DRUGS AND THE FUTURE[1]

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SUMMARY

The pharmacotoxicology of the third millennium will not be able to help rethinking and possibly remedying the conjectures and teachings of the past, which will need to be systematically refuted. The application of the general model of the law of mass action itself, of the achievement of precocious, dynamic, statistical equilibria, may reap fresh successes in describing with bionanotechnologies; preprogrammed touchchip sensors/processors, also developed in Italy; peptide and gene chips; “lab-on” chips; multiple array screenings and related integrated multidimensional automatic processes, the effects and interactions of individual submolecular events in triggering and superimposing themselves on only apparently uniform statistical samples in the space, kinetic, time and frequency domains, up to the more complex relationships. These may range from lower-threshold concentrations in minimal distribution microvolumes to the reciprocal relationships of higher saturations, including saturations of indirectly involved, phenotypically acquired, individually and personally characterised polymorphic genomic receptor sites.

The prerequisite of the revolution now in progress, though not yet generally recognised not to mention practised, is the alternative systematic adoption of non-invasive, multiparametric, simultaneous analytical and exploratory *in* and *ex vivo* observation techniques, both experimental and clinical, and of globalised models referring primarily to “auto-controlled” individual cohorts, as well as the adoption of the attribution of greater descriptive impact to ongoing pathophysiological staging.

Another, equally significant, prerequisite for future projections in the sector is, as far as Italy is concerned, that credits and accreditations be granted uncompromisingly for the permanent updating of professional education. In addition, and this applies also to the relevant international organisations, tangible de-bureaucratisation processes and efficient use of resources should be implemented in such a way as to ensure safer environmental monitoring and a verifiable availability of food and essential medicines in the framework of a globalised setting, which, if not ethical, should at least be characterised by a modicum of human conscientiousness and conscience.

KEY WORDS: complexity, pharmacokinetics, methodology, -omics, trials.

The concept of future development, the "white man's dream" of the Eton-speaking Cameroonians, performs the same function for Western society as the myths of the so-called "primitive" societies.. Aime M, Le risposte della leggerezza, pp. 145-148. In: Le radici nella sabbia, Turin, Italy EDT: 1999.

INTRODUCTION

"Predictions are always difficult, especially for the future", as the theoretical physicist's adage goes*;* moreover, there are people who *"never think about the future; it comes too soon!".* In the case of the *future of drugs*, predictions are indeed difficult, but the issue reflects the continuity of the original initiatives adopted over the thirty years since the foundation of the Pharmacotoxicology Sector of Ancona University. Civil progress is always rooted in the past and evolves along with the history of culture. So does *anthropology* and its problematic issues, above and beyond the traditional Kantian distinctions between *theoretical, pragmatic* and *moral*, in an awareness of *the social and functional conditioning which the individual cultural models exert upon the basic personalities of the members of the various groups* involved (including, of course, patients!). In this context, *structuralism* relies upon the common primeval unconscious, and *neo-evolutionism* regards as being of decisive importance the technico-economic factors made obsolete by *transactional and cognitivist* interpretative perspectives, up to and including the *constructivist* semiotic practices tending towards auto-interpretation [1].

Being admirers, albeit very humble ones, of brilliant Vito Volterra [2], though obviously subject to the critique of confutations and falsificability [3], and well aware of the limitations of "evidence-based medicine", which is a purely intentional object with the legitimacy of an oracular creed and an example of the self-constitution of a temporal framework [4, 5], we would like here to provide above all an update regarding the essential themes addressed at the time of the first deciphering of the genome map, which marked the advent - as revolutionary as it was globalising – of the pharmacotoxicology of the third millennium, in the meeting on 7 April 2000 of the Academy of Sciences, Letters and Arts of the Marche Region [6]. We also wish to contribute to the discussion of the more topical themes of this period, which are reported below [7, 8].

A FUTURE OF COMPLEXITY

Extending the accurate predictions of Newtonian deterministic mechanics, of reductionist mechanics applied to idealised systems, the *future of pharmacotoxicology,* at one and the same time analytical and exploratory [9], is represented as bordering on chaos by the current simulation tools. Chaos is characteristic of *integrated*, interacting complex systems and is described by continuously evolving laws, whose behaviour is recognised as being qualitatively different from those governing the individual component units [10]. The *catastrophic revolution* currently under way, has, unfortunately only recently acknowledged the misdeeds of the ongoing biased and misleading mainstream research, which is an expression of dichotomies that are not even recognised by the “translational” lines themselves, are not improved by “functional genomics and proteomics”, and are not yet properly targeted at patients [11-14]. We need only mention here, as a further example, the errors committed in the study of molecular medicine, where researchers have recognised, but neglected, the synergisms deriving from the activation of lysed and purified systems, which are more pronounced in intact cells *in vivo* [15].

Indeed, when exploring complex fields and issues [10, 16-17], it is essential to cease ignoring, e.g. in the development of the pharmacotoxicological references of the neurosciences, experimental contributions that can be integrated into the theories of bistability [18-22]; it is also important to recognise, in biomedicine, the independence or otherwise of variables that can potentially be put into relation within the analysis of correlations between causes [23-25], and to abandon plainly absurd randomisations in the ethical design of clinical trials, in the stratifications of subjects, in the evaluation of social risks, particularly as regards long-term projections, and in the very assessment of economic conditioning factors [26, 27]. There has been no tangible acknowledgement of the ambiguity resulting from these errors nor of the shortcomings of the current scientific evidence, which courts have failed to recognise [28]. Even the increasingly widespread need for combinatorial analyses of bio-informatics exploration acknowledges errors of assessment where correlations between mRNA and post-translational protein modifications have apparently proved to be by no means negligible in frequency [29-35].

With reference to the biophysical-molecular issues preliminary to the development of the *future of drugs*, and after identifying the structural compositions of families consisting of

substantial numbers of receptors and recognising the possibilities of the persistence of activated stages and levels even in the absence of agonists-antagonists, including intrinsic and inverse ones, we are now tackling with growing success models involving molecular dynamics simulations of biomolecules in environmental situations of increasing complexity, which are essential for recognising the fluctuations of functions [36-46]. Indeed, even in the forms judged to be naturally occurring, proteins must be considered as statistical sets whenever there exist local fluctuating instabilities of the same conformations of sequences of residues of few amino acids, and forms of locoregional as well as more extended regulatory-allosteric cooperation of expression (cf. conformational maps, related probability distribution functions, and local structural fractional persistence kinetics of naturally occurring forms, produced by the COREX algorithm [47-52]). The need is increasingly felt to design “adaptive ligands” opposing the hypotheses of the invariance of binding sites: genetic polymorphism, which has also been highlighted at Ancona University [6-8], makes an appropriate thermodynamic study of an array of new descriptors indispensable to define optimised kinetic conditions and a dynamic re-balancing between the specificities of analogue families, selectivity of iso-groups and affinities that no longer regard, and not solely, single molecular targets but also increasingly complex protein systems: in particular, molecular flexibilities should no longer be introduced arbitrarily, but be directed towards those targets that present greater mutational probabilities. They will be offset by interaction factors able to maintain the most appropriate affinities, efficacies, and efficiencies, and will require specific knowledge of the most favourable contraposition of enthalpies and entropies, which concur to define the binding affinities as well as the intrinsic efficacies of individual molecules [53-56]. As research proceeds ever more systematically with large-scale assessments of protein interactions [57], to which reference will also be made in the paragraphs below, the recognised locoregional similarities of human genomic polymorphisms, which may extend over much greater distances than those identified by traditional pharmacotoxicokinetic investigations and studies of localisation of the imbalances of combinations [58-62], can no longer be ignored.

PHARMACOKINETICS IN THE TIME AND FREQUENCY DOMAINS

Ever since the foundation of Ancona Medical School, the Pharmacotoxicology sector has been characterised, and not only at the local and national levels, by the work of the initiators of Biomathematics and Pharmacotoxicogenetics, two courses which have later, for no good reason, been abandoned. Despite this, and drawing comfort from the recognition of these scientific fields as no less essential components of the *future of drug research and development* in both the official regulatory and entrepreneurial quarters of what is now a consolidating globalisation process, contributions have continued to be made, in terms of updated teaching practices and the development of targeted methodologies (which will also be referred to in a later paragraph below), usually in the reserved manner proper of the academic staff concerned (e.g.. the Course of the Postgraduate School of Hospital Pharmacy of the University of Camerino, the first to be approved in Italy, along with the Postgraduate Schools of General Pharmacology, Chemotherapy, Clinical Pharmacology and Toxicology of the University of Ancona).

Undeniably, the foundation of the new scientific orientation by Professors Emilio Beccari and Giorgio Segre preceded Professor Aldo Rescigno's authoritative call to institute university chairs in Ancona for the teaching first of Biomathematics and then of Pharmacokinetics. After recognising that the compartmental modelling theory is no longer compatible with recent data regarding known levels of complexity, particularly of supramolecular-multisubstrate energetic and metabolic nature [63] (as confirmed by research postulating, for instance, that redox dynamic kinetics actually enhance specificities [64]), the need has been expressed for an extension of "chronopharmacology" oriented towards observing differences in circadian sensitivities [65], including analysis of basic components, which can potentially be unified in the first place in the *spatial domain* [66]; above all, the advisability has been suggested of redefining the primary parameter of (instantaneous) distribution volumes so as to encompass not only the study of their instability, but also, abandoning the systematic errors now tolerated, the study of (sub)cellular and tissue concentrations effected by means of non-standardised measurements of current parametrisation systems on dynamic biomedical samples, something which is of not inconsiderable significance for the *future of drugs*. Lastly, for strictly pharmacotoxicokinetic parametrisation, *time and frequency domain* analyses

should be integrated (cf. [6] and the previous programmatic notes, [67] and [68], appearing in *Lettere dalla Facoltà*).

It is worth stressing once again that the *substantially ignored* differences of a *spatial nature* in concentrations expressed dogmatically as “instantaneous and coincidental” are now recognised as being decisive and therefore no longer negligible for the ethics of scientific progress (see the examples, limited to a number of integrated pathophysiological conditions, in refs. [69, 70], [71] and [72, 73]). It is also a strained practice, if not a farce *tout court*, to limit work, incoherently, to the functional descriptions peculiar to “reductive (and utilitarian) realism – which we would prefer to define as non-scientific –, to mediated central parametrisations, with estimates of variability indices based on models of randomisation of events of no clearly ascertained demarcation (or nature), ignoring the passage of time as a non-independent factor (cf. *time domain* analysis) in the process of verifying the undecidability of null hypotheses in terms of deviations from possibly equally significant hypotheses according to the stated probability connotations. Indeed, researchers are still proceeding all too often, sometimes omitting to analyse the results of their experimental observations, *without admitting the a priori significance of time-dependent variations, that is to say, without measuring the exponential spectral powers and/or variabilities, typical of analyses in the frequency domain, with a loss of indispensable items of scientific knowledge, where the exploration of the demarcation boundaries between information content and noise assumes an increasingly marked and persistent problematic significance that is also borne out by the integration of levels of complexity of relevance for the future of pharmacotoxicology.*

After reflecting on previous contributions (see also refs. [74] and [75]), a number of recent results are recalled, as usual by way of an example, in reference [76-88], whereas in reference [89-106] we indicate a field in which, working along the lines of the models indicated, research can overcome the current phase of repetitive self-limitation.

FUTURE OF METODOLOGICAL UPDATING

The approach developed in the 2nd Subject of the Research Doctorate in Biomedical Modelling [107] reached its maturation with the participation in the founding of the first Interuniversity Centre, where the only Ancona University section was a section of Human Pharmacotoxicology. A plan was laid for the founding a Large Facility Regional Centre in Ancona with, it was hoped, contributions also from other Faculties, all of which could collaborate advantageously in the Network described in the Proceedings marking the First Twenty Years of the University [108]. This Network has been extended to many other national and international centres and regions. It relies on exclusively public funding, which is allocated under the Ancona "landslide" law as well as by the Marche Regional Council [[2]], and the central Italian research organisations, for coordination purposes, within the framework of the programmes of prevalent national interest of the Italian Ministry of Education, of the University and Scientific and Technical Research and the National Research Council, as well as of the Institute of Biodiagnostics of the Canadian National Research Council, a co-founder [107][[3]].

This approach should be able to meet the requirements of public proteomics [109] and may eventually involve private sector research in this field [110]. In fact, as also emerges in a recent issue of *Trends in Molecular Medicine* focusing on molecular diagnostics and discussing the orientations and most promising developments in the fields of interest for the *future of drugs*, where "the best is yet to come" [111-117], the development of the new "systemic -omics" – genomics and chemogenomics, phospho-, nitro- and glycoproteomics, metabonomics/metabolomics, etc., - and the quality leap of renewal which has been rewarded elsewhere require the urgent restructuring of institutes, departments, interdisciplinary, interfaculty and interuniversity centres. Previous, separate, seminal contributions to a number of non-invasive methodologies available here require to be integrated, at least on a locoregional scale. This could be achieved by potentiating the programmes of collaborative research, which justify the investments already resolved upon, thus making it possible for this research to evolve, by focusing on light microscopic,

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[[2]] Resolution n. 7001, 22.12.1986, Marche Regional Council.

[[3]] NRC-CNRS, Institute for Biodiagnostics, Partnersips and International Activities, University of Ancona (Italy): Pharmacological Agents – Biosystems, Foundation Document, Annual Report 1992/1993, p 25.

fluorimetric and near-infrared spectrometric techniques, such as mass and NMR spectrometry, addressed at the time of the Centre's foundation, and combining them with (sub)cellular electrophysiological procedures [118-127], in which there is now a widespread general revival of interest. The biotechnological information boom, which is generating a growing number of journals, mainly rests on the evolution of nano-biotechnology structures applied to the architectures of smart microarrays and biochips - gene chips, substrate-peptide-protein chips, lab-on chips, touchchips, etc. – some of them produced in Italian centres of acknowledged excellence (cf. STMicroelectronics) [128-137] – where problems of interpretation and standardisation nonetheless abound [138].

In particular, optical, near-infrared spectrometry and multichannel fluorescence *biochemical in vivo read-out* measurement technologies, including the most rapid, originally presented and recognised by the international scientific community, have then also been developed in Italy in the Interuniversity Centre mentioned above [6, 108]. These techniques, in connection with which we have participated in the EvIdent Programme of image analysis in the time and frequency domains offered to the University of Ancona [**4**] - an indispensable reference – have come to be very extensively used and present very high sensitivity in measuring the response to the administration of even individual molecules [139-155]. As regards the advances of mass spectrometry and NMR techniques, the reader is referred to our more recent papers [7, 8] as the following update covers only a number of aspects of the present specific topic.

[**4**] Cf. F 287, 22.12.1999: Making available EvIdent software (NRC Canada, Institute of Biodiagnostics) for self-classification analyses, also of a multidimensional type, in the time and frequency domains, of IR functional images, near-IR images, NMR spectrometric images, microscopy, perfusion dynamics, kinetics, etc.

(CHEMO)GENOMICS AND PROTEOMICS

The genomic variations involving substitutions of individual bases (cf. SNPs), insertions and deletions, correspond to modifications in cuts and post-translational protein, the interactions of which need to be mapped in order to define both the integrated structural sets and their expressions in the various cells and tissues, combining their functions in both normal, physiological stages of development and in those of primary interest for the *future of drugs,* namely pathological processes.

In man, approximately 40,000 genes have been identified. The proteomic finding of a million or more protein variants has made it necessary - in order to accelerate their identification, develop new molecules, and rehabilitate the drugs already in use, among other things by reviewing their most favourable action sites and, where possible, eliminating adverse factors - to break these variants down into subproteomic classes associated with pathological conditions selected on the basis of their therapeutic relevance. The relationships of the “associations, errors and complexities” of controls of transactional genotype-phenotype interactions are studied in greater depth [156, 157]; the coding role of exons is analysed [158]; and polymorphisms are reclassified and grouped together as isoproteins in relation to individual genes (cf. [159, 160]) by promoting convergences of trait complexities peculiar to multifactorial diseases, using multivariate, at times even dated, strategies [161-168], weighting susceptibilities to diseases [57, 169-173], also for the purposes of genetic counselling. Similarly addressed is the new possible reclassification of toxicology, of exposure to risks, also in the context of settling toxic tort personal injury litigation [174].

In actual fact, researchers are now proceeding with the typing of gene functions also on a large scale, specifically for the development of better drugs directed against what are regarded as more promising targets [159, 160, 175-177]. As already summarised [8], the applications of pharmacogenetics, now genomics, have proved capable of resolving at least some of the main ethical issues in the present-day clinical trials process [178-189].

In general, proteomic analysis, which has become quantitative also in the solid phase [190-192], though not to the extent of reaching the picomolar limits of the naturally occurring functional ranges of receptors as biomedical sensors [193], is capable of contributing to structure-function predictions [194] of complex substructures [195], including human ones [196]. Its now consolidated use for the *future of drugs* [197] is spreading with rapid technical advances (cf., for example, [198-202]) and is becoming

increasingly essential for the diagnostic routine in human diseases, as mentioned above [8] (cf. [203-206]); indeed, the fast technological evolution has achieved such spatial resolution for tissue imaging that amount and distributions of potentially altered molecular species can now be studied [207].

In particular, while advances are being made in nitroproteomics [8], the techniques of fractioning, enrichment, and identification (also functional) of subphosphoproteomics have now achieved widespread and highly convincing levels of standardisation [208-214].

METABONOMICS

The observations and measurements of the different methods of magnetic resonance of various nuclei are used increasingly, indeed, perhaps more than 18-fluorodeoxyglucose positron emission tomography, whose relevant characteristics in relation to the present topic have been discussed elsewhere (cf. [74], [75]; for the clinical significance of PET scanning see ref. [69, 70, 215]). Unfortunately, however, they are still used only to study contrast-enhanced dynamic images for purposes other than primarily metabolic investigations, while elsewhere joint studies using these methods are undertaken at centres of excellence (cf. the Houston Interdisciplinary Centre, described last year; previous instances discussed in refs. [74] and [75], and above all, as regards the analytical procedure, operational only in Italy, in ref. [7], with the update cited in ref. [216]; see also refs. [217-223] and [224-228]).

Also as regards the aspects more strictly relevant to the *future of drugs*, *it should again be emphasised that we are witnessing a revival of the technology,* well beyond the traditional interests, biomedical development applications [217-228], and the ever essential analytical chemico-pharmaceutical applications of medicinal products, including recent biotechnological ones [229, 230]. In point of fact, the integrated modelling analyses, on an increasingly extensive scale [231, 232], peculiar to the current genomic-proteomic technological revolution permit the global study of energetic-metabolic networks in different physiopathological phases, which are highly significant and indeed absolutely *essential for defining the basis for the rational development of drugs, and are being increasingly used* with the indispensable contribution of specialised NMR technologies.

In conclusion, then, now that NMR technologies, in private [233] as well as public research (including biomedical schools) [234-239], are bearing the brunt of commitment and responsibility, not least ethical commitment, involving, as they do, the necessary planning of investments in facilities, and particularly in the training of specialist staff, we can only express our satisfaction at having acted with foresight and at the right time both in the drafting of proposals for the setting up of facilities and instruments at locoregional level and in the timely adoption of the above-mentioned early developments [**5, 6**].

[**5**] Rossini L, Principal Investigator: Studies of regulation of metabolism and function in heart. Part I, Part II: 1994; Research approved at the National Research Council Canada; Institute of Biodiagnostics, NRC, Winnipeg, Manitoba, Canada.

[6] Rossini L, Ischemic preconditioned cardiac adaptation and recovery. Effects of some most recent pharmacological tools on phosphorylative, redox and nitrinergic modulations in cultured rat heart myocytes and Langendorff preparation while phosphate, redox and nitrositative/nitrative potentials simultaneously monitored by non invasive techniques. Cofinancing of Research Programs of National Interests: Application Proposal 2003, DM 20.02.03, n. 21.

CLINICAL TRIALS AND CLINICAL PRACTICE

In four recent papers published in *Circulation* [240] by researchers from Duke University, Wisconsin, the Agency for Health Research and Quality (AHRQ) and the US Centres for Education and Research on Therapeutics (CERTs), the authors discuss the lessons learned from randomised clinical trials of the past 15 years and the principles relevant to clinical practice. Though referring specifically to cardiovascular trials, these topics largely appear to confirm some misgivings regarding the persistent shortcomings of such trials. These studies confirm the risks of accepting the results of surrogate measures, which may prove invalid (ALLHAT, CAST, GUSTO vs AMI, TIMI trials), particularly when single biological markers have failed to predict integrated systemic effects and when composite clinical end-points are pooled for which similar statistical weights are uncritically accepted. Even the NHLBI trials, regarded as the best and not only for cardiovascular disease, such as BHAT, CIBIS II, COPERNICUS, ELITE I and II, MERIT, PRAISE I and II (see also ref. [241-243] for those relating to hormone replacement therapy; cf. WISDOM, interrupted on 23 October, 2002 [244]), typically designed to identify effects in the entire population, lack adequate numbers to ensure recognition of distinct subgroups, e.g. ethnic or genetic. Different results obtained for subgroups must thus be confirmed independently, avoiding a premature acceptance of findings and the adoption of inadequate, unnecessary and wasteful treatments.

With the genomic era under way, and the possibility of achieving diagnostic identification of individual polymorphisms, the current optimised trials, which have proved outdated, should be abandoned for ethical reasons. Nevertheless, the best of those currently in progress will need to comply with the principles outlined in an authoritative overview (cf. paper II, ref. [38]). This regards particularly the need to minimise bias, the need for flexibility with negative trends and “non-inferiorities”, the need for independent statistical evaluations, which must be accurate in the reporting of declared and undeclared financial incompatibilities or excessive remuneration (“conflicts of interest” and direct/indirect forms of medical bribery), the need for the publication of negative results and, crucially, the need for rapid and complete, fully qualified and competent compliance with statutory pharmacovigilance regulations on the part of both the sponsors of the trials and the investigators conducting them, who obviously need to work in complete autonomy from the Regulatory Authorities themselves (see also [253], [254-276], here below).

The experience of the individual clinician in deciding which therapy to adopt is not valid, as proved yet again recently by the disasters caused by the use of anorexants ("fen-fen"), antiarrhythmia agents (cf. CAST), calcium antagonists (mibefradil), endothelin antagonists (bosentan), H-1 inverse agonists (astemizole, terfenadine), inotropic agents (flosequinan, vesnarinone), psycothropics (amineptine, …), statins (cerivastatin), rofe- and possibly other cox-2 inhibitors. Moreover, as experience teaches us, anecdotal, observational post-marketing surveillance, though inadequate for the lack of control groups and denominator estimates, has filled the legal gap and continues to be the accomplishment and to reflect the merits of ethical, competent and permanently up-to-date health-care professionals. This form of collaborative health-care feedback, which is indispensable for the academic, makes up for failure to appreciate and/or detect qualitative and quantitative interactions in trial phases I to III (where financed according to the current clinical trial system) which continues to exclude health-care professionals from making their contribution, exploring common targets and effects which are unexpected, unwanted and not envisaged in the planned trial design.

It is, however, comforting to note that it is becoming increasingly clear that clinical trials need to be conducted over longer time periods, if not for the entire natural life of drugs. Equally satisfying is the fact that potentially different "class effects" are being recognised for each drug and dosage ranges, and for the sites and continuities of the effects of the various prescription rationales. We need, in fact, to understand that the classification of potentially homogeneous profiles, that is to say, of the "class effects", on which our current pharmacological treatises are firmly based, is a nonsensical hypothesis of a theorem which has proved counterproductive.

There are cases in which it has been ascertained that "therapeutic substitution" in the context of effects of classes which have been proved to be heterogeneous has drawn attention to the irrationality of this policy. This irrationality is thoroughly ignored by administrative measures dogmatically defined as socio-economic, which, in the absence of basic long-term studies, often surreptitiously invoke and impose the law of so-called "management savings". There is therefore a need to conduct prospective studies over adequate periods, alongside assessments of pharmacotoxicological and clinical cost-benefit ratios, by means of the transparent computerisation of databases relating to "incremental cost-effectiveness-efficiency indices", the management of which investigators should become familiar with and learn through high-level updating courses.

PROFESSIONAL ETHICAL SOCIAL AND HEALTH-CARE ASPECTS

Every health-care operative, like every citizen, is aware of the burden entrusted to and taken on by the WHO in issuing technically updated cultural and intellectual guidelines directed at rationalising integrated sustainable development in the field of the preventive, therapeutic and rehabilitative safeguarding of health. The Organisation, which is recognised *de facto*, should be assisted in continuing to exercise its powers as a global reference of excellence and prestige, and, if possible to increase them progressively, avoiding the wastefulness of futile alternatives but at the same time demanding debureaucratisation and a more effective, coherent presence in the various territories.

The future of the necessary health-care globalisation process does not lie merely in the implementation of traditional policies, like proposals of lists of essential drugs, but in making drugs effectively available (exploding the myth of compatible costs) and in assuring their widespread, rapid and direct distribution by adopting a paradigmatic shift towards the catering for the medical needs of increasingly small segments of the population down to single individuals (cf, the future of “druglets”); above all, it will be necessary to adopt automatic preparation systems of single-dose drugs according to prescriptions, updated with optimised kinetic iterative standardised modelling criteria, including personalised feedback pharmacovigilance information on use and abuse (cf. the evolution of the Homerus programme, devised and implemented in Italy).

Equally desirable is that fully transparent, computerised checking and monitoring systems be not confined to products that can be used after patent expiry; indeed, the same entrepreneurial design rationalisation should be implemented without delay for all products judged to be effectively necessary. Every stage in the chain of conception, design, research, development and use of any drug product, including those provided by the most recent decentralised biotechnology boom, can make a useful contribution, within the framework of the globalised civil process, to the computerised structuring of feedback information retrieval and collection, which is a functional *sine qua non* for the ongoing education and training of health-care and academic personnel, as well as for effective institutional regulatory activity and activity in the industrial and entrepreneurial sector.

Discussion of the contribution of WHO-Italy [245-251][7], which was addressed in a previous workshop in this series [252], has therefore been updated in relation to the WHO 1988 document [253] and to a whole series of very recent important scientific publications [254-276]. Also necessary is an approach that integrates the contribution of ethnomedicine in the process of creation of new drugs [277]. It is important to achieve the fullest possible knowledge of every aspect involved, including the dynamics and kinetics associated with the structures, as a prerequisite for the development of better drugs. The chemico-pharmaceutical sciences of the twentieth century [278-288] are, in this new century, in a position to tackle and benefit from the developments of evolutionary medicine, where the discrepancies between responses and selective adaptation counter-reactions are assessed, identifying niches where there is more likely to be persistence both of the dynamics of pathogenic mechanisms and of the efficacy of treatments [289]. The need to ensure the integrity of scientific research is strongly perceived [290], and perhaps so is the need for adequate guarantees of continuity in the assigning of credits in institutes of further education, as well as in the verifying of unconditioned accreditations and clear-cut motivations of territorial services of analytical and exploratory clinical pharmacotoxicology. A measure of general and public awareness of these issues, as in the U.K., would probably be useful (cf. [291]).

We insist once again that what is needed is a whole series of no less essential prerequisites for the future development of drugs reviewed in this paper, that is to say of principles now globally shared and which we ourselves have always, consistently, adhered to and complied with ([245-251], [252], [292-295][8]). Nevertheless, it is comforting that public misgivings regarding the delays in the fulfilment of our expectations have undoubtedly grown, as emerges in the media, particularly in the field of “genomic genetics”, where expectations are perhaps still unrealised, and that there is now an awareness of the important insights of genetics in terms of the expression of gene similarities and interchangeability, a principle judged to be a powerful factor for the future development of Medicine and which also promises to be a fundamental factor in the future of drugs [296].

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[7] "Considerations on the subject of clinical trials suggested by the biometrist, pharmacologist and specialist in internal medicine. Ancona Charter", Workshop on "Problems Related to the Experimentation of Drugs in Man", Medical School of the University of Ancona, 29 April 1974. In: Rassegna Clinico Scientifica 1977; 53: 17-8.

[8] Introductory Address 6th Interregional Meeting of SIF, Pharmacology Today – Researchers Comparing Notes …"There is increasingly less justification for treating or not treating a patient on the basis of epidemiological studies and conventional small-sized, short term therapeutic trials. Comparative studies need to be conducted for the various drugs in the various new and old therapeutic classes. In view of the possibly overwhelming and prohibitive costs of long-term ad hoc explorative-epidemiological studies, the alternative consists in the analytical, systematic study by comprehensive observation of the very largest number of patient cohorts throughout informatic processing". Medical School, of The University of Ancona, Portonovo, 23 April 1991.

REFERENCES

1. See entries for “antropologia culturale”, “antropologia filosofica” and “antropomorfismo”. In: Enciclopedia Garzanti di Filosofia, 1993: 41-5, and in: Lalande A, Vocabulaire technique et critique de la philosophie. Paris: Presses Universitaires de France, 1926; Milano: ISEDI, 1971: 43-5.
2. The Scientific Thought of Vito Volterra. Marche Region Academy of Sciences, Letters and Arts Institute and University of Ancona. Ancona: La Lucerna Ed, 1990.
3. Popper K R, Conjectures and refutations, London: Routlege and Kogan Paul, 1969; Congetture e Confutazioni. Lo sviluppo della conoscenza scientifica, Vol. I, II. Bologna: Il Mulino Ed, 1972.
4. Gadamer HG, Wahrheit und Methode. Tubingen: JCB Mohr (Paul Siebeck), 1965; Verità e Metodo. Milano: Mondolibri Ed, 2000.
5. Husserl E, Die Krisis der europaischen Wissenschaften und die transzendentale Phanomenologie. L’ Aja: Martinus Nijhoffs Boeckhandel en Vitgeversmaotshappij, 1959; La crisi delle scienze europee e la fenomenologia trascendentale. Milano: EST, 1997.
6. Rossini L, Bernardi M, Galeazzi G, Moroni L, Pettinari F, Pigini P, Rossini P, Tonnini C, Vagionis G, Violet C, Time and frequency domains in biomedical phenomena, II. Proceedings, Marche Region Academy of Sciences, Letters and Arts, Ancona, 2003, in press.
7. Rossini L, Bernardi M, Galeazzi G, Gatti G, Moroni L, Pettinari F, Rossini P, Violet C. Marche Region. The University-Hospital Pole, II. The Clinical Pharmacology and Toxicology Service: the most recent developments of aspects of diagnostic monitoring and preventive, therapeutic and rehabilitative farmacotoxicological tests. WorKshop 2003, in press.
8. Rossini L, Bernardi M, Galeazzi G, Gatti G, Moroni L, Pettinari F, Rossini P, Violet C, Mencarelli R. Marche Region. The University-Hospital Pole, III. Other developments of post-genomic aspects of diagnostic monitoring and preventive, therapeutic and rehabilitative farmacotoxicological tests: structural proteomic-metabonomic analytic and exploratory pharmacotoxicological involvements. WorKshop 2003, in press.
9. Black J, A personal view of pharmacology. Ann Rev Pharmacol Toxicol 1966; 36: 1-33.
10. Vicsek T, The bigger picture. Nature 2002; 418: 131.
11. Neuroscience in the post-genomic era. Nature Neuroscience 2003; 6: 1.
12. White C, Little evidence for effectiveness of scientific peer review. Brit Med J 2003; 326: 241.
13. Van Leeuwen B. Keeping scientific advice non-partisan. Lancet 2003; 361: 527.
14. Pesson CGA, Erjefalt JS, Uller L, Andersson M, Greiff L. Unbalanced research. Trends Pharmacol Sci 2001; 22: 538-41.
15. Schmidt K, Schrammel A, Koesling D, Mayer B, Molecular mechanisms involved in the synergistic activation of soluble guanylyl cyclase by YC-1 and nitric oxide in endothelial cells. Molecular Pharmacol 2001; 59: 220-4.
16. Morton T. Meeting the challenge of the modern complexity. Scientific Computing World 2002; 67: 64-5.
17. Much ado about data. Nature Medicine 2001; 7: 751.
18. Koulakov A, Raghavachari S, Kepecs A, Lisman JE, Model for a robust neural integrator. Nature Neurosci 2002; 5: 775-82.
19. Pouget A, Latham P, Digitized neural networks: long-term stability from forgetful neurons. Nature Neurosci 2002; 5: 709-10.

20. Ramnani N, Lee L, Mechelli A, Phillips C, Roebroeck A, Formisano E. Exploring brain connettivity: a frontier in systems neuroscience. Trends Neurosci 2002; 25: 496-7.
21. Bevan MD, Magill PJ, Terman D, Bolam JP, Wilson CH. Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. Trends Neurosci 2002; 25: 525-31.
22. Dinner AR, Karplus M, The roles of stability and contact order in determining protein folding rates. Nature Structural Biol 2001; 8: 21-2.
23. Ray LB, Gouch NR, Orientering strategies for a signaling maze. Science 2002; 296: 1632-3.
24. Devlin K, Kurt Godel-Separating truth from proof in mathematics. Science 2002; 298: 1899-900.
25. Shipley B, Cause and correlation in biology: A user's guide to path analysis, structural equations and causal inference. Cambridge University Press, 2001.
26. Issa AM, Ethical perspectives on pharmacogenomic profiling in the drug development process. Nature Reviews Drug Discovery 2002; 1: 300-8.
27. Somerville MA, A postmodern moral tale: the ethics of research relationships. Nature Reviews Drug Discovery 2002; 1: 316-20.
28. Faigman DL, Is science different for lawyers?. Science 2002; 297: 339-40.
29. Jansen RC, Nap JP, Mlynarova L, Errors in genomics and proteomics. Nature Biotech 2002; 20: 19.
30. Guet CC, Elowitz MB, Hsing W, Leibler S, Combinatorial synthesis of genetic networks. Science 2002; 296: 1466-70.
31. Agrafiotis KD, Lobanov VS, Salemme FR, Combinatorial informatics in the post-genomics era. Nature Reviews Drug Discovery 2002; 1: 337-46.
32. Brazhnik P, De la Fuente A, Mendes P, Gene networks: How to put the function in genomics. Trends Biotech 2002; 20: 467-72.
33. Chicurel M, Bioinformatics: Bringing it all together. Nature 2002; 419: 751-7.
34. Couzin J, Chaos reigns in RNA transcription. Science 2002; 298: 1538.
35. Leahy D, In silico sapiens. Sci Comp World 2002; 66: 14-6.
36. Karplus M, McCammon JA, Molecular dynamics simulations of biomolecules. Nature Structural Biol 2002, 9: 646-51.
37. Kukreja RC, NFkB activation during ischemia/reperfusion in heart: friend or foe?. J Mol Cell Cardiol 2002; 34: 1301-4.
38. Ting AY, Endy D, Decoding NF-kB signaling. Science 2002; 298: 1189-90.
39. Hoffmann A, Levchenko A, Scott ML, Baltimore D, The IkB-NF-kB signaling module: Temporal control and selective gene activation. Science 2002; 298: 1241-4.
40. Winfree AT, On emerging coherence. Science 2002; 298: 2336-7.
41. Samoilov M, Arkin A, Ross J, Signal processing by simple chemical systems. J Phys Chem A 2002; 106: 10205-21.
42. Boehning D, Snyder SH, Carbon monoxide clocks. Science 2002; 298: 2339-40.
43. Morse D, Sassone-Corsi P, Time after time: inputs to and outputs from the mammalian circadian oscillators. Trends Neurosci 2002; 25: 632-7.
44. Lambert GW, Reid C, Kaye DM, Jennings GL, Ester MD, Effect of sunlight and season on serotonin turnover in brain. Lancet 2002; 360: 1840-2.
45. Fu L, Pelicano H, Liu J, Huang P, Lee CC. The circadian gene Period2 plays an important role in tumor suppression and DNA damage response in vivo. Cell 2002; 111: 41-50.
46. Rutter J, Reick M, Wu LC, McKnight SL, Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. Science 2001; 293: 510-4.

47. Suel GM, Lockless SW, Wall MA, Ranganathan R, Evolutionarily conserved networks of residues mediate allosteric communication in proteins. Nature Struct Biol 2003; 10: 59-68.
48. Havranek JJ, Harbury PB, Automated design of specificity in molecular recognition. Nature Struct Biol 2003; 10: 45-59.
49. Hammarstrom P, Wiseman RL, Powers ET, Kelly JW, Prevention of transthyretin amyloid disease by changing protein misfolding energetics. Science 2003; 299: 713-6.
50. Jansens A, van Duijn E, Braakman I, Coordinated nonvectorial folding in a newly synthetized multidomain protein. Science 2002; 298: 2401-3.
51. Garcia-Mira MM, Sadqi M, Fischer N, Sanchez-Ruiz JM, Munoz V, Experimental identification of downhill protein folding. Science 2002; 298: 2191-5.
52. Freire E, Can allosteric regulation be predicted from structure ?. Proc Nat Ac Sci 2000; 97, 11680-2.
53. Kenakin T, Onaran O, The ligand paradox between affinity and efficacy: can you be there and not make a difference? .Trends Pharmacol Sci 2002; 23: 275-80; Id, 2003; 24: 5-6.
54. Kenakin T, Efficacy at G-protein-coupled receptors. Nature Rev Drug Discovery 2002; 1: 103-10.
55. Freire E, Designing drugs against heterogeneous targets. Nature Biotech 2002; 20: 15-6; Paintand G, Wakelkamp M, The efficiency concept in pharmacodynamics. Clin Pharmacokinet 1999; 36: 375-89.
56. Clarke WP, Bond RA, The elusive nature of intrinsic efficacy. Trends Pharmacol Sci 1998; 19: 270-6.
57. Smith NGC, Lercher MJ, Regional similarities in polymorphism in the human genome extend over many megabases. Trends Genetics 2002; 18: 281-3.
58. Mering C, Krause R, Snel B, Cornell M, Oliver SG, Fields S, Bork P, Comparative assesssment of large-scale data sets of protein-protein interactions. Nature 2002; 417: 399-403.
59. Legrain P, Protein interactions contribute to protein function. Trends in Genetics 2002; 18: 432.
60. Jain E, A practical introduction to bioinformatics. Trends Biotec 2002; 20: 226.
61. Veeramalai M, Gilbert D, Bioinformatics tools for protein structure. Sci Comp World 2002; 64: 12-7.
62. Martz E, Protein explorer: easy yet powerful macromolecular visualization. Trends Biochem Sci 2002; 27: 107-9.
63. Rossini L, Bernardi M, Concettoni C, De Florio L, Deslauriers R, Moretti V, Piantelli F, Pigini P, Re L, Rossini P, Tonnini C, Some approaches to the pharmacology of multisubstrate enzyme systems. Pharmacol Res 1994; 29: 313-35.
64. Danon A, Redox reactions of regulatory proteins: do kinetics promote specificity?. Trends Biochem Sci 2002; 27: 197-203.
65. Rossini L, Bernardi M, Chronobiology as applied to the non-invasive pharmacotoxicology of metabolic-signal fluctuations. Report to the 4th National Conference, Gubbio, 1-2 June 1996, Summary Book, 74.
66. Rossini L, Catecholamine-enteramine rate and dishinibition reactions of thermal nature. Boll Soc It Biol Sper 1964; 40: 673-76.
67. Rossini L, Time and frequency domains in biomedical phenomena. Lettere dalla Facoltà, I, II 1999; 6: 21-5.
68. Rossini L, Time and frequency domains in biomedical phenomena. Lettere dalla Facolta', II, II 1999; 9: 23-6.

69. Luisi AJ, Fallavollita JA, Suzuki G, Canty JM, Spatial inhomogeneity of sympathetic nerve function in hibernating myocardium. *C*irculation 2002; 106: 779-81.
70. Ungerer M, Hartmann F, Karoglan M, Chlistalla A, Ziegler S, Richardt G, Overbeck M, Meisner H, Schomig A, Schwaiger M, Regional in vivo and in vitro characterization of autonomic innervation in cardiomyopathic human heart. Circulation 1998; 97: 174-80.
71. Forgione MA, Cap A, Liao R, Moldovan NI, Eberhardt RT, Lim CC, Jones J, Goldschmidt-Clermont PJ, Loscalzo J, Heterozygous cellular glutathione peroxidase deficiency in the mouse. Abnormalities in vascular and cardiac function and structure. Circulation 2002; 106: 1154-8.
72. Bers DM, Ziolo MT, When is cAMP not cAMP? Effects of compartmentalization. Circ. Res, 2001; 89: 373-5.
73. Beavo JA, Brunton LL, Cyclic nucleotide research - still expanding after half a century. Nature Mol Cell Biol 2002; 3: 710-8.
74. Rossini L, Bernardi M, Cavalieri L, Cintolesi F, Concettosi C, Fulgenti G, Galeazzi G, Graciotti L, Jacussi M, Lamura E, Maurelli E, Moretti V, Moroni L, Pettinari F, Pigini P, Rossi C, Rossini P, Tonnini C, Violet CA, Violet G, Dynamics of cell cycles and apoptosis: current biomedical references. In: Breast Tumors. Updates. Adria Medica Monographs, Ancona, 1998: 32-56.
75. Rossini P, Galeazzi G, Rossini L, Considerations regarding the updating of current basic knowledge in the field of drug-taking and drug addiction. Adria Medica Monographs, Ancona, 1998; 23: 13-43.
76. Menaker M, Circadian photoreception. Science 2003; 299: 213-4.
77. van Gelder RN, Wee R, Lee JA, Tu DC, Reduced pupillary light responses in mice lacking cryptochromes. Science 2003; 299: 222-47.
78. Ruby NF, Brennan TJ, Xie X, Cao V, Franken P, Heller HG, O'Hara BF, Role of melanopsin in circadian responses to light. Science 2002; 298: 2211-3.
79. Panda S, Sato TK, Castrucci AM, Rollag MD, DeGrip WJ, Hogenesch JB, Provencio I, Kay SA, Melanopsin (Opn4) requirement for normal light-induced circadian phase shifting. Science 2002; 298: 2213-6.
80. Nakamura W, Honma S, Shirakawa T, Honma K, Clock mutation lengthens the circadian period without damping rhythms in individual SCN neurons. Nature Neurosci 2002; 5: 399-10.
81. Lopez JC, It's all in the rhythm. Nature Neurosci 2002; 3: 495; Reppert SM, Weaver DR, Coordination of circadian timing in mammals. Nature 2002; 418: 935-41.
82. Reed SI, Cell cycling? Check your brakes. Nature Cell Biol 2002; 4: E199-E200.
83. Van den Pol AN, Obrietan K, Short circuiting the circadian clock. Nature Neuroscience 2002; 5: 616-8.
84. Boehm S, Kubista H, Fine tuning of sympathetic transmitter release via ionotropic and metabotropic presynaptic receptor. Pharmacol Res 2002; 54: 43-99.
85. Doyle MR, Davis SJ, Bastow RM, McWatters HG, Kozma-Bognar L, Nagy F, Millar AJ, Amasino RM, The ELF4 gene controls circadian rhythms and flowering time in Arabidopsis thaliana. Nature 2002; 419: 74-7.
86. Mehta RH, Manfredini R, Hassan F, Sechtem U, Bossone E, Oh JK, Cooper JV, Smith DE, Portaluppi F, Penn M, Hutchinson S, Nienaber CA, Isselbacher EM, Eagle KA, Chronobiological patterns of acute aortic dissection, Circulation 2002; 106: 1110-5.
87. Sakata K, Kumagai H, Osaka M, Onami T, Matsuura T, Imai M, Saruta T, Potential sympathetic nervous and renin-angiotensin systems reduce nonlinear correlation

between sympathetic activity and blood pressure in conscious spontaneously hypertensive rats. Circulation 2002; 106: 620-5.
88. Reppert SM, Weaver DR, Molecular analysis of mammalian circadian rhythms. Ann Rev Physiol 2001; 63: 647-76.
89. Bezanilla F, Perozo E, Force and voltage sensors in one structure. Science 2002; 298: 1562-3.
90. Xu W, Liu Y, Wang S, McDonald T, Van Eyk JE, Sidor A, O'Rourke B, Cytoprotective role of Ca^{2+}-activated K^{+} channels in the cardiac inner mitochondrial membrane. Science 2002; 298: 1029-33.
91. Xia X-M, Zeng X, Lingle CJ, Multiple regulatory sites in large-conductance calcium-activated potassium channels. Nature 2002; 418: 880-4.
92. Shi J, Krishnamoorthy G, Yang Y, Hu L, Chaturvedi N, Harilai D, Qin J, Cui J, Mechanism of magnesium activation of calcium-activated potassium channels. Nature 2002; 418: 876-80.
93. Toyoshima C, Nomura H, Structural changes in the calcium pump accompanying the dissociation of calcium. Nature 2002; 418: 605-11.
94. Yellen G, The voltage-gated potassium channels and their relatives. Nature 2002; 419: 35-42.
95. Perozo E, Kloda A, Cortes DM, Martinac B, Physical principles underlying the transduction of bilayer deformation forces during mechanosensitive channel gating. Nature Structural Biol 2002; 9: 696-703.
96. Betanzos M, Chiang C-S, Guy HR, Sukharev S, A large iris-like expansion of a mechanosensitive channel protein induced by membrane tension. Nature Structural Biol 2002; 9: 704-10.
97. Terentev D, Viatchenko-Karpinski S, Valdivia HH, Escobar AL, Gyorke S, Luminal Ca^{2+} controls termination and refractory behavior of Ca^{2+}-induced Ca^{2+} release in cardiac myocytes. Circ Res 2002; 91: 414-20.
98. Petrashevskaya NN, Koch SE, Bodi I, Schwartz A, Calcium cycling, historic overview and perspectives. Role for autonomic nervous system regulation. J Mol Cell Cardiol 2002; 34: 885-6.
99. MacLennan DH, Abu-Abed M, Kang CH, Structure-function relationships in Ca^{2+} cycling proteins. J Mol Cell Cardiol 2002; 34: 897-918.
100. Maier LS, Bers DM, Calcium, calmodulin, and calcium-calmodulin kinase II: Heartbeat to heartbeat and beyond. J Mol Cell Cardiol 2002; 34: 919-39.
101. Guatimosim S, Dilly K, Santana LF, Jafri MS, Sobie EA, Lederer WJ, Local Ca^{2+} signaling and EC coupling in heart: Ca^{2+} sparks and the regulation of the $[Ca^{2+}]_i$ transient. J Mol Cell Cardiol 2002; 34: 941-50.
102. Hasenfuss G, Pieske B, Calcium cycling in congestive heart failure. J Mol Cell Cardiol 2002; 34: 951-69.
103. Bernardi M, Deslauriers R, Docherty J, Rossi C, Rossini L, Rossini P, Tonnini C, Spectral analysis of intercycle heart fluctuations in the diethyl-ether-anaesthetized or pithed rat treated with prazosin, dl-propranolol, endothelin-1, alpha-r atriopeptin and ACE-inhibitors. J Auton Pharmacol 1998; 18: 271-80.
104. Meyer M, Keweloh B, Guth K, Holmes JW, Pieske B, Lehnart SE, Just H, Hasenfuss G, Frequency-dependence of myocardial energetics in failing human myocardium as quantified by a new method for the measurement of oxygen consumption in muscle strip preparations. Mol Cell Cardiol 1998; 30: 1459-70.
105. Bernardi M, Deslauriers R, Docherty J, Galeazzi G, Rossini L, Rossini P, Spectral analysis of intercycle heart fluctuations in the diethyl-ether-anaesthetized or pithed rat treated with l-hyoscyamine. J Auton Pharmacol 1997; 17: 27-34.

106. Bernardi M, Deslauriers R, Docherty J, Rossi C, Rossini L, Rossini P, Tonnini C, Spectral analysis of intercycle heart fluctuations in Xenopus laevis, conscious or spinalized, treated with calcium channel blockers. Part I. Gen Pharmac 1997; 29: 477-81.
107. Rossini L, Re L, Tonnini C, Didactic experimentation and progress of research in physio-pharmacological and clinical applications of non-invasive in-vivo biochemical read-out techniques. Quad March Med 1985; 4: 213-5.
108. Di Sarra B, Piantelli F, Moretti V, Re L, Rossini L, Tonnini C, Physio-pharmaco-toxicological in vivo read-out: an interuniversity integrated analytical center. Issues, results and perspectives. Quad March Med. Special Issue 20th Anniversary of Ancona University 1989; 5: 183-5.
109. Aebersold R, Watts JD, The need for national centers for proteomics. Nature Biotech 2002; 20: 651.
110. Lacky L, The public and private approach to proteomics. Scrip Magazine, 2001; March: 16-17.
111. Farkas DH, Molecular diagnostics: the best is yet to come. Trends Mol Med 2002; 8: 245.
112. Tonnies H, Modern molecular cytogenetic techniques in genetic diagnostics. Trends Mol Med 2002; 8: 246-50.
113. Walter G, Bussow K, Lueking A, Glokler J, High-throughput protein arrays: prospects for molecular diagnostics. Trends Mol Med 2002; 8: 250-3.
114. Todd R, Margolin DH, Challenges of single-cell diagnostics: analysis of gene expression. Trends Mol Med 2002; 8: 254-7.
115. Klein D, Quantification using real-time PCR technology: applications and limitations. Trends Mol Med 2002; 8: 257-60.
116. Fortina P, Surrey S, Kricka LJ, Molecular diagnostics: hurdles for clinical implementation. Trends Mol Med 2002; 8: 264-6.
117. Negm RS, Verma M, Srivastava S, The promise of biomarkers in cancer screening and detection. Trends Mol Med 2002; 8: 288-93.
118. Re L, Cola V, Fulgenzi G, Marinelli F, Concettoni C, Rossini L, Postsynaptic effects of methoctramine at the mouse neuromuscular junction. Neuroscience 1993; 57: 451-7.
119. Rossini L, Rossini P, Chance B, Continuous read-out of cytochrome b, flavin and pyridine nucleotide oxido-reduction processes in the perfused frog heart and contracting skeletal muscle. Pharmacol Research 1991; 23: 349-65.
120. Re L, Moretti V, Rossini L, Giusti G, Sodium-activated potassium current in mouse diaphragm. FEBS Letters 1990; 270: 195-7.
121. Re L, Rossini L, Electrophysiological analysis of the cholinergic effects of cimetidine and ranitidine. Pharmacol Res Commun 1984; 16: 381-99.
122. Bergamini PG, Palmas G, Piantelli F, Sani M, Cingolani ML, Leone L, Re L, Roda G, Rossini L, A multi-lamda device for bioluminescence measurements in vivo, Chem Biomed Environ Instrumentation 1980; 10: 289-309.
123. Rossini L, Larner J, Conformational transitions of glycogen synthase forms studied with fluorescent probes. Atti Accad. Fisiocritici Siena 1977; 9: 53-75.
124. Chance B, Mayer D, Rossini L, A time sharing instrument for direct readout of oxidation-reduction states in intracellular compartments in cardiac tissue. IEEE Trans Biomed Eng 1970; BME-17: 118-21.
125. Terzuolo CA, Handelman EJ, Rossini L, An isolated crustacean neuron preparation for metabolic and pharmacological studies. In: Invertebrate Nervous System, CAG Wiersma Ed 1967, 55-64.

126. Rossini L, Cohen HP, Handelman E, Lin S, Terzuolo CA, Measurements of oxidoreduction processes and ATP levels in an isolated crustacean neuron. Ann NY Ac Sci 1966; 137: 864-75.
127. Terzuolo CA, Chance B, Handelman E, Rossini L, Schmelzer P, Measurements of reduced pyridine nucleotides in a single neuron. Biochim Biophys Acta 1966; 126: 361-72.
128. Schaferling M, Kruschina M, Meerkamp M, Ortigao F, Kambhampati D, Smart sensor architectures: Importance of microarray sensor surface in conducting high quality functional genomic analysis. PharmaGenomics 2002; 2: 36-44.
129. Dai J, Tu J, Anderson LN, Bao JJ, Liu C, Quay B, Wehmeyer KR, High-Throughput separations: using multiplexed capillary electrophoresis with laser-induced fluorescence detection. PharmaGenomics 2002; 2: 46-57.
130. Robinson WH, et al., Autoantigen microarrays for multiple characterization of autoantibody responses. Nature Med 2002; 8: 295-301.
131. Battersby BJ, Trau M, Novel miniaturized systems in high-throughput screening. Trends Biotech 2002; 20: 167-73.
132. Templin MF, Stoll D, Schrenk M, Traub PC, Vohringer CF, Joos TO, Protein microarray technology. Trends Biotech 2002; 20: 160-66.
133. Choavan T, Guttman A, Microfabricated devices in biotechnology and biochemical processing. Trends Biotech 2002; 20: 116-22.
134. Karumanchi RSMS, Doddamane SN, Sampangi C, Todd PW, Field-assisted extraction of cells, particles and macromolecules. Trends Biotech 2002; 20: 72-8.
135. Nolan JP, Sklar LA, Suspension array technology: evolution of the flat-array paradigm. Trends Biotech 2002; 20: 9-12; DNA Microarrays: Gene expression applications. B Jordan Ed., Springer 2001.
136. Methods of microarray data analysis. S Lin, K Johnson Eds, Kluwer, 2001.
137. Blagoev B, Pandey A, Microarrays go live – new prospects for proteomics. Trends Biochem Sci 2001; 26: 639-41.
138. Ball CA, et al, A guide to microarray experiments – an open letter to the scientific journals. The Lancet 2002; 360: 1019.
139. Levene MJ, Korlach J, Turner SW, Foquet M, Craighead HG, Webb WW, Zero-mode waveguides for single-molecule analysis at high concentrations. Science 2003; 299: 682-6.
140. Schuler B, Lipman EA, Eaton WA, Probing the free-energy surface for protein folding with single-molecule fluorescence spectroscopy. Nature 2002; 419: 743-7.
141. Dong F, Miller RE, Vibrational transition moment angles in isolated biomolecules: a structural tool. Science 2002; 298: 1227-30.
142. Nighswander-Rempel SP, Shaw A, Mansfield JR, Hewko M, Kupriyanov VV, Mantsch HH, Regional variations in myocardial tissue oxygenation mapped by near-infrared spectroscopic imaging. J Mol Cell Cardiol 2002; 34: 1195-203.
143. Sato M, Ozawa T, Inukai K, Asano T, Umezawa Y, Fluorescent indicators for imaging protein phosphorylation in single living cells. Nature Biotech 2002; 20: 287-94.
144. Foldes-Papp Z, Demel U, Tilz GP, Detection of single molecules: solution-phase single-molecule fluorescence correlation spectroscopy as an ultrasensitive, rapid and reliable system for immunological investigation. J Immunol Meth 2002; 260: 117-24.
145. Medalia O, Weber I, Frangakis AS, Nicastro D, Gerisch G, Baumeister W, Macromolecular architecture in eukariotic cells visualized by cryoelectron tomography. Science 2002; 298: 1209-13.

146. Sharpe J, Ahlgren U, Perry P, Hill B, Ross A, Hecksher-Sorensen J, Baldock R, Davidson D, Optical projection tomography as a tool for 3D microscopy and gene expression studies. Science 2002; 296: 541-5.
147. Reininger-Mack A, Thielecke H, Robitzki AA, 3D-biohybrid systems: applications on drug screening. Trends Biotech 2002; 20: 56-61.
148. Liu L, et al, Visualization and quantification of T cell-mediated cytotoxicity using cell-permeable fluorogenic caspase substrates. Nat Med 2002; 8: 185-9.
149. Van Roessel P, Brand AH, Imaging into the future: visualizing gene expression and protein interaction with fluorescent proteins. Nature Cell Biol 2002; 4: E15-E20.
150. Foldes-Papp Z, Demel U, Tilz GP, Ultrasensitive detection and identification of fluorescent molecules by FCS: impact for immunobiology. Proc Natl Acad Sci 2001; 98: 11509-14.
151. Brown BE et al, In vivo measurement of gene expression, angiogenesis and physiological function in tumors using multiphoton laser scanning microscopy. Nature Med 2001; 7: 864-8.
152. Wouters FS, Verveer PJ, Bastiaens PIH, Imaging biochemistry inside cells. Trends Cell Biol 2001; 11: 203-11.
153. Ihee H, Lobastov VA, Gomez UM, Goodson BM, Srinivasan R, Ruan C-Y, Zewail AH, Direct imaging of transient molecular structures with ultrafast diffraction. Science 2001; 291: 458-62.
154. Hovius R, Vallotton P, Wohland T, Vogel H, Fluorescence techniques: shedding light on ligand-receptor interactions. Trend Pharmacol Sci 2000; 21: 266-73.
155. Dixon AK, Richardson PJ, Pinnock RD, Lee K, Gene-expression analysis at the single-cell level. Trends Pharmacol Sci 2000; 21: 65-70.
156. Lazzeroni LC, Karlovich CA, Genotype to phenotype: associations, errors and complexity. Trends Genetics 2002; 18: 283-84.
157. Pradet-Balade B, Boulme F, Beug H, Mullner EW, Garcia-Sanz JA, Translation control: bridging the gap between genomics and proteomics?. Trends Biotech Sci 2001; 26: 225-9.
158. Brent MR, Predicting full-lenght transcripts. Trends Biotech 2002; 20: 273-5.
159. Tomaselli GF, Ed, Thematic Series on Emerging Genomics Technology. 1st note: Cook SA, Rosenzweig. DNA microarrays. Implications for cardiovascular medicine. Circ Res 2002; 91: 559-64.
160. Rappsilber J, Mann M, What does it mean to identify a protein in proteomics?. Trends Biochem Sci 2002; 27: 74-8.
161. Phillips TJ, Belknap JK, Complex-trait genetics: emergence of multivariate strategies. Nature Rev Neurosci 2002; 3: 478-85.
162. Bradu D, Di Sarra B, Concettoni C, Moretti V, Pagelli P, Re L, Rossini L, Tonnini C, Characterization of the rabbit aorta endothelium-dependent cholinergic receptor by agonist equipotent molar doses. J Pharmacol Methods 1989; 22: 219-31.
163. Cingolani ML, Re L, Rossini L, 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 1985; 17:1-22.
164. Bradu D, Cingolani ML, Ferrante L, Re L, Rescigno A, Rossini L, A contribution to the advancement of the computational procedures as applied to the classification of drug and receptor congeners. Highlights in Receptor Chemistry, C Melchiorre, M Giannella Eds., Amsterdam: Elsevier Science Publishers,1984; 251-94.
165. Rossini L, Bastianelli P, Bradu D, Cingolani ML, Ferrante L, Gamba G, Re L, Ordering and grouping drug analogues and receptor effects. In: Manell P Johannson

SG, eds. The impact of computer technology on drug information. Amsterdam: North-Holland, IFIP-IMIA 1982: 181-3.
166. Rossini L, Reclassifying cholinergic receptors. Trends Pharmacol Sci 1981; 2: I-IV.
167. Rossini L, Bastianelli P, Cingolani ML, Gamba G, Giannella M, Gualtieri F, Leone L, Martorana F, Melchiorre C, Moretti V, Periti PF, Pigini M, Pigini P, Re L, Roda G, Tuccella S, Pattern recognition in profiling pharmacological receptors. De Martinis C Rossini L, eds. Portonovo Conferences II. Padova: Piccin Int Ed, 1978: 257-90.
168. Rossini L, Martorana F, Periti P. Clustering cholinergic receptors by muscarine and muscarone analogues. In: Bergamini N Bachini V, eds. Rationality of drug development. Amsterdam: Excerpta Medica-American Elsevier, 1976: 223-8.
169. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn, Meta-analysis of genetic associations studies supports a contribution of common variants to susceptibility to common disease. Nature Genetics 2003; 33: 177-82.
170. Fujikawa A, Shirasaka D, Yamamoto S, Ota H, Yahiro K, Fukada M, Shintani T, Wada A, Aoyama N, Hirayama T, Fukamaki H, Noda M, Mice deficient in protein tyrosine phosphatase receptor type Z are resistant to gastric ulcer induction by VacA of Helicobacter pylori. Nature Genetics 2003; 33: 375-81.
171. Zazopoulos E, Huang K, Staffa A, Liu W, Bachmann BO, Nonaka K, Ahlert J, Thorson JS, Shen B, Farnet CM, A genomics-guided approach for discovering and expressing cryptic metabolic pathways. Nature Biotech 2003; 21: 187-90.
172. Glazier AM, Nadeau JH, Altman TJ, Finding genes that underlie complex traits. Science 2002; 298: 2345-9.
173. Pagon RA, Genetic testing for disease susceptibilities: consequences for genetic counseling. Trends Mol Med 2002; 8: 306-7.
174. Marchant GE, Toxicogenomics and toxic torts. Trends Biotech 2002; 20: 329-32.
175. Abuin A, Holt KH, Platt KA, Sands AT, Zambrowicz BP, Full-speed mammalian genetics: in vivo target validation in the drug discovery process. Trends Biotech 2002; 20: 329-32.
176. Croston GE, Functional cell-based uHTS in chemical genomic drug discovery. Trends Biotech 2002; 20: 110-5.
177. Johnson JA, Evans WE, Molecular diagnostics as a predictive tool: genetics of drug efficacy and toxicity. Trends Mol Med 2002; 8: 300-5.
178. Bohannon J, The human genoma in 3D, at your fingertips. Science 2002; 298: 737.
179. Varmus H, Getting ready for gene-based medicine, N Engl J Med 2002; 347: 1526-7: 1st Note of the Series: Guttmacher AE, Collins FS, Genomic Medicine – A primer. N Engl J Med 2002; 347: 1512-20.
180. Marks L, Power E, Using technology to address recruitment issues in the clinical trial process. Trends Biotech 2002; 20: 105-9.
181. Roden DM, George Al Jr, The genetic basis of variability in drug responses. Nature Rev Drug Discovery 2002; 1: 37-44.
182. Ginsburg GS, McCarthy JJ, Personalized medicine: revolutionizing drug discovery and patient care. Trends Biotech 2001; 19: 491-6.
183. Pirmohamed M, Park BK, Genetic susceptibility to adverse drug reactions. Trends Pharmacol Sci 2001; 22: 298-305.
184. Spear BB, Heath-Chiozzi M, Huff J, Clinical application of pharmacogenetics. Trends Mol Med 2001; 7: 201-4.
185. Peltonen L, McKusick VA, Dissecting human disease in the postgenomic era. Science 2001; 291: 1224-9.
186. Ensom MHH, Chang TKH, Patel P, Pharmacogenetics, the therapeutic drug monitoring of the future?. Clin Pharmacokinet 2001; 40: 783-802.

187. Evans WE, Relling MV, Pharmacogenomics: translating functional genomics into rational therapeutics. Science 1999; 286: 487-91.
188. Ingelman-Sundberg M, Oscarson M, McLellan RA, Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. Trends Pharmacol Sci 1999; 20: 342-49.
189. Levy G, Predicting effective drug concentrations for individual patients, determinants of pharmacodynamic variability. Clin Pharmacokinet 1998; 34: 323-33.
190. Steen H, Pandey A, Proteomics goes quantitative: measuring protein abundance. Trends Biotech 2002; 20: 361-4.
191. Houseman BT, Mrksich M, Towards quantitative assays with peptide chips: a surface engineering approach. Trends Biotech 2002; 20: 279-99.
192. Zhou H, Ranish JA, Watts JD, Aebersold R, Quantitative proteome analysis by solid-phase isotope tagging and mass spectrometry. Nature Biotech 2002; 20: 512-5.
193. Famulok M, Bringing picomolar protein detection into proximity. Nature Biotech 2002; 20: 448-9.
194. Norin M, Sundstrom M, Structural proteomics: developments in structure-to-function predictions. Trends Biotech 2002; 20:79-84.
195. Lopez-Otin C, Overall CM, Protease degradomics: a new challenge for proteomics. Nature Rev Mol Cell Biol 2002; 3: 509-19.
196. Zhou Z, Licklinder LJ, Gygi SP, Reed R, Comprehensive proteonomic analysis of the human spliceosome. Nature 2002; 419: 182-5.
197. Ong SE, Pandey A, Using mass spectrometry for drug discovery. Trends Biotech 2002; 20: 227.
198. Ranish JA, Yi EC, Leslie DM, Purvine SO, Goodlet DR, Eng J, Aebersold R, The study of macromolecular complexes by quantitative proteomics. Nature Genetics 2003; 33: 349-55.
199. A Trends Guide to Proteomics. A Supplement to Trends Biotech 2002; 20: (12, S1-S51).
200. Malmstrom L, Malmstrom J, Marko-Varga G, Westergren-Thorsson G, Proteomic 2DE database for spot selection, automated annotation and data analysis. J Proteome Res 2002; 1: 135-8.
201. Rejtar T, Hu P, Juhasz P, Campbell JM, Vestal ML, Preiser J, Karger BL, Off-line coupling of high-resolution capillary electrophoresis to MALDI-TOF and TOF/TOF MAS, J Proteome Res 2002; 1: 171-80.
202. Zhang R, Regnier FE, Minimizing resolution of isotopically coded peptides in comparative proteomics. J Proteome Res 2002; 1: 139-48.
203. Petricoin E III, et al, Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002; 359: 572-7.
204. Pearl DC, Proteomic patterns in serum and identification of ovarian cancer. Lancet 2002; 360: 169-71.
205. Pang JX, Ginanni N, Dongre AR, Hefta SA, Opiteck GJ, Biomarker discovery in urine by proteomics. J Proteome Res 2002; 1:161-70.
206. Paweletz CP et al, Rapid protein display profiling of cancer progression directly from human tissue using a protein biochip. Drug Development Res 2000; 49: 34-42.
207. Stoeckli M, Chaurand P, Hallahan DE, Caprioli RM, Imaging mass spectrometry: a new technology for the analysis of protein expression in mammalian tissues. Nature Med 2001; 7: 493-6.
208. Dishman R, Rationalizing proteonomics new strategies for streamlining drug discovery. PharmaGenomics 2002; 2: 58-62.

209. Mann M, Ong SE, Gronborg M, Steen H, Jensen ON, Pandey A, Analysis of protein phosphorylation using mass spectrometry: deciphering the phosphoproteome. Trends Biotech 2002; 20: 261-8.
210. Ficarro SB, McCleland ML, Stukenberg PT, Burke DJ, Ross MM, Shabanowitz J, Hunt DF, White FM, Phosphoproteome analysis by mass spectrometry and its application to Saccharomyces cerevisiae. Nature Biotech 2002; 20: 301-5.
211. Houseman BT, Huh JH, Kron SJ, Mrksich M, Peptide chips for the quantitative evaluation of protein kinase activity. Nature Biotech 2002; 20: 270-4.
212. Carroll AS, O'Shea EK, Pho85 and signaling environmental conditions. Trends Biochem Sci 2002; 27: 87-91.
213. Sato M, Ozawa T, Inukai K, Asano T, Umezawa Y, Fluorescent indicators for imaging protein phosphorylation in single living cells. Nature Biotech 2002; 20: 287-94 (quoted under [49]).
214. Williams DM, Cole PA, Kinase chips hit the proteomics era. Trends Biochem Sci 2001; 26: 271-3.
215. Coleman RE, Value of FDG-PET scanning in management of lung cancer. Lancet 2002; 359: 1361-2.
216. Ingwall JS, Is creatine kinase a target fpr AMP-activated protein kinase in the heart?. J Mol Cell Cardiol 2002; 34: 1111-20.
217. Perin EC, et al, Assessing myocardial viability and infarct transmurality with left ventricular electromechanical mapping in patients with stable coronary artery disease. Validation by delayed-enhancement magnetic resonance imaging. Circulation 2002; 106: 957-61.
218. Cai J-M, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan CY, Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002; 106: 1368-73.
219. Attwell D, Iadecola C, The neuronal basis of functional brain imaging signals. Trends Neurosci 2002; 25: 621-5.
220. Lawler A, White house stirs interest in brain –imaging initiative. Science 2002; 297: 748-9.
221. Leshe RA, James MF, Pharmacological magnetic resonance imaging, a new application for functional MRI. Trends Pharmacol Sci 2000; 21: 314-8.
222. Shulman RG, Rothman DL, 13-C NMR of intermediary metabolism: implications for systemic physiology. Ann Rev Physiol 2001; 63: 15-48.
223. Martin G, Chauvin MF, Baverel G, Model applicable to NMR studies for calculating flux rates in five cycles involved in glutamate metabolism. J Biol Chem 1997; 272: 4717-28.
224. Bernardi M, Galeazzi G, Lamura E, Piantelli F, Rendell J, Rossini P, Rossini L, (Ecto)nucleotidase kinetic observed by 31P-NMR spectroscopy: resolution of signals. Pharmacol Res 1997; 36: 353-61.
225. Lee JWK, Rossini L, Saunders JK, Deslauriers R, Seasonal variation in isolated perfused Xenopus Laevis heart as characterized by 31P and 13C MR spectroscopy: a new digitalis effect. European Society for Magnetic Resonance in Medicine and Biology 1996; Twelfth Annual Meeting, Nice.
226. Olsen JI, Rossini P, Schweizer MP, Bernardi M, Moretti V, Re L, Rossini L, A 31-P nmr spectroscopy study of Xenopus laevis heart perfused in vitro with creatinol-o-phosphate, phosphocreatine, adenosine triphosphate, fructose diphosphate and ouabain. Pharmacol Res 1993; 28: 135-51.
227. Olsen JI, Schweizer MP, Piantelli F, Bernardi M, De Florio L, Re L, Rossini L, Ongoing characterization of energy phosphate metabolism of amphibia heart in vitro. Eurospin Quarterly 1992; 31: 77-81.

228. Bernardi M, De Florio L, Gatti L, Olsen JI, Moretti V, Periti F, Piantelli F, Ripamonti A, Re L, Rossini L, Schweizer MP, Upgradings on the energetics of amphibia heart in vitro. Ann NY Ac Sci 1992; 671: 501-4.
229. Service RF, Propelled by recent advances, NMR moves into the fast lane. Science 2003; 299: 503.
230. Shuker SB, Hajduk PJ, Meadows RP, Fesik SW, Discovering high-affinity ligands for proteins: SAR by NMR. Science 1996.
231. Ideker T, Thorsson V, Ranish JA, Christmas R, Buhler J, Eng JK, Bumgarner R, Goodlett DR, Aebersold R, Hood L, Integrated genomic and proteomic analyses of a systematically perturbed metabolic network. Science 2001; 292: 929-34.
232. Jeong H, Tombor B, Albert R, Ottvai ZN, Barabasi A-L, The large-scale organization of metabolic networks. Nature 2000; 407: 651-4.
233. Pellecchia M, Sem DS, Wuthrich, NMR in drug discovery. Nature Rev Drug Discovery 2002; 1: 211-9, 2002; Keifer PA, NMR spectroscopy in drug discovery: tools for combinatorial chemistry, natural products, and metabolism research. Progress Drug Res 2000; 55: 137-12.
234. Nicholson JK, Connelly J, Lindon JC, Holmes E, Metabonomics: a platform for studying drug toxicity and gene function. Nature Rev Drug Discovery 2002; 1: 153-61.
235. Cascante M, Boros LG, Comin-Anduix B, Atauri P, Centelles JJ, Lee PWN, Metabolic control analysis in drug discovery and disease. Nature Biotech 2002; 20: 243-9.
236. Camp RL, Chung GG, Rimm DL, Automated subcellular localization and quantification of protein expression in tissue microarrays. Nature Medicine 2002; 8: 1323-7.
237. Brindle JT, Antti H, Holmes E, Tranter G, Nicholson JK, Bethell HWL, Clarke S, Schofield PM, McKilligin E, Mosedale DE, Grainger DJ, Rapid and noninvasive diagnosis of the presence and severity of coronary heart disease using IH-NMR-based metabonomics. Nature Medicine 2002; 8: 1439-44.
238. Lindon JC, Nicholson JK, Holmes E, Everet JR, Metabonomics: metabolic processes studied by NMR spectroscopy of biofluids. Concepts Magn Res 2000; 12: 289-320.
239. Nicholson JK, Lindon JC, Holmes E, 'Metabonomics': understanding the metabolic responses of living systems of pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data. Xenobiotica 1999; 29: 1181-9.
240. De Mets DL, Califf RM, Lessons learned from recent cardiovascular clinical trials: Part I. Circulation 2002; 106: 746-51; Part II. Id, 880-6; Califf RM, DeMets, Principles from clinical trials relevant to clinical practice: Part I. Circulation 2002; 106: 1015-21; Part II. Id, 1172-5.
241. Solomon CG, Dluhy RG, Rethinking Postmenopausal Hormone Therapy. New Engl J Med 2003; 348: 579-80.
242. Grodstein F, Clarkson TB, Manson JE, Understanding the divergent data on postmenopausal hormone therapy. N Engl J Med 2003; 348: 645-50.
243. Cherry N, et al, Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomized placebo controlled trial. Lancet 2002; 360: 2001-8.
244. Ramsay S, End of WISDOM. Lancet 2002; 360: 1398.
245. Rossini L, Bernardi M, Cavalieri L, Concettoni C, Galeazzi G, Gentili M, Moretti V, Moroni L, Pettinari F, Picchi L, Pigini P, Rossini P, Tonnini C, Violet C, International pharmacovigilance: use ad abuse of drugs. Proceedings, Marche Region Academy of Sciences, Letters and Arts 1996; 29: 151-98.

246. Rossini L, Bernardi M, Moretti V, Picchi L, Rossi C, Rossini P, Availability of essential medicinal products in Italy: a justified shortage?. Adria Medica 1988; 23: 49-55.
247. Vth Meeting of the Representatives of National Centres participating in the WHO International Drug Monitoring Scheme, and Seminar on receipt, processing and use of suspected adverse reaction reports: a discussion of current procedures and experience. WHO-ITA/ITA-OMS, University of Ancona Medical School, Portonovo, October 4/8, 1982.
248. XIX Congress of the Italian Pharmacological Society; First Joint Meeting of Yugoslav and Italian Pharmacological Societies, and Second "Portonovo Conference on Biomathematics", September 24/27, 1978. Second Round Table, Post-marketing surveillance-monitored release-side effects monitoring. University of Ancona Medical School, Proceedings, 261-406.
249. Rossini L, Clinico-pharmacological aspects of medical experimentation of drugs in man. In: I diritti dell'uomo nell'ambito della Medicina Legale. Napoli: Giuffrè Ed, 1981: 453-7.
250. Rossini L, Monitored temporary recording: a proposed verification procedure. In: Nuovi aspetti di Tossicologia sperimentale e clinica. Torino: CG Edizioni Medico Scientifiche, 1979: 457-70.
251. Rossini L, Leone L, Development of the WHO international pharmacovigilance program in Italy. Rassegna Clinico-Scientifica 1977; 53: 3-19.
252. Rossini L, Introductory considerations, I; Concluding considerations, II.. Proceedings International Workshop on History, Anthropology and Epistemology of Medicine, Healing: Structure of the Cure-Way of Recovery, Senigallia, 1987; November 27. Firenze: Leo Olschki Ed, 1993: 219-23.
253. How to develop and implement a national drug policy. Updates and replaces Guidelines for Developing National Drug Policies. 1988; Geneva: WHO 2nd Ed, 2001.
254. James A, Medicines, society, and industry. Lancet 2002; 360: 1346-7.
255. Collier J, Iheanacho, The pharmaceutical industry as an informant. Lancet 2002; 360: 1405-9.
256. Abraham J, The pharmaceutical industry as a political player. Lancet 2002; 360: 1498-1502.
257. The Lancet, Improving ADR reporting. Lancet 2002: 360: 1435.
258. Rogers A, European parliament approves pharma law overhault. Lancet 2002; 360: 1397-8.
259. Mann Howard, Clinical trial protocols: agreements between the FDA and industrial sponsors. Lancet 2002; 360: 1345-6.
260. Sandercock P, Roberts I, Systematic reviews of animal experiments. Lancet 2002; 360: 586.
261. Ashby Sharpe V, Bioethics: centres reveal sponsors but not policy. Nature 2002; 417: 583.
262. Mann H, Research ethics committees and public dissemination of clinical trial results. Lancet 2002; 359: 406-8;.
263. Calman KC, Communication of risk: choice, consent, and trust. Lancet 2002; 360: 166-8.
264. Boers M, Seminal pharmaceutical trials: maintaining masking in analysis. Lancet 2002; 360: 100-1.
265. Trouiller P, Olliaro P, Toreele E, Orbinski J, Laing R, Ford N, Drug development for neglected diseases: a deficient market and a public-health policy failure. Lancet 2002; 359: 2188-93.

266. Koh THHG, Budge D, Collie L, Prescribing errors. Lancet 2002; 360: 255-6.
267. King TE, Racial disparities in clinical trials. N Engl J Med 2002; 346: 1401-2.
268. Lewis JA, Jonsson B, Kreutz G, Sampaio C, Va Zwieten-Boot B, Placebo-controlled trials and the declaration of Helsinki. Lancet 2002; 359: 1337-40.
269. Roberts MJ, Reich MR, Ethical analysis in public health. Lancet 2002; 359: 1055-9.
270. Nelson K, Stimulating research in the most neglected diseases. Lancet 2002; 369: 1042.
271. Schulz KF, Grimes DA, Unequal group sizes in randomised trials: guarding against guessing. Lancet 2002; 359: 966-71.
272. Mason S, Nicholl J, Lilford R, What to do about poor clinical performance in clinical trials. Br Med J 2002; 324: 419-2.
273. Lenfant C, Clinical research skills development a new approach. Circulation 2002; 105: 1751-2.
274. Faxon DP, The chain of scientific discovery. The critical role of the physician-scientist. Circulation 2002; 105: 1857-60.
275. Miller FG, Rosenstein DL, Reporting of ethical issues in publications of medical research. Lancet 2002; 360: 1326-8.
276. Bossuyt PMM, Lijmer JG, Mol BWJ. Randomised comparisons of medical tests: sometimes invalid, not always efficient. Lancet 2000; 356: 1844-7.
277. Ethnomedicine and drug discovery. Advances in Phytomedicine I. MM Iwu, JC Wootton Eds, Elsevier Science, 2002.
278. Jackson B, The deeper the knowledge the better the drugs?. Scrip Magazine 2002; 31-3.
279. Altman RB, Klein TE, Challenges for biomedical informatics and pharmacogenomics. Ann Rev Pharmacol Toxicol 2002; 42: 113-32.
280. McLeod HL, Evans WE, Pharmacogenomics: unlocking the human genome for better drug therapy. Ann Rev Pharmacol Toxicol 2001; 41: 101-22.
281. Chan PLS, Holford NHG, Drug treatment effects on disease progression. Ann Rev Pharmacol Toxicol 2001; 41: 625-60.
282. Xie H-G, Kim RB, Wood AJJ, Stein CM, Molecular basis of ethnic differences in drug disposition and response. Ann Rev Pharmacol Toxicol 2001: 41: 815-50.
283. Ohlstein EH, Ruffolo RR, Elliott JD, Drug Discovery in the next millenium. Ann Rev Pharmacol Toxicol 2000; 40: 177-92.
284. Debouck C, Metcalf B, The impact of genomics on drug discovery. Ann Rev Pharmacol Toxicol 2000; 40: 193-208.
285. Holford NHG, Kimko HC, Monteleone JPR, Peck CC, Simulation of clinical trials. Ann Rev Pharmacol Toxicol 2000; 40: 209-34.
286. Houghten RA, Parallel array and mixture-based synthetic combinatorial chemistry: tools for the next millenium. Ann Rev Pharmacol Toxicol 2000; 40: 273-82.
287. Waring JF, Ulrich RG, The impact of genomics-based technologies on drug safety. Ann Rev Pharmacol Toxicol 2000; 40: 335-52.
288. Rossini L, Cingolani ML, The development of the chimico-pharmaceutical sciences in the twentieth century. Proceedings Marche Region Academy of Sciences, Letters and Arts, Memoirs and Reports No. 34 (1981-1984), Vol I (part one), 39-71, 1986.
289. Hofbauer KG, Huppertz C, Pharmacotherapy and evolution. Trends in Ecology & Evolution 2002; 17: 328-34.
290. The Lancet, The next step: ensuring integrity of scientific research. Lancet 2002; 360: 499.
291. The Economist, Leaders, On the road to ruin; Britain, Higher education: The ruin of Britain's universities. The Economist 2002; 12: 32.

292. Rossini L, The Ancona University-Hospital Pole – Clinical Pharmacology and Toxicology Service. Proceedings, Marche Region Academy of Sciences, Letters and Arts, 2003, in press.
293. Rossini L, Teaching Experience and Updating of the "New Table XVIII" – Scientific Discipline Sector E07X – Pharmacology. Proceedings, Marche Region Academy of Sciences, Arts and Letters, 2003, in press.
294. Rossini L, Monographic Course "Clinical experimentation of drugs and pharmacovigilance", Faculty of Medicine, University of Ancona, 12 April-3 May 2002, May 7-14, 2003.
295. Anonymous, For european experimentation. La Professione 2000; 2(3): 11-2.
296. Flickinger B, Providing a forum for the future. PharmacoGenomics 2002; 5: 74.