fiat 500, often getting lost in the fog at Colfiorito, travelling nearly always by night, at a time when the motorway was just Turin to Milan, and later Turin to Bologna. I left Camerino on Saturdays at 1 p.m., after the last class scheduled by the Director, and on Monday mornings I left Turin to get back in time for the first lesson, which began at 8:30 a.m. In the winter everything was frozen, and from Castelraimondo to Camerino you could meet hungry wolves on the roads.... I was a fairly good driver and among my passengers I boasted the Chancellor, Professor of Jurisprudence, and director of a section of the Alfa Romeo factory in Milan. I will never forget the way he'd circle the car to check the tires' conditions before getting in. There I took my third degree, in Pharmacy, after the terrible professor of Pharmaceutical Chemistry, Mrs. Steiner, had tried to fail me by asking me the phases of the synthesis of several β -lactams, penicillins and cephalosporins of fungal and artificial origin in the smallest detail. Before the opening of the new facility out of town, I lived in a period building in the old town. My aged landlady didn't hesitate to enter my bedroom to use her antique Singer or Necchi treadle sewing machine to sew and embroider even as I was sleeping. I

regularly played my Steinway, now moved to an abandoned church. At other times, Periti drove the two of us down to the valley, where he glutted himself with beer, repeatedly recounting his dreams of successful research, and I had to put him to bed after driving us back in his Ford. We very often traveled in Giorgio Segre's Giulietta, driving to meetings chiefly in Pavia (the headquarters of big shot Mascherpa), or Perugia, Genoa, Florence, Naples, Ferrara, Verona, and Rome (to the ISS). We were a competitive group, and the cofounders of the Italian Society of Molecular Biology. Camerino was a top university, especially the chemistry section, which also included Antonini, who died young, Brunori, and Cerletti (Jr.), all of them from Rome's Biochemistry. We soon learned that, at Olivetti in Ivrea, Director Giorgio Segre had designed and developed an early industrial pharmacology research lab, which preceded the one set up by Silvio Garattini, in Via Negri, Milan. Our good father, boss, and master Giorgio Segre often took us to lunch, sometimes even to Piacenza or Turin, and always chose certain places where he'd systematically refuse the proffered wine, which was actually excellent. Once as I went to the restroom to wash my hands a waiter came out of the kitchen carrying a steaming plate of risotto, and after saying "For the Jew", he spat on it. When I went back to the table, I said nothing and never knew who had been served that plate.

With time, I got tired of going back to Turin every weekend. I used to travel by train in a second class car with Segre, but it was always overcrowded with migrants and their bloated suitcases, typically tied up with string to prevent them from breaking open. Instead of getting a mistress, on Sundays I began to attend a flight training course at the former military airport in Foligno, to get a pilot license (which I got) for the Macchino. The aircraft had a 6-meter wingspan and was riddled with the holes of the bullets it had received in the battles it had won. My flight instructor was crazy: he used to make the aircraft stall at a high altitude also over built-up areas, and once ended up nosing over in a ploughed field with a full reserve tank that he had completely forgotten about – a double mistake that was really unforgivable and convinced me that I had to quit.

When Paolo Mantegazza was recalled from Siena to Milan, soon becoming the Chancellor of the four departments of that megalopolis, which was the actual capital of Europe, Segre was called to Siena. The political party for which Giorgi had acted as his electioneer settled him in the town of the Palio, where he collaborated with bank Monte dei Paschi.

The Dean of Camerino, the general physiologist Tedeschi, asked me to accept an appointment as Director. I accepted it, only to live in a nightmare through the worst three months of my career. "You couldn't know that Marches are the preserve of Rome's School. You'll find yourself alone and lose the open competition, and first of all your Pharmacology teaching job, if you don't come to Siena with me right away..." advised Giorgio Segre. Even though I had a degree in both general and human physiology, I was too afraid of not being allowed to go back to Turin, so I gave in. Moreover, a very bitter event had troubled my otherwise privileged existence there. I was attending a congress when, at least two days after the fact, I learned that while my wife was working at the hospital, our housemaid had left Paola alone, waiting for her grandpa, and had thoroughly searched the flat and stolen everything we had, including the silver dollars we had saved in the US and the family jewels. She had a lover, a thief she had just met, who had talked her into cleaning our place out. We never managed to get anything back – we had no insurance and the jewels, which had been purchased from Cirio and in America, were melted and lost for good. We didn't report the theft and we let our maid have her employment card when she had already fled abroad, but we informed her new employer. In Siena we soon lost the excellent Periti. Without his knowledge, his parents had gone to Segre, asking him to favor their son. Francesco got mad at them but also at Segre, whom he called "a Nazi". That was really too much, and earned him the exclusion from every job. Francesco, whose father was the head of the psychiatry dept in Piacenza and a Mason, was soon proposed as a professor of General Pathology in Pavia, but he preferred to devote himself to his wife and daughter, working as a radiologist. Once he called me and together we cycled by the restaurants and buildings that had belonged to him. He told me that he had been disinherited because he had got married without his parents' consent. He also confided that he had self-diagnosed some, by then untreatable, metastases of a prostate cancer. He died shortly afterwards. Every year we call his wonderful widow, a teacher, and his daughter, two extraordinary persons of unparalleled, crystal-clear honesty just like my dear, irreplaceable, esteemed colleague. Meanwhile, as Segre fought with the old pharmacologist of the School of Pharmacy, Italo Taddei, I neglected all the rest and worked alone -I could (26) - or with his excellent technician Carlo Arezzini (27), then with Francesco Periti and with the equally keen, younger assistant Paolo Dal Pra (18), who also died very young. I no

longer drove a car, but rode, enjoying especially the sharp turns of the Genova-Serravalle and San Gimignano roads, a brand-new, three-cylinder, two-stroke Kawasaki, up to and over 15,000 rpm, a real Cagniard de La Tour siren. . I later learned that it was called "the human coffin", but that is not what happened to me: while I was riding at about 245 km/h in the vicinity of the Monteriggioni straight stretch on the Siena-Florence, the engine seized. I wasn't fast enough to disengage the clutch and was shot forward, rolling on the clearway. Sand entered through my skin into all my joints down to the bone, even though none broke. I fainted only when I was taken back to my lodging, in a tower along the town walls, where a radiologist colleague also lived. Actually she was driving in the opposite direction when, as I fell, my bike pushed me into the opposite lane, and she nearly run me over. She then drove me to my lodgings, put me in the shower and left, and there I fainted. But worse was to come, since when she dressed my wounds with penicillin-medicated gauze I developed an allergy in little more than a week and one night, when I was alone again, I woke up breathing heavily and realized that I had acute Quincke's edema, close to choking. I managed to drag myself down to the central pharmacy, where the chemist on duty saved my life by injecting just antihistamines, no cortisone and/or adrenaline. All this happened while my family was at the seaside in Sestri Levante: I told them that I was busy and would join them in two more weeks.

Work was obsessing and took up all my time. One day I got a call from my brother in Turin: "Today I noticed that Dad talks and discusses everything correctly, but doesn't realize that there is a word he can't say, which he drops systematically; moreover, he does multiplications and divisions correctly, but miscalculates simple sums by millions". I called Dad, who greeted me cheerfully. I said "I'm coming over, on my bike". Talking about this and that, we went together up to the fourth floor of the Neurological clinic of Molinette hospital, where he was examined by two acquaintances Bergamini and Schiffer, who were puzzled but didn't find any additional deficits. I accompanied him down to the basement and was there during his cerebral arteriography: as soon as the iodinated agent spread he gave a sort of start and lost consciousness, never to regain it. My poor Dad, lost at 63 years of age. His brain was completely riddled and was immediately considered inoperable by Maspes, a Milan neurosurgeon, and by a luminary in Zurich. All we could do was to place him, at home, into the care of my contemporary, the ECG specialist Riccio, who a few days after I had

gone back to work certified his death. I recounted this highly distressing fact to the neurologists of Siena and Ancona, who however did not offer any plausible explanation for my father's mathematical and linguistic behavior, the only apparent, conclusive sign of a functional and organic impairment.

References

26. L. Rossini, Noradrenaline reversal of papaverine, *Pharmacol Res Commun* 2: 121-126 (1971);
27. C. Arezzini, L. Rossini, G. Segre, Effects of group Selective reagents on the receptors for histamine and acetylcholine in Guinea pig ileum. *Pharmacol Res Commun* 1,3: 295-302 (1969).

4.

Siena and Ancona

Eventually also the construction work for the new preclinical facilities of the Medical School began, not in Camerino, but in Ancona, where the engineering faculty had already been founded. The Medical School was founded by the mayor (and later Christian Democratic senator Alfredo Trifogli); the surgeon Gian Carlo Castiglioni from Rome's Catholic University of the Sacred Heart in Piacenza; the Sicilian microbiologist Michele La Placa (of the Republican party and a follower of Giorgio La Malfa) from Bologna university; the pharmacologist Giorgio Segre, whom I have defined an aspiring socialist; and the gastroenterologist Francesco Orlandi, formerly in Perugia and well known in Camerino. Segre, while I believed I was being supported by the pharmacologist, and after I had advanced my candidature for the third year of the degree course, wanted me to remain in Siena as his assistant to share, as I did, the teaching burden and to shoulder the further specialist courses. However, after his heart attack, he supported the assignment to Orlandi's wife, Ms Anna Marie Jezequel, a well-known Belgian researcher, of the hospital's Liver and Drugs Center, while I waited in vain to be appointed to Clinical Pharmacology and Toxicology. I had the luck of being able to block her assignment to Cell Pharmacology, a subject that I didn't know was up for appointment, and which would otherwise have been swiftly given to her by the faculty. The Dean was the neurologist, and later Chancellor, Franco Angeleri, who once said that in his life he had discovered a single protester within the faculty. Orlandi went on to become a good academic and gastroenterologist and his former assistant Benedetti disrupted the sequence of expected Deans. The next was the current Dean, hygienist Marcello Mario D'Errico. At the time when the Medical School was founded, the academics, and especially the technical and administrative staff, were informally "appointed"

by politicians.

The building in Posatora, which was later assigned to the Agricultural faculty, grew in the shadow as the tall, modernist building of the Engineering faculty already towered on the highest of the hills around Ancona. The Biology dept was far removed and awaited the move with the inauguration of the Azienda Ospedaliera Clinica Generale Regionale at Torrette, which was very distant from the city center. The Medical School was designed and built in a muddy depression that may have been part of the historical landslide area. Be as it may, after the first earthquake tremor it was inundated and the ground floor, including the pharmacology lab, was swamped. I lost my whole library, including my own books, the recently completed equipment of the CNR and my own, which I had taken with me from the US, Turin, and Siena. I also lost the archives, all current research records, and the material for the scheduled lab sessions, which involved the researchers, technicians, and interns (thus training them in the basic notions that would later help their research work). *I was never refunded or offered replacements, something that I had to achieve with external funding that I procured myself* (for the complete story the reader is referred to (28)). While I was waiting to be offered tenure in the US, I had accepted the appointment from Ancona Medical School to start not only the course of General Biological Pharmacology, but also the clinical branch, as Toxicology. But *neither the initial contract nor the subsequent changes were respected, even when we moved to the new Torrette buildings*, and this regarded only us. So much so that in November 2013 I closed, saying goodbye to my colleagues and also sending a formal letter to the local and higher control bodies (29) (together with the list of the works published well after my retirement). I have never received a reply, but any chance of coherent development of the Sections has been delayed without justification. All of this prompted me to try and go back to Canada, hoping to convince my family to live there, but I couldn't. I used to follow the construction work at first from lodgings in Falconara. There, I was offered the opportunity of purchasing for the negligible sum of 30 million the 17th century villa Domini, built on a hilltop, with a double row of cypress trees bordering the avenue leading to it, as in Bolgheri (the first researcher I was assigned, the enthusiastic Dr. Cingolani Belli, was a relative of the Director of the Fine Arts dept and, unasked endorsed the purchase). It had an immense hall with wonderful frescoes and antique furniture (that I later saw in

the shop windows of the antique dealers along via Flaminia), a central chapel and two apartments at the sides. One would have been sufficient, and its restoration would have been partially paid for by the Fine Arts Superintendence if I agreed to keep it open to visitors one day a week. The other could have served to accommodate the increasing number of our guests, who came to conduct research and teach in Ancona. We didn't buy it, also to avoid being tied up by this agreement, and opted for a two-bedroom flat, where I moved by Steinway, but I managed to host the geneticist and pianist, and renowned enzymologist Charles Walter from Houston, with whom I co-authored a chapter in the Proceedings of the First Portonovo Biomathematics Conference. My wife came in the summer, although we also met in Sestri Levante or at Monterosso (Liguria). Moreover, the first earthquake tremors, not an uncommon event in Ancona, contributed to her decision to go back to Piedmont, to her maternal and professional duties. I finally found a property along the panoramic road that connects Ancona to the seaside area of Portonovo. It was a ruined house standing high on the cliff at a height of 120 m, with a pinewood that extended down to the beach. On the beach the fishermen had dug 18 caves into the face of the cliff for their boats and equipment. We began restructuring the house and were sued no less than seven times by the neighbors (these are penal offenses in Italy). All suits eventually resolved and I was finally awarded the three year test period (*straordinariato*), last among the 12 academics of the Medical School. The restoration work at home was so slow that we had to sleep on the second floor terrace in a tent, before we were granted permission to build the roof and an attic. Recently, on November 5th, 2015, we tested and finished the PV plant that, with the acquisition of the newest batteries, will shortly make us independent of our utility, which buys from us the excess power and sells it back at 100fold prices. I'm still bothered by the institution of the Parco del Conero, where our house is included. The Park dispossessed us of the pinewood, with more than 3000 trees, and has since neglected it, not even tending to the underwood. In the past I used to go down the path early in the morning, before going to the lab around 8 am. I used to swim in the open sea, and I had trained my first two Alsations to swim with me and tow me back if I needed it. The third, Sancho, only ever learned to float upright, but he's much more affectionate. The first one day swam back before me and smelled a large barbecue where the fishermen were roasting spider crabs. When they saw him he had already eaten them all. That incident

started a cold war with the "cave people", whose caves were unauthorized, but who were extremely arrogant, potentially dangerous, spiteful and menacing. We had to build a large rainwater reservoir with a pump and two nozzles, since in the case of a fire we would have to keep the fire at bay until the fire brigade arrived... . Nice people: they have now become owners, through positive (albeit controversial) prescription, of these picturesque and unique caves, which we have never been able to enjoy, as if pretending we were survivors on a desert island. Moreover, they clearly never obeyed the mayoral ban (no. 11 of 16.7.2006) and the Harbor Police ban (no. 37 of 1996) forbidding access and stopping over along the coast, nor did they accept our offer of September 5, 1986, which allowed them to remain provided they left one cave for our use. Nevertheless, they invoked positive prescription, which contrasts with the above bans. It is however a scandal that the park managers first sized our 4.84 hectares of wood and then just abandoned them. Yet a ministerial decree (of 30.10.2007, GU n. 40, 15.2.2008) clearly states that the wood should be at least disinfested of processionary moths (*Traumatocampa pityocampa*), a pest whose nests severely damage the pines, and which I have to remove annually, at least as long as I can afford it. Moreover, they produce a terrible toxin and our third Alsatian was nearly killed when he ate one as a puppy. The poison induces mucosal necrosis and he survived only because for months I fed him liquid food directly into the mouth every couple of hours, day and night. The new Dean, and later Chancellor, the clinical surgeon Salvatore Occhipinti, referred me to Trabucchi in Milan, an unexpected help and one that was offered without strings attached by a real gentleman that I remember with great humility. This is not because my mentor abandoned me. Indeed, years later he visited my wife, who had by then moved to Ancona, asking if she agreed to move the family to Rome: at the Istituto Superiore di Sanità, where he had been offered the chair, or at the Catholic University, where he had been offered the direction of the Pharmacology dept, which later went to Preziosi from Naples (incredible for the Catholic university: a non-practicing Jew and an openly anticlerical one to boot), but nothing came of it. That for me was a period of intense work and interesting results in new fields, at least in pharmacology, that I have mentioned above. In (30) there are a few more, but I'm prepared to discuss them only with interested readers. Events that cannot be described as other than bewildering

happened, too, and here I want to tell about one, without comment. Maria had never found the time to devote herself to gastronomic biochemistry, but she soon became a much sought after hostess and cook for faculty members, gate crashers, presidents and heads of national bodies, colleagues, foreign guests and visitors from the WHO, all of whom praised her immensely ("the best restaurant in Ancona", sic the impudent, if this is a merit). Chairman Joseph Lerner came with his wife, who was delighted by the school of Marche cuisine; so was the clinical pharmacologist Ferid Murad, later a Nobel prize winner, from his new department in Virginia, who contributed to the discussion - also by presenting his work (31) - of the Second Portonovo Biomathematics Conference, which centered on our topics (32). Soon Lerner was able to forget that during his visit to Naples his uninsured Rollei had disappeared from the taxi. After a meeting with Vittorio Erspamer, he presented to the 19th Congress of the SIF and Associates his latest review (33), to great acclaim and - as he confessed to me - intense personal satisfaction. The medical clinician Carlo De Martinis, co-organizer of the Congress and co-founder of the Ancona Institute of Experimental and Clinical Medicine, was a frequent guest and sometimes brought fresh crustaceans and fish that we cooked together. One day we decided to prepare as a surprise an omelet with "French onions", which grew in the garden and we dried in the sun, thinking it was shallot. In fact it was a case of severe poisoning that ended with us vomiting grey material reminiscent of an unsuccessful Exorcist. We called straightway the Siense colleague Taddei, a pharmacognosist and toxicologist, who confirmed the etiological diagnosis of potentially lethal scillaridine poisoning, since the plant was actually *Scilla maritima* and required an emergency gastric lavage. De Martinis, who was eventually offered a chair at the first university of Rome, refused the lavage on the grounds that he'd find his assistant (who was later hired in Teramo and next at Ancona's INRCA) on duty at the ED. These are anecdotes that remain in one's mind even though they have no relation to work. Like the case of our student, who during a pause of a local motocross competition inadvertently ate some *Atropa belladonna* fruits. The two motorcycle-mounted Carabinieri who were carrying the antidote, neostigmine, from Rome (because it was out of supply in Ancona) had an accident due to the rain, but the patient made it. Maria finally won a public competition in Macerata, and was offered a position at the Ancona obstetric gynecological hospital, where her 20 year experience

as a specialist surgeon was never exploited in the ambulatory visits she was assigned to. Much later she was transferred to the General Hospital, where - after being an academic in Turin - she was at least no longer required to do also research and teaching. A very negative and disagreeable battle was undertaken by Extraordinary Director, radiologist Alfio Montesi, who after calling the first Regional Healthcare Service Conference (Loreto, 21-22.6, 2001; (34)), in which the Service of Clinical Pharmacology and Toxicology clearly participated, surreptitiously tried to cancel it with an infamous administrative and penal measure that was never upheld by the board of directors and that had been inspired by the Chancellor, who to his shame lost the rich, useful and well-organized Toxicology Service. Montesi was later appointed a (powerless) coordinator of MRI magnet purchases in Marche and had an early retirement. Even worse for the Institute and the Services was the position offered to the physicist Aldo Rescigno, a mistake I made myself, since the offer should have been conditioned to specific programs, requirement and results, which I didn't set. Although he took part in a few summer courses, he never systematically taught his biomathematics and later pharmacokinetic courses (two complementary subjects), for which he had been offered the position and for which he was exceptionally qualified in terms of skills and teaching and academic degrees. Similarly, he refused to sit on examination boards and to vote the purchase of any piece of equipment; he even opposed the acquisition by others of indispensable equipment. He clearly could not sustain the teaching load of Pharmacology I and II or of Clinical Pharmacology or Experimental and Clinical Toxicology. Rich only in theoretical knowledge, he never followed a single student's thesis of specialist dissertation, nor did he manage to convince the founding members to follow him to a hypothetical department of the Biology or the Engineering faculties. Supported by our only associate professor, Luciana Leone, he proposed his candidature as Institute Director, proving only as an element of rupture and chaos, and was luckily away most of the time. His models and theories have never agreed with any of the experimental results we have obtained. I have never expressed an opinion before: his pharmacokinetic is now well known all over the world but it never worked while he was with us, and I'm unable to assess his competence and originality, since I've always dealt with the pharmacokinetics of power spectra of time series

(35). Always a guest, he never even looked for critical support from Giorgio Segre (who had indeed advised me against him) and myself, for his future academic career, and disappeared.

Nearly every year, I used to go back to the very active foreign labs where I had worked, spending three months (once six, for several reasons), with Larner in Virginia (1970-1977), with Deslauriers in Canada (1984-2003), at Utah university (2004), and twice at Texas university in Houston (2004, 2005). These facts are dealt with below.

References

28. L. Rossini, Didattica vissuta e aggiornamento della "Nuova Tabella XVIII", Proc, Acc March Scienze, Lettere Arti Ancona 38: 123-142 (2005);
29. Statement to the Authorities 4 November 2013, and list of papers written after retirement, below, after my CV;
30. L. Rossini, Reclassifying cholinergic receptors, Trends Pharmacol Sci, Editorial 3, 9: I-V (1981); L. Leone, L. Rossini, B. Lumachi, B. Valsecchi, G. Coppi, The therapeutic use of cholinergic drugs acting on the Vegetative Nervous System, Il Farmaco 36, 10: 827-837 (1981); L. Re, M. L. Cingolani, C. Concettoni, L. Rossini, Cholinergic effects of cimetidine and ranitidine, Pharmacol Res Commun 15, 5: 485-527 (1983); D. Bradu, M. L. Cingolani, L. Ferrante, L. Re, A. Rescigno, L. Rossini. A contribution to the advancement of the computational procedures as applied to the classification of drug and receptor congeners. In: Highlights in receptor chemistry, C. Melchiorre, M. Giannella Edts, Elsevier Sci Pub B.V. (1984) 251-294; D. Bradu, B. Di Sarra, V. Moretti, L. Re, An alternative to ANOVA: a maximum likelihood approach, Quaderni didattici ERSU 15: 5-22 (1984); M. L. Cingolani, L. Re, L. Rossini, The usefulness, in pharmacological classification, of complementary pattern-recognition techniques and structure modelling, as afforded by the iterative collation of multiple-trial data in data banks, Pharmacol Res Commun 17- 1: 1-22 (1985); D. Bradu, B. di Sarra, C. Concettoni, V. Moretti, P. Pagelli, L. Re, L. Rossini, C. Tonnini, Characterization of the rabbit aorta endothelium-dependent cholinergic receptor by agonist equipotent molar doses, J Pharmacol Methods 22, 4: 219-231 (1980); P. Rossini, L. Rossini, Evoluzione di alcune conoscenze base in tema di tossicoassunzioni e tossicomanie. Quinquennio 1998-2003, Lettere dalla Facoltà, 8, 7-8: 19-26 (1095); L. Rossini, Global recurrent classification in experimental and clinical pharmacotoxicology, Pharmacologyonline Newsletter 3: 12-15 (2012);
31. F. Murad, Role of cyclic nucleotides and feedback system to regulate cyclic AMP accumulation and action, 1st Portonovo Conference, On endocrine pharmacology: Compartmental models and control systems, Cofese Ed Palermo, Piccin Int Ed (1974): 107-114;
32. L. Rossini, P. Bastianelli, M. L. Cingolani, G. Gamba, M. Giannella, F. Gualtieri, L. Leone, F. Martorana, C. Melchiorre, V. Moretti, P. F. Periti, M. and P. Pigni, L. Re, G. Roda, S. Tuccella, Pattern recognition in profiling pharmacological receptors. In: 2nd Portonovo Conference On biomathematics, Cofese Ed Palermo, Piccin Int Ed, September 27-28 (1978): 257-290;
33. J. Larner, J. C. Lawrence, J. P. Roach, A. A. De Paoli-Roach, R. J. Walkenbach, J. Guinovart, R. J. Hazen, Two biochemical

mechanism of action of insulin to control glycogen synthesis. In: Volume of the contributions, Proc. of the XIX Congress of the Italian Pharmacological Society, and associated National Scientific Societies, 1st Joint Meeting of Yugoslav and Italian Pharmacologists, (Ancona, 24-27 September 1978): 205-243;

34. L. Rossini, Unita' Operativa Farmacologia clinica e Tossicologia: Attivita' peculiari, di eccellenza, programmatiche ed in corso. Prot F 297, la Conferenza sulla sanita'. Realizzazioni, problemi aperti, ed indicazioni, Loreto, 21-22 giugno 2001;
35. M. Bernardi, R. Deslauriers, I. Docherty, C. Rossi, L. Rossini, P. Rossini, C. Tonnini, Spectral analysis of intercycle heart fluctuations in *Xenopus laevis*, conscious or spinalized, treated with calcium channel blockers, Part 1- Gen Pharmacol 29, 3: 477-481 (1997); M Bernardi, R Deslauriers, J Docherty, G Galeazzi, L Rossini, P. Rossini. Spectral analysis of intercycle heart fluctuations in the diethyl-ether-anesthetized or pithed rat treated with l.hyoscyamine. J Autonomic Pharmacology, 17: 27-34 (1997); M. Bernardi, R. Deslauriers, J. Docherty, C. Rossi, L. Rossini, P. Rossini, C. Tonnini. Spectral analysis of intercycle heart fluctuations in the diethyl-ether-anesthetized or pithed rat treated with prazosin, dl-propranolol, endothelin-1, α -r atriopeptin and ACE-inhibitors, J Autonomic Pharmacol 18: 1-10 (1998).

5.

VISITING PROFESSOR IN VIRGINIA, UTAH, WINNIPEG, AND HOUSTON

1. Back to mentor Larner

Since the time of my first stay in Minnesota, I had continued to keep in touch with the lab that has nurtured five Nobel laureates in Medicine, assisting Joseph Larner and Villar Palasi in their work. In the next room, one day the lab technician of Ferid Murad, who was then in the Pharmacology section of the new hospital, was using nitroprusside to obtain inhibition in an in vitro test, but in fact noted dilation and activation. Larner said: the salt is very pure, recrystallized, and well preserved, it must therefore be a new effect. It was the first case of NO-induced activation of guanylate cyclase, the system that Ferid then isolated and for which he earned the Nobel prize of "the three NOs" for Medicine in 1988 together with Furchgott and Ignarro. Larner, who in the UK had honed the technique developed by Sanger for insulin, asked me to study the amino acid sequences of the dependent and independent forms of glycogen synthase (UDPG: glycogen α -4-glucosyltransferase, EC 2.4.1.11), activated or not activated by G6P, the very first example of allosteric regulation he analyzed. For me this involved spending nearly all my three-month vacation from Italy again in the cold room digesting peptides modified by the specific reaction of the amino acid sequences studied with Segre in the mentioned receptors (27), separating then by high-voltage electrophoresis

according to Sanger. A first paper, describing the selectivity of the aromatic tyrosine hydroxyl, blocked by nitrating tetranitromethane, a key residue for catalysis, not for allostery, together with a host of other specific or selective reagents, was published before my return to Italy (36). Two further papers by myself alone did not persuade the suspicious Larner, and were put aside awaiting my return (37). Incidentally, when I was accepted in Houston in 2004-5, Murad asked me to study the nitration of tyrosine residues of his NO synthase, as well as to complete the work on glycogen synthase, extending it to "his" enzyme. This could not be done, because my wife and daughter could no longer bear the length of our migrations.

References

36. Larner, D. Benjamin, L. Rossini, Effects of group selective reagents on Rabbit muscle glycogen synthase. Molecular & Cellular Biochemistry 6: 65-70 (1975); L. Rossini, J. Larner, The inhibition of UDPG-glycogen synthase activity in vivo and in vitro, by Cinchona alkaloids, Pharm Res Commun 3: 21-35 (1971);
37. L. Rossini, J. Larner, C. Villar Palasi, An "in vitro" cycle of modulation of glycogen-synthase activity from skeletal muscle. Submitted to the Chairman 1-18 (1975); L. Rossini, J. Larner, C Villar Palasi, Unprimed UDPG incorporation by an highly purified glycogen synthase from rabbit skeletal muscle. Submitted to the Chairman 1-19 (1975).

2. A parenthesis at Utah University

The Mormons, those of the strange traditions, chose for themselves a magnificent valley, and as rumor had it Utah university paid lower salaries because the place was very attractive in itself, with the enchanting houses in woods visited by deer, the nearby ski slopes, and the heated swimming pools on the rooftops. Nothing of this was true, but my daughter and I had a splendid accommodation in a guesthouse with a Viennese grand piano at the entrance. However, I practically lived in the Pharmacy department lab, where Martin Schweizer, who had been a contract teacher in Ancona, managed the still only NMR spectrometer, which he employed to resolve micro-RNA strands. I proceeded by systematically learning to use it every day and night, while in my leisure time I exploited the nearby presence of the best known specialist in liquid chromatography-mass spectrometry in the US. I occasionally met the two chemistry researchers from my wife's Waldense valley, who had been involved in the controversial beginning of cold fusion. This time Paola had been very sad about leaving Italy for a place where I would gladly have moved my family for good, a place that was more interesting also in winter, compared with icy Minnesota and Manitoba.

The city was ordered, modern and well kept, except for the peculiar temples. The acoustics in the concert hall and the direction of the choir were exceptional; and the five national parks - there are 25 in the US! - the mighty five, Arches, Bryce, Canyon Lands, Capitol Reef, and Zion - were fantastic. Paola, a neoAmerican, had by then forgotten the time when in Tokyo she had been expelled from the country after only 5 days, and on her first turn around the world had been celebrated in Canberra and Sydney. My promising student Dr. Marina Bernardi, who had had to postpone her Italian wedding by three months, to be in the US long enough to master those no less than extreme techniques, was not equally amused.

3. Back to Winnipeg

While we were in Manitoba, Paola went back to visit nearby Minneapolis, where she had been born, then flew with her mother to Churchill Bay, to see the annual return of the bears from the pack for the Arctic winter, an unforgettable sight. I lived in the comfortable 5 star downtown hotel and regularly swam in the Olympic swimming pool, devoting the rest of my leisure time to honing my beloved Beethoven's Op. 101 and Rachmaninoff's variations on a Theme of Corelli. I had my own office and lab, and watched together with the engineers and physicists the design, construction, and biomedical applications of clinical MR scanners, including the original titanium device that could be moved to the neurosurgery theater. I hoped to bring back to Ancona an NMR (micro)spectrometer, maybe also an infrared one. At last, the General Director offered me for Ancona the most advanced apparatus used by the clinicians, and another for my lab, with a 50% discount including maintenance, cryogens and upgradings for five years. I gave the quote to the Chancellor, Angeleri, asking him to invite the Director for a lecture, maybe offering an honorary degree, but he forgot to reply to the quote, and I was left with egg on my face. I'm Piedmontese and obstinate, and bought a 300 mc Brüker apparatus with the research funds of 15 years, but after a while I could no longer support its operating cost alone, even though it had been approved and financed by the Regional Government with an ad hoc measure. All my colleagues know that my successor has authorized the scrapping of the apparatus despite the fact that it was still competitive, functioning, and even still on the catalog, a shameful event that I have not shared before. All of this notwithstanding, I successfully applied my favorite preparation after

the one of Minnesota to the heart and muscle of *Xenopus laevis*, and to finalize my research on digitalis that was presented in Nice, France (22), where samples had been subjected to magnetization transfer with results that were absolutely original. Unlike Britton Chance's data on heterothermic decapod crustaceans, employed and proposed with Carlo Terzuolo in Minnesota, my data remained unpublished, because it was impossible to establish whether the tissue was damaged by the heat generated by this staggering technique. After my retirement I tried to go back at least to the National Biodiagnostics Institute, to conclude the research work I had been forced to interrupt in Ancona, which involved the observation, at least by $^{31}\text{P-NMR}$, of retrogradely perfused rodent heart (Cf: 2). However, I discovered that the facility was in disuse and the wonderful group of the Director had been moved, and she was now head of Waterloo University Thunder Bay Regional Research Institute, now more generously funded (the interested reader is referred to the 269 papers by Roxanne Deslauriers, including ours, easily found by Google).

4. Last two escapes to Houston

.....In the US, Larner introduced me to Murad, who welcomed me kindly. At the time he was very busy in his three capacities as Chairman of three merged departments (Biology, Physiology and Pharmacology), head of the Institute of Molecular Medicine, and head of the Chinese University in Hong Kong. I lived in the exceptionally well-appointed guesthouse, where I had room for my family, and I was the sole full professor helping him out in the discussions with his researchers, which were held on Monday mornings around the Director's oval table. For two years I worked intensely with the technician Meng Zhong in collaboration with Emil Martin's group, on the epigenetic significance of the nitration of the various hydroxyl, aromatic, tyrosine (38) - where I later found a clerical mistake in the published text in the names of the two inhibitors used (not their doses) - and non-aromatic residues. I filled two notebooks with data, most of which preliminary - due to the involvement of the serine and threonine residues, which were detected at first with selective antibodies and subsequently with chemical analytical techniques. These notebooks, the sole repositories of these data, I was authorized by the Director to take with me to Italy. In sum, I was again on the spot when the decision between analytical, especially NMR, non-invasive or invasive spectrometry, including isotope mass spectrometry, and the

neonate proteomics was being made. I then had to go back to Italy because my family needed me As I mentioned above, it may be significant that chronic aspirin blocks irreversibly all the free-NH₂ guanidinium groups of arginine, resulting in NO synthesis inhibition. The issue warrants further exploration, for example with DFMO (difluoromethylornithine), which can be measured non-invasively in vivo (38); the block of arginine can be explored in rat models of Alzheimer's disease.

Today I called Houston: Dr Alan Frazer, Ph.D., is the new head of the Pharmacology department of the University of Texas Health Science Center Medical College, while Dr. Emil Martin has moved to Vascular Surgery, but neither replies. All facts of this world that take place there, too.

References

38. L. Rossini, E Martin, M. Zhong, Nitration of inducible nitric oxide synthase tyrosine residues in Raw 264.7 macrophages, *Pharmacologyonline* 2: 1-23 (2005);
39. S. Bompadre, M.L. Cingolani, B. Di Sarra, V. Moretti, P. Pigni, L. Re, L. Rossini, C. Tonnini, *Spettrometria NMR dei farmaci e metaboliti fluorurati. Atti XXXVI Congresso nazionale AiPAC, II Congresso internazionale* (Ancona, 21-24 May, 1986):441-452.

Letter to the Research Student

(Sunday, 9th November, 2015)

Summing up Lorenzo's invitations and hopes, and after stressing the salient points that regard teaching in (28), I feel I must to write a letter to the Research Student. "Always observe closely" and "You see what you know" are the researcher's tenets, although they do not always agree. Indeed, Eugenio Meda called Camillo Lenti's attention on me when, at Angelo Mosso (Colle dell'Olen, Mount Rosa), I mixed sugar and water in a cup and said to myself "there's something odd, there are bubbles here". I've always felt that it was not worth learning too much of the work of others, unless it was to study and reproduce it based on original papers. I therefore suggested to the students who came, asking to write their dissertation thesis in Pharmacology, to spend two years to become competent on a topic they found interesting to develop. Then we'd decide together, first of all whether they could be sent to the lab of the researchers currently studying the topic in question, to work first with them; then we would meet again to find some unpublished aspects of the issue. It is useful for a public employee with a stable job to be so lucky as to find an original theme that can be developed for years. The topic may be found serendipitously, but the find won't be accidental if one subtracts it to a colleague, maybe even one

who is more deserving. In addition, if one has got hold of a topic that becomes increasingly interesting during one's lifetime, one is more confident of being able to develop it over time. Interesting topics are endless, unless one wants to change university, running after new public and private funders. A model has to be developed, it is a key step, but it does not have to be mathematical. I've often found that mathematicians tend to ignore experimental results that do not fit, confiding that they'll be able to account for them theoretically. Against the constant advice to go farther, I say that one should not forget that reinforcing a complex system of separate, discordant data is useful in itself. I'd like to recall a poem by C.P. Cavafy, which here is not dedicated to his mother, Anna Dassené, or to his wife or the daughter he could not have, but is appropriate for any couple of researchers:

In the golden bull that Alexios Comnenos issued

To prominently honor his mother

the very sagacious Lady Anna Dalassené,
distinguished in her works, in her ways

there are many words of praise:

here let us convey of them

a beautiful, noble phrase

"Those cold words "mine" or "yours" were never spoken". Source:

<http://users.hol.gr/~barbanis/cavafy/anna.html>

7.

1. Luigi Rossini, *Curriculum vitae et studiorum*

Born in Turin, Italy, on July 27th, 1933, married Maria Franchino M.D., Ph.D., Ophthalmologist in 1963. One daughter, Paola, born in Minneapolis, Minnesota, January 8th, 1965.

First degree: Medicine, University of Torino, magna cum laude (1957); second degree: Chemistry, University of Torino (until 1963), interrupted due to move to Camerino; third degree: Pharmacy, University of Camerino, magna cum laude (1968). Specializations: Occupational Medicine, University of Torino, magna cum laude (1959).

1st Ph.D. degree equivalent: General Physiology (Ministerial Decree 20.9.1963); 2nd Ph.D. degree equivalent: Pharmacology and Pharmacognosy (MD 20-2.1969), and 3rd Ph.D. degree equivalent: Biochemistry (MD 1.9.1971).

Fulbright Scholar, Research Fellow, and then Research Associate at the Laboratory of Neurophysiology, University of Minnesota (Head: Carlo Terzuolo) 1964-1965; Research Associate, Department of Biophysics and Physical Biochemistry, University of Pennsylvania (Head: Britton Chance) 1965-1966; Visiting Professor, Department of

Pharmacology, University of Virginia School of Medicine (Head: Joseph Lerner) 1970-1977, usually three-month stages each year; Faculty of Pharmacy, Laboratory of Magnetic Resonance Spectroscopy, University of Utah (Head: Martin Schweizer) 1978-1980; National Research Council Canada, Magnetic Resonance Spectroscopy Laboratory, Ottawa, Ontario (Head: Roxanne Deslauriers) 1983; NRC, Canada, Institute of Biodiagnostics, Winnipeg Manitoba, Section of Biology (Head: Roxanne Deslauriers, co-founder, Section of Pharmacology) 1984-2000, usually three-month stages each year; University of Texas, Houston Medical Center, Department of Integrative Biology, Physiology and Pharmacology (Chairman: Ferid Murad) 2004, 2005. Assistant Professor of Physiology, then in Biochemistry, next in human Genetics, and later in Pharmacology at the University of Torino; thereafter assistant in Pharmacology and Toxicology at the Universities of Torino, Camerino, Siena, and Ancona (Italy). Professor of Physiological Techniques at the Science Faculty, University of Torino, 1964; Professor of Pharmacometrics at the University of Camerino (since 1965), of Human Genetics at the University of Siena (1969), and Pharmacology, and Pharmacology, Toxicology and Clinical Pharmacology (since 1972) at the cofounded Ancona Medical School, later Polytechnic University of Marche, Ancona. Since 1973, the cofounded Institute of Experimental and Clinical Medicine (IECM) had been under the Clinical Pharmacology and Toxicological Hospital Service of Regione Marche, as were the Analytical interdisciplinary units of gas, HPLC, mass and NMR in vitro-in vivo spectroscopy. In 1974 I was appointed Official WHO Adviser, and delegated to set up the National Collaborative WHO-ITA/ITA-OMS Office, designated by the WHO General Assembly as a National Drug Monitoring Center, affiliated to WHO-Geneva and to the International Uppsala Monitoring Center. Since 1975, the WHO-ITA/ITA-OMS Center had been the sole National Italian center officially responsible for setting up and developing pharmatoxicovigilance research and practice in Italy, as designated and delegated by the Health Minister (M.D. 230/36.40/4.10.14, 26.3.75). Based on an Official WHO declaration, this Center was in charge of the interactive network connecting Ancona University, WHO HQ, the Uppsala International Collaborating Center, and the other National participating Centers. In 1978, the National Congress of the Italian National Pharmacological Society, the National Italian Society of Clinical Pharmacology, the National Italian Society of

Chemotherapy, the National Italian Society of Toxicology, the National Italian Society of Pharmacy, and the Italian National Society of Clinical Pharmacy, held their First Joint Meeting with the Yugoslav Pharmacological Society, organized by the IMSC at Ancona University, in association with the 1st Portonovo Congress of Biomathematics and Endocrinology. In 1982, the 5th International Meeting of the then 23 countries participating in the WHO-International Drug Monitoring Program was held at the same venue, together with the the 2nd Portonovo Conference on Biomathematics and Autoclassification Statistics.

Since 1982: Coordinator, Research Doctorate on Pharmacological Sciences "Biomedical Modeling: Pharmacokinetics and Bioengineering"; since 1988: Promoter and Co-organizer of the Interuniversity Interdepartmental Center for the Study of Biophysical and Biochemical Interactions within Molecules and Organisms (IMO, first the cofounders Ancona and Siena Universities, then Bologna and Cagliari Universities too).

More than 400 personal papers published; more than 300 co-authored papers published by the Research and Collaborative Staff of the new IECM, including researchers and associate professors Pietro Giusti, Chemotherapy; Luciana Leone, Clinical Pharmacology and Giorgio Roda, General Pharmacology) and full professors Salvatore Amoroso, Pharmacology II, and the late Aldo Rescigno, Biomathematics & Pharmacokinetics. Contract professors each year taught more than 25 lectures, mostly on Statistics (Dan Bradu), Magnetic resonance spectroscopy and imaging (Martin Schweizer), Drug abuse and analytical clinical pharmacy (Vincenzo Moretti), Integrated mass spectrometry and chromatography (Charles Gardiner Edmonds). Basic research largely addressed biophysicochemical and pharmacotoxicological in vitro and in vivo readout, pattern recognition techniques applied to classification of drug analogs and iso-receptors (ongoing collaboration, up to 2012, with Dan Bradu, initially with the University of South Africa at Witwatersrand); and in epidemiological clinical pharmacotoxicology.

The final list contains the 291 papers by Luigi Rossini and those of the Collaborators, at the time of the IMSC foundation (1974) until those accepted in 1993. In the same period, 203 Communications and Posters were presented to National and International Congresses. During my 6-month sabbatical before my retirement on October 31, 2008, conferences and lectures had been presented at the Universities of Roma, Torino, Milano, Siena, Firenze, Napoli, E.

Maiorana Center (Trapani), Paris, London, Berlin, Tokyo, Canberra, and UNAM, Utah, Johnson Research Foundation (Philadelphia, Pennsylvania), Houston (Texas), Winnipeg (Manitoba), Manova (Hawaii), Columbia, Minnesota, Stanford (Massachusetts), and Virginia.

We continue to maintain updated the close collaboration network now involving 150 national Collaborating Centers, as our contribution, at all Annual Meetings of the Representatives of these Centers, as summed up at the Ottawa Meeting (15-17 September, 1992) by live discussion of 10 Communications on different topics, which were stated to be developed throughout the ongoing International Research Program. With the late Prof. Dan Bradu, at the University of Tel Aviv (Israel), in 2010-2012 I drew up an objective autoclassification Program that we distributed to all current participating Centers with a view to developing uniformly and evaluating national and regional studies in drug monitoring, associated but independent of those worked out at Geneva and Uppsala. A list of the last related 6 co-authored papers, and of other 23 from the final collaborations within the Medical School and the IMO, is reported in (29). **2. Reference # 29, A goodbye to Colleagues and Formal statement to the competent Authorities (sent November 4, 2013)**

To the Honorable Minister of University, Research and Education, ROME

To the Honorable Health Minister, ROME

To the Court of Auditors, ANCONA,

To the Chancellor and Board of Administrators, Polytechnic University of Marche, ANCONA

To the Dean and Faculty of Polytechnic University of Marche Medical School, ANCONA

To the President of Marche Government, the Health Councilor, and the Collegiate Bodies, ANCONA

To the General Director and Administrative and Healthcare Bodies, Azienda Ospedali Riuniti di Ancona, ANCONA

To the General Director and Administrative and Healthcare Bodies, I.N.R.C.A., ANCONA and c/c to

the President and Board of Accademia Marchigiana Scienze, Lettere ed Arti, Ancona; Colleagues Professors Paolo Bruni, Saverio Cinti, Giovanni Danieli, Mario Governa, Rodolfo Montironi, Leandro Provinciali, Antonio Procopio, Alessandro Rappelli, Paolo Russo, Ugo Salvolini, Vincenzo Suraci, Adriano Tagliabracci, and Ivano Testa.

RE: Transmission of the copy of papers.

The list, written at the behest of the Dean, of

the communications presented and accepted more than 13 years ago by invitation from the Accademia Marchigiana has finally been published, after being announced in 2012 (3 references in the paper and reference list).

I left my teaching and research work in the US (Universities in Minnesota, Virginia, Utah, and Texas) and Canada (National Research Council, Ontario and Manitoba) to respond to the invitation to set up the new Medical School in Ancona and its Clinical Pharmacology and Toxicology Service, and work full time there.

The Toxicology Service was originally the first in the List of the Founding Document of 3.7.1985. It was planned here with collaborators, who were trained over time. The plan included the acquisition of complex, unique and highly expensive equipment using exclusively public, specifically allocated funds approved on different occasions by the Regional Government. This is a unique case, **not only because not even the tiniest *ad hoc* operative space was ever provided**, in the same way to all colleagues and researchers, including those that I later called, meeting their legitimate professional requests also by voting in Faculty meetings, but also **without ever exhaustively discussing what I had been offered by INRCA, Ancona** (Cf: Villa Gusso; Agreement drafted by University of Ancona Central Administration, sent to the Faculty Proceedings by Chancellor Paolo Bruni), with undeniable, growing and irreversible damage, both of general professionalism and of normal, confident expectations, which have always been respected by the operators. **I'd also like to stress here that the same initial founding document, containing the agreement, clearly described the refunds that the hospital was to provide to the university for failing to provide spaces for healthcare services in buildings belonging to the university. This has never been upheld for the Clinical Pharmacology and Toxicology that I had founded and developed.**

Significantly, the original documentation of the more recent activities, entrusted exclusively to this Academy, which provided updates on the ongoing developments, has not yet been published after six years.

It should also be noted that the university and hospital staff that had been allocated to the above-mentioned program were never even completely provided, on the contrary (!), and that the Service I have set up and developed has been excluded without any formal reason from the subdivision of the funds (which were then assigned to others) that the Azienda ospedaliera had duly set aside, no less

than 5%, for personnel teaching full time, as envisaged by the C.C.N.L. 8.6.2000, arts. 57-70. It even happened that my full time position (for instance in 2000-2004, but other periods, too) was not recognized, unilaterally and without any communication of the fact. In addition, I was never refunded the small documented expenses, both for the university and for items that were included in the yearly budgets with a 100% rating by the ad hoc official joint committees, for instance for the last three years I was in service, 2005-2008, and for those minimum but essential expenses incurred for medical assistance. Moreover, still without any reason, we failed to receive the first 60 million Lira tranche that had been approved by the Minister on 26.11.1993 for the continuation of a set of experiments that had already been decided, financed, and successfully completed, money that was subsequently assigned by the Health Ministry Study Center (Cf: CS/413/FARM/93/AG/1526). **As if this were not enough, the perfectly functioning and highly accessorized 7 Tesla NMR apparatus was inexplicably and absurdly scrapped when it could have easily been sold, since it was still being produced and was in the catalog of Brüker, the world renowned manufacturer.**

The case calls for an overdue, **necessary in depth analysis of whether the basic principles of good administration were violated**, documented and never consistently and coherently equal against common sense and common management of constitutional action and failed control. This is not hot air: I believe that it is impossible to refrain from continue, if we are to be protected from the repetition of similar behaviors, which cannot but bring severe and irreversible harm to all, with the denial, if not the disappearance, of institutional dignity and rationale.

I'm available for any question and clarification.

Luigi Rossini, Via Conero 115 A, 60129 Ancona.

Documents not reported, but formally included in the statement were: **Report in extenso on the activity provided for the hospital, asked by the Dean: 1st, 2nd and 3rd part, cited there; List of the 141 national specialist Centers from the 137 member Countries, that received the Calculation program with reference to the last six papers published with colleague Dan Bradu in the framework of the voluntary collaboration offered to the WHO DRUG MONITORING Program, of which the ITA-OMS/WHO-ITA, National Collaboration Center was a founder together with five other Countries, by appointment of the Italian Health Minister, which was confirmed at the WHO**

world meeting. Moreover, copy of the document from the Faculty meeting of 15.5.1979 mentioning the Medical School's commitment (which was never then honored) to set up and structure the Toxicology service, and recent report on the Services of Clinical Pharmacology and Toxicology in Italy, generally in the wake of the Italian (and European) trailblazer. Moreover

3. List of the 29 papers published after my retirement, or without university funding (ref. # 29)

1. Rossini L. Global recurrent classifications in experimental and clinical pharmacotoxicology. *Pharmacologyonline Newsletter* 3:12-15 (2012);
2. Bradu D, Rossini L. December 25, 2011. Letter to the Editor in Chief, *Pharmacologyonline Newsletter*. *Pharmacologyonline Newsletter* 3, 99: 991-992 (2011);
3. Rossini P, Rossini L. Postherpetic neuralgia in the elderly; an update. *Pharmacologyonline Newsletter* 3, 82: 826-847 (2011);
4. 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, 64: 701-836 (2011);
5. Bradu D, Rossini L. Biosimilar branded iodinated contrast agents related to the largest number of reports to the WHO-Pharmacovigilance system over the first 40 years of the Programme. Fifth WHO-ITA/ITA-OS 2010-2011 contribution. *Pharmacologyonline Newsletter* 2, 78: 929-962 (2011);
6. Bradu D, Rossini L. 4,436 reports from Italy, accepted in the WHO-UPM 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, 98: 1140-1160 (2011);
7. 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);
8. Bradu D, Rossini L. Contrast agents – Iodinate 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);
9. Bernardi M, Bradu D, Di Sarra B, Galeazzi G, Marcucci M, Montecchiani G, Moretti V, Moroni L, Re L, Rossini L, Rossini P, Tonnini C. Ionic and nonionic contrast agents. A contribution by WHO-ITA and the Drug Documentation and Information Centre of Regione Marche. *Pharmacologyonline Newsletter* 2:497-517 (2019);
10. De Martinis C, Rossini L. Some internal medicine and pharmacotoxicological 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);
11. Rossini L, Rossini P. After the new "year of Darwin". *Pharmacologyonline Newsletter* 1:754-771(2010);
 12. Rossini P, Rossini L. Experimental and clinical pharmacology 2009. Narrative upgradings mostly related to cognitive neurosciences. *Pharmacologyonline Newsletter* 3:443-457 (2009);
- Other papers not financed by the university, written in the last few years before retirement:**
13. Rossini L, Rossini P. Medical pharmacotoxicology today. *Pharmacologyonline Newsletter* 3:85-108 (2008);
 14. Rossini L. Pre- and post-marketing pharmacovigilance: The myths of the placebo effects and of the off-label use of drugs. *Pharmacologyonline Newsletter* 2:80-94 (2008)
 15. Rossini L, Rossini P. Requirements for the assessment of pharmacokinetic, pharmacodynamic and mixed population models and some topical considerations: A seminar. *Pharmacologyonline Newsletter* 2:48-72 (2007);
 16. Rossini L, Violet C, Rossini P, Johnson CW. Epicardial autofluorescence NAD(P)H kinetics in ischemically preconditioned Langendorff rat heart. Effects of capsaicin. Part 2. *Pharmacologyonline* 3:18-63 (2006);
 17. Rossini L, Rossini P. Pharmacotherapeutic receptor specificity and selectivity classes, and placebo effects: A perspective. *Pharmacologyonline* 2:206-235 (2006);
 18. Rossini L, Kuzio B, Deslauriers R, Johnson CV. Epicardial autofluorescence NAD(P)H kinetics in the ischemically preconditioned Langendorff rat heart. Effects of capsaicin. Part 1. *Pharmacologyonline* 3:125-176 (2005);
 19. Rossini L, Martin E, Zhong M. Nitration of inducible nitric oxide synthase tyrosine residues in Raw 264.7 macrophages. *Pharmacologyonline* 2:1-23 (2005);
 20. Rossini L. Drugs and the future. *Pharmacologyonline* 1:12-44 (2005);
 21. Rossini P, Rossini L. Evoluzione di alcune conoscenze base in tema di tossicoassunzioni e tossicomanie. *Quinquennio* 1998-2003. *Lettere dalla Faccolta' VIII*, 7/8:19-26 (2005);
 22. Rossini L, Bernardi M, Galeazzi G, Moroni L, Pettinari F, et al. Domini del tempo e di frequenza in fenomeni biomedici. Il°. *Relazione sugli sviluppi del primo trentennio della linea delle ricerche coordinate per il Settore Disciplinare ex E07X, Bio-14, Area Biologica-05, Facolta' medica dell' Universita' di Ancona. Memorie Atti Acc March Sci Lett Arti Ancona* 38:211-256 (2005);
 23. Rossini L. Didattica vissuta e aggiornamento della nuova tabella XVIII, Settore scientifico disciplinare Farmacologia. *Memorie Atti Acc March Sci Lett Arti Ancona* 38:323-342 (2005);
 24. Rossini L. Regione Marche, Il Polo universitario-ospedaliero di Ancona. Il Servizio di Farmacologia clinica e Tossicologia. *Memorie Atti Acc March Sci Lett Arti Ancona. Accettato per le stampe, Lettera del Presidente Prot 21, 2.2.2007;*
 25. Rossini L, Gatti G, Galeazzi G, Moroni L, Pettinari F, Violet C. Regione Marche, il Polo universitario ospedaliero dorico, II. Il Servizio di Farmacologia clinica e Tossicologia: *Sviluppi piu' recenti di aspetti del monitoraggio diagnostico e delle verifiche preventive, terapeutiche e riabilitative farmaco tossicologiche. Memorie Atti Acc March Sci Lett Arti Ancona. Accepted, Lettera del Presidente Prot 21, 2.2.2007;*
 26. Rossini L, Galeazzi G, Gatti G, Moroni L, Pettinari F, et al. Regione Marche, Il Polo universitario-ospedaliero dorico, III°. Il Servizio di Farmacologia clinica e Tossicologia. *Altri sviluppi degli aspetti post-genomici del monitoraggio diagnostico e delle verifiche preventive, terapeutiche e riabilitative: coinvolgimenti farmaco tossicologici analitici ed esplorativi proteomici-metabolomici strutturali. Memorie Atti Acc March Sci Lett Arti Ancona. Accettato per le stampe, Lettera del Presidente Prot 21, 2.2.2007;*
 27. Rossini L. Neuropatia post-erpetica nell' anziano. Un seminario. *New Entries in Pharmacology II*, 1/2:3-14 (2007);
 28. Rossini L, Rossini P. Esigenze di valutazioni dei modelli farmacocinetici, farmacodinamici e misti, delle popolazioni, e riflessioni attuali. Un seminario. *New pages of therapy* 6,1/2:3-23 (2007);
 29. Rossini L. Sperimentazione dei farmaci e Farmacovigilanza. *Corso Monografico. New Entries in Pharmacology* 1:3-22 (2006).