DRUGS AND THE FUTURE

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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 2\textsuperscript{nd} 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,


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.

(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].

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 (mibebradil), endothelin antagonists (bosentan), H-1 inverse agonists (astemizole, terfenadine), inotropic agents (flosequinan, vesnarinone), psychothrops (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].

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.
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