Editorial

Are the ALTERNATIVES in pharmacology and toxicology real alternatives?

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In the contemporary medicine, the word *"alternative"* is frequently used to characterise diagnostic, therapeutic and experimental methods or procedures that may substitute for the recently used ones. The two most frequently applied meanings imply the extremes of "alternative" approaches used in pharmacology, pharmacotherapy and toxicology. One involves homeopathy and some of the so-called natural drugs and the other extreme covers substitution of isolated cell cultures for whole animal pharmacological and toxicological studies. When analysing these *"alternatives"*, we should keep in mind along with the generally accepted aims, i.e. publication of results crediting the work of the researcher and preparation of a sound basis for future research in the field, that the main task of all scientific activities is to provide correct information with minimum of false data.

Medicine was in its beginning more an art than a science. In ancient times, medication was based more on the faith than on the rationality. Although primitive tribes empirically got to know the relationships between the action (e.g., analgesic, narcotic, euphoric, diuretic, laxative) of natural substances and the physical and psychological condition of man, nevertheless they tried to free themselves from diseases by supernatural mystic remedies. Treating ceremonies and rituals, which *via* their magic strength led patients into ecstasy, would be defined today probably as placebo effects, a subjective psychological phenomenon accompanied by measurable influence on pathophysiological processes. At that time, the patient rather than the disease was in the centre of interest. Improvement of knowledge about the cause and pathological processes of diseases, and about the mechanisms of action of drugs, as well as the experimental methods and techniques that developed over the last two hundred years led to the replacement of the organism, organ and tissue by cell cultures in characterising pathological, therapeutic and toxicological processes. Consideration of the whole organism became less prominent and of course the personality of the patient has been neglected.

The life expectancy was more than doubled in the 20^{th} century. A significant part of this prolongation resulted from enormous improvement of pharmacotherapy. Even though more than 95% of the drugs used in current therapy were introduced in the last century, people all over the world are disappointed by the frequent helplessness of medicine. In spite of repeated futurological prophecies, science did

not succeed in discovering extraordinary drugs The overestimated belief in the omnipotent properties of drugs along with their overconsumption accompanied by side and toxic effects became the hotbed and hatchery for the expansion of unscientific therapeutic behaviour The providers of *"alternative"* treatment, some of them lacking relevant professional skill, are taking advantage of the diminishing belief in official medicine They however, exhibit not only a significant interest in the personality of the patient but as good businessmen, they manipulate his/her faith in the effectiveness and safety of herbal remedies compared to synthetic ones However, controlled clinical trials demonstrated in the last decades that many *alternatives* do not provide an effective choice (Ernst 1997, Wise 1997, Linde et al 1999, Ernst and Pettler 2000, Sutton 2001)

Nature supplies us with various biologically active substances Some of them are really *alternatives* to synthetic drugs The homo naturalis is inclined to associate the notion of artificial with dangerous and of natural with useful or healthy While refusing synthetic drugs, she/he bravely consumes everything which is of herbal and animal origin, perhaps not recognising that nature is producing also miscellaneous toxic substances Since some plants are toxic, only those could be consumed with clear conscience which had been already systematised, characterised and their dosage determined A plant-produced steroid, alkaloid, etc , like digitalis or muscarine might be both an effective drug and a poison Similarly as the chemist, nature tries to synthesise different substances The key difference is that those provided by the chemical expert and characterised by the pharmacologist, pharmacists and toxicologist are precisely targeted

During hundreds and thousands of years, at high cost in human lives were the effective and non toxic natural substances gradually selected from ineffective and toxic ones The use of the up-to-date scientific methods for selection and development of new drugs reduces the number of victims Thus however, the obtained drug loses its natural mysteric property The synthetic and the well defined drugs prepared from natural sources could hardly have *alternatives* in the highly toxic extracts, e g , from Amanita phaloides or bile of the Fugu fish On the other hand, infinite dilution of drugs or toxins resulting in homeopathics, are according to homeopathic literature only "energised" solvents (e g , distilled water, ethanol), without even a molecule of the effective or toxic substances They are said to have only "left" their traces in the solvent The problem with homoeopathy is not only that the "infinite dilutions" of the agents used cannot possibly produce, except for the placebo effect, any significant pharmacodynamic action There is also missing evidence which would prove the ability of homeopathics to influence significantly morbidity or mortality, and that in any part of the world, even where they are widely spread Homeopathy is an excellent test-case for the assessment of *alternative medicine*, since it is amenable to randomisation and double-blinding, the hallmarks of proper methodological evaluation of medical interventions In fact, it is more than that, it is also a blank control A randomised trial of "solvent only" versus "infinite dilutions" is a game of chance between two placebos It is unconceivable how such "therapy", which is scientifically implausible might be con-

sidered an *alternative medication* at the beginning of the 21st century, even in the industrialised part of the world. Recent double-blind randomised placebo-controlled studies comparing the action of homeopathics with that of placebos, in prophylaxis of migraine, in HIV infection, in delayed onset of muscle soreness, in trigeminal neuralgia, etc. found insufficient evidence that homoeopathy is clearly efficacious for any single clinical condition. Moreover, from the study sets investigated, there was clear evidence that studies with better methodological quality tended to yield less or no positive results (Vickers et al. 1997; Whitmarsh et al. 1997; Rastogi et al. 1999; Turp and Gobetti 2000).

The herbal remedy contains frequently the same effective substance as the synthetic one, only in a less exact dosage. Absolutisation of natural drugs may be essential for reaching some business people's goals and mystify the laymen. It is incredible that misleading of patients by uncontrolled disinformation, raising the placebo effect to a rank of effective therapy, brain-washing which jeopardises the patient's life in diseases (e.g., cancer, infections, heart attack) when delay may be fatal, remains without any sanctions. Moreover, on the market there are several homeopathics still containing effective concentrations of biologically active substances, and thus they are not homeopathics. It is important to remember that homeopathy neglects basic principles of medicine and therapy. These preparations are freely available in the market for human medication without controlled preclinical and clinical studies, without established effects and toxicity. In an era, when certificates are strictly requested not only for real drugs but also for food, and their quality, composition, efficacy and safety are permanently verified, the *"alternative medication"*, such as homeopathy, evades not only the generally accepted principles of therapy but also the law on the rights of consumers to know what they are consuming.

The second extreme *"alternative"* is the general substitution of *in vivo* studies, of experiments on tissues, organs and animals, by *in vitro* biochemical and biophysical methods and by simplified models in cell cultures for discovery and characterisation of the action and toxic properties of new potential drugs (Zbinden 1988; Prati et al. 1993; Adophe 1995; Horáková 1999; Schmuck 2001). These *alternatives*, introduced under the pressure of a misled general awareness, conceal as high a risk as homeopathy. Whatever is happening in randomised trials of homoeopathy might also happen in preclinical pharmacodynamic, toxicological studies and in randomised trials of allopathic medicine, especially when the stakes are high. It might be impossible to identify the real drug action and toxicity on the whole organism from a single cell because the thresholds of the sensitivity of receptors, second messengers, feedback and amplifying mechanisms in activation of effectors of various cells differ significantly. Our belief in the proposed mechanisms of drug action in trials could blind us to the possibility that the trial results may be wrong when false – positive or negative – findings are obtained. Even if we are seemingly penetrating into the basic principle, we are not allowed to extrapolate to the whole body, e.g., to explain heart arrest, reflex alterations of blood pressure, bowel atonia, malformations, etc.

These pitfalls highlight the essential problem which is at the root of the role of evidence in medicine: what is a fact? The answer, from fields as diverse as history and philosophy of science, has been remarkably similar: events become "facts" when they support a theory. *"Alternative"* provides the choice between things. Any one of the things to be chosen should substitute the other, and supplementation of one thing by the other has to yield the same result. Neither homeopathy as an alternative of allopathic medication nor *in vitro* studies as alternatives of *in vivo* studies meet this requirement. Thus not even the seemingly most suitable *"alternative"* approaches do fulfil the necessary demand, not to mentioning the improper ones. Experimental findings of scientists in biomedical disciplines, and experimental as well as empiric experience of clinicians, demonstrate that to reveal the placebo effect in homeopathies and to prevent the risk of a new Contergan affair requires a complex approach, which should include both the molecular, cellular and the tissue, organ, organism level

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