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SCIENTIFIC EVIDENCE IN COMPLEMENTARY MEDICINES

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TRADITIONAL CHINESE MEDICINE

The monumental theoretical edifice of traditional Chinese medicine (TCM) cannot be neglected by anyone seeking to practice the art of medicine, but will continue to take a back seat whenever attempts are made to furnish convincing scientific explanations of the mechanisms of action involved and make efficacy assessments. The following chapter will address only the subject of acupuncture and the related technique of moxibustion, excluding any mention of traditional phytotherapy (which, moreover, is an integral part of TCM). Three reviews of Chinese phytotherapy have been included in the bibliography (Chan, 1995; Zhu *et al.,*1995; Ergil and Kramer, 2002).

Mechanisms of action of acupuncture

Acupuncture-moxibustion is a complex treatment system, whose action is due to several mechanisms, which can be broadly classed under the following three headings:

- neuroendocrine regulation;
- reflex action;
- analgesia.

The sheer scale of this definition accounts, on the one hand, for the large number of indications for which acupuncture-moxibustion is proposed, and, on the other, for its intrinsic limitations. A good patient response to this therapy, in fact, is likely to require the integrity and efficiency of various neuroendocrine mechanisms.

Neuroendocrine regulation

Assays carried out during electro-acupuncture performed for analgesic purposes have demonstrated an increase in beta-endorphins in plasma (Abbate *et al.*, 1980), and in cerebral beta-endorphins, metenkephalins and leu-enkephalins, as well as in dynorphins in cerebrospinal fluid (Sjolund *et al.*, 1977). A typical antiprostaglandin effect consisting in a lowering of plasma concentrations of potassium ions, histamine and bradykinin (peripheral blood) has also been described (Zhang Xiangtong, 1986). Whereas to date little is known about the effect of acupuncture on prostaglandins and

thromboxanes, our knowledge of the relationships between acupuncture and *endogenous opiates* is fairly good.

Endorphins, enkephalins and dynorphins are known to be produced by the cells of many tissues. They control (stimulation, inhibition, modulation, integration) many functions of the body, such as endocrine secretions and visceral activity rhythms (e.g. release of oxytocin by the neurohypophysis, digestive tract peristalsis, lymphocyte activity, cardiac and respiratory rhythms, uterine response to oxytocin stimulation, etc.) (Gessa *et al.*, 1987).

The effects of acupuncture on a series of body functions (nervous, endocrine, immune, cardiocirculatory, digestive, urinary) are probably due to variations in plasma or tissue levels of opioid substances or other mediators. For instance, traditional acupuncture is capable of increasing the beta-endorphin content of mononuclear cells of peripheral blood and of affecting (increasing) mitogen-induced lymphocyte proliferation (Bianchi *et al.*, 1991; Petti *et al.*, 1998).

Apart from the effects on levels of endogenous opiates, various studies have investigated other endocrine responses to acupuncture (Qi-Wen Xie, 1982).

- At the level of the *hypothalamus* and *posterior hypophysis*, acupuncture induces depletion of neurosecretory granules in the supraoptical nucleus and secretion of oxytocin.
- At the level of the *anterior hypophysis*, in addition to the above-mentioned gonadotropin modulation, acupuncture induces the secretion of prolactin and ACTH.
- At the level of the *thyroid*, reductions in thyroid volume and in increase in thyroid activity (with depletion of colloid substances in the follicles) have been observed in patients suffering from endemic goitre treated with acupuncture. The opposite effects are believed to be observed in the case of hyperfunction.
- At the level of the *adrenal cortex*, acupuncture induces an increase in cortisol secretion. Experiments in rats have shown that this effect is modulated by sex hormones: testosterone in the male and the follicular phase of the cycle in the female reduce the corticosteroid response to acupuncture.
- At the level of the *female gonad*, the action of acupuncture is probably due to gonadotropin modulation. In particular, evidence has been found for a reduction in oestrogen secretion in cases of hyperoestrogenism.

Reflex action

The reflex therapy theory claims that reflex responses can be triggered in the body using superficial stimuli of various types (acupuncture-moxibustion, massage, digital pressure, joint mobilisation, vertebral manipulation). Various studies have shown correlations between the paths of acupuncture meridians, head dermatomeres and Jarricot reflex dermalgia zones (Bossy, 1986). There is also a good measure of correspondence between trigger points and a number of acupuncture points (Melzack *et al.*, 1977).

The acupuncture stimulus is believed to travel along a reflex arc: sensory afferent - posterior horn of the spinal cord – anterior horn – motor efferent (visceral or somatic) – target organ. This simple basic scheme is actually complicated by interference with and by superior levels of the nervous system, the description of which goes beyond the scope of this study.

It is likely, moreover, that the neuromediator theory (outlined in the section “Neuro-endocrine regulation”) and the reflex-therapy theory can be integrated in a single scheme. One should therefore be talking not about the mechanism but about the mechanisms of acupuncture-moxibustion. For example, the anti-inflammatory effect obtained in the rheumatological field is probably the combined expression of the effect of acupuncture on the autonomic nervous system, on the local circulation, on cell immunity and on the endocrine system (Zhang Xiangtong, 1986).

In any event, as regards the visceral reflex effects of acupuncture-moxibustion mediated by the autonomic nervous system, sympathomimetic, parasympathomimetic or parasympatholytic effects on the cardiovascular system of the dog have been reported according to the point stimulated (Do Chil Lee *et al.*, 1976). Other animal experiments have demonstrated an effect on the respiratory (rhythm, bronchiolar diameter), digestive (peristalsis, secretions), and urinary (renal filtration, ureteric peristalsis, bladder detrusor performance) as well as on metabolism (Zhang Xiangtong, 1986).

Analgesia

The analgesic action of acupuncture (which has been used both in the field of surgical anaesthesia, sometimes with spectacular results, and in that of acute and chronic pain therapy) is due to a combination of central and peripheral mechanisms (Han *et al.*, 1982; Bossy, 1986; Zhang Xiangtong, 1986; Shen, 2001).

Schematically, the various levels involved are:

- **spinal cord:** the acupuncture stimulus, conducted along the large A-beta fibres, activates the inhibitory interneurons of the spinal reticular formation, which operate a blockade (postsynaptic) of the neurons of the dorsal horns, from which the paleo- and neo-spinothalamic ascending bundles originate;
- **medulla oblongata:** the acupuncture stimulus, via the ventrolateral bundle, reaches the reticular formation of the medulla oblongata, from which depart descending signals that partly inhibit the thin afferent pain fibres (A- and C-delta) leading to the spine (presynaptic inhibition);
- **midbrain:** the acupuncture stimulus, after reaching the midbrain reticular formation, induces a descending inhibitory signal to the dorsal horns of the spinal cord and a direct ascending inhibitory signal to the parafascicular nucleus of the thalamus;
- **neuromediators:** as mentioned above, acupuncture causes an increase in cerebral beta-endorphins and enkephalins and an increase in dynorphins at CSF level. Acupuncture analgesia is partly inhibited by naloxone and also by pharmacological blockade of acetylcholinergic receptors. An increased cerebral serotonin content (serotoninergic tone) enhances acupuncture analgesia, as does pharmacological blockade of adrenergic receptors. The analgesic response to acupuncture is therefore conditioned by an important array of individual factors (serotoninergic tone, endorphin response, inhibition of adrenergic tone);
- two other factors are involved in acupuncture analgesia: as mentioned earlier, acupuncture may reduce the concentrations of potassium ions, histamine and bradykinin (algogenic substances) in peripheral blood; what is more, psychological factors may undoubtedly play a role in raising the pain threshold in patients receiving acupuncture treatment, but the efficacy of this therapy in the veterinary field rules out any possibility that this role may be decisive (Vierck *et al.*, 1974).

In a nutshell, then, the pain signal, after entering the central nervous system, has to travel a considerable distance to reach the cortex; in its path the posterior horn of the spinal cord and the parafascicular nucleus of the thalamus are probably two key centres that receive and transmit pain sensations. On the other hand, a number of

CNS centres, when excited, are capable of inhibiting the transmission and reception of pain signals. These centres are the caudate nucleus, the mesencephalic periaqueductal grey matter, the nuclei of the raphe magnus and their ascending and descending pathways. The acupuncture signal probably acts by improving the performance of this inhibitory system (in which the endorphinergic neurons play a fundamental role) and its effects on the parafascicular nucleus of the thalamus and on the dorsal horn of the spinal cord.

Efficacy assessment

Clinical research on acupuncture-moxibustion has developed since the late ‘sixties in China, where an enormous number of non-randomised, uncontrolled clinical studies have been conducted regarding a wide range of diseases. These reports are still of substantial interest today, particularly as preliminary or pilot studies, but cannot considered reliable or exhaustive as regards their ability to demonstrate efficacy.

The ‘eighties and ‘nineties witnessed a world-wide expansion of knowledge in the field of clinical epidemiology and, as a result, controlled clinical trials began to be conducted and published also in the field of acupuncture-moxibustion.

A review published by the *British Medical Journal* (Tang *et al.*, 1999) analyses the quality of 414 randomized controlled trials published in Chinese scientific journals and concludes that the quality is generally poor owing to a lack of blindness, of medium- and long-term follow-up, of intention-to-treat analyses, and of data on compliance and side effects. In addition, the vast majority of these trials report positive results, suggesting a strong publication bias.

Vickers and co-workers (Vickers *et al.*, 1998) queried whether only positive results are published in certain countries, given that, in a selection of 252 acupuncture trials, they found that all those conducted in China, Japan and Hong Kong reported findings indicating therapeutic efficacy. The same authors also postulate a publication bias and invite those engaged in systematic reviews to bear this possibility in mind, whenever dealing with data from such countries.

In the western world, on the other hand, only a few research centres have invested funds and energy in clinical research on acupuncture-moxibustion. Consequently, the trials conducted in western countries are still very limited in number and vary very considerably in quality, although, in recent years, they have tended to show a distinct

improvement. An important sign of this tendency has been the *JAMA* edition devoted entirely to trials of complementary and alternative medicine, which included a trial of ours on the efficacy of moxibustion in obstetrics (Cardini *et al.*, 1998).

The very limited number of published trials and, above all, the mediocre quality of a substantial proportion of them, mean that there are still very few systematic reviews of acupuncture-moxibustion and that such reviews as there are often hang judgement, concluding that further well-designed studies are needed in order to furnish a reliable assessment of efficacy (Vickers, 1996; National Institutes of Health, 1997; Chen, 1997; Van Tulder *et al.*, 1999; White and Ernst, 1999; Smith *et al.*, 2003).

What we have said so far reveals the need, on the one hand, to channel more resources into the field of clinical research on acupuncture-moxibustion, and, on the other, to improve the quality of clinical trials in this field. The methodological problems involved in this latter undertaking are by no means easy to solve. The scientific debate is focused on what kind of placebo has to be used in comparison with acupuncture, on how the individualisation of acupuncture therapy can be safeguarded in trial protocols and on how the efficacy of the multiformula phytotherapy preparations typical of the Chinese tradition can be assessed in clinical trials. The Traditional Medicines Programme of the World Health Organisation is currently preparing an update of the methodological guidelines for research into traditional medicine.

With regard, lastly, to the indications for acupuncture therapy of proven efficacy, it may be useful to quote the conclusions reached by the Consensus Conference organised by the American National Institutes of Health (National Institutes of Health, 1997): "*promising results have emerged with the use of acupuncture in the treatment of post-operative and post-chemotherapy nausea and vomiting (and probably also in the nausea of pregnancy), of post-surgical pain in adults and of post-operative dental pain. There are also a number of other conditions, such as drug addiction, post-stroke rehabilitation, headache, dysmenorrhoea, tennis elbow, fibromyalgia, muscle fascia pain, osteoarthritis, low back pain, carpal tunnel syndrome and asthma, for which acupuncture may be useful as an adjunctive treatment or as a reasonable alternative or, even, as a complementary measure in a multifactorial therapy plan. It is likely that further research will succeed in identifying new areas in which acupuncture treatment may prove useful".*

Discussion and critical evaluation

TCM includes modalities such as acupuncture, moxibustion, massage, a traditional pharmacopoeia, and indications as to diet and lifestyle. This ancient and complex form of medicine has been described here only summarily and in terms of its main aspects. The texts from which these medical practices and experiments originated and which constituted the empirical basis for them date back to time immemorial and today are hardly amenable to any kind of verification of reliability. Among the main aspects of TCM theory, the concept of “energy”, which is one of its cornerstones and is deeply rooted in its theoretical and philosophical fabric, has been presented in its original meaning of “breath of life” or “*Qi*”. It should be noted that this way of using the concept of energy, typical of Chinese medicine, poses serious problems of integration with our scientific physicochemical language, where “energy” represents a *physical parameter* (meaning the ability to perform a certain amount of work), measurable in discrete quantities (Joules). Moreover, according to the theory of relativity, energy equals mass multiplied by the speed of light squared, but it is hard to see in this anything more than a remote analogy with Chinese philosophical thought.

Also the fact that man is an open energy system, closely connected to the surrounding environment with which he interacts in an incessant exchange of energy, is indisputable and, perhaps for this very reason, constitutes a very general, almost self-evident affirmation, barely amenable to scientific investigation. Various “laws” of the Chinese system (Yin-Yang, five elements, emptiness-fullness, etc.) and its complex anatomico-physiological relationships constitute an integral, self-referencing system, which the physician seeking to learn the rudiments of TCM must necessarily take on board as intrinsically valid, if he is to correctly administer any kind of therapy (identification of specific acupoints, prescription of drugs and diets). We should also add there has been no lack of attempts to explain acupuncture on the basis of anatomico-physiological correlates (nerve reflexes), but these hypotheses account only to a very limited extent for the therapeutic effects of TCM in its various fields of application.

One positive aspect of this traditional medicine is semeiology (observation of the patient, palpation, observation of tongue, etc.): this subtle ability to assess the clinical status by simple, non-invasive means is at serious risk of being lost in our high-tech

western medicine. The theory and diagnostic-therapeutic system of TCM are expressly analogical and therefore cannot be catered for by any precise definition of cause-and-effect relationships, though this does not prevent the results from being evaluated by appropriate statistical methods. There have been many clinical studies, but most of these have failed to provide concordant results, amongst other things on account of the difficulty of implementing rigorous double-blind protocols. The efficacy of acupuncture in the long list of diseases, that are often mentioned in the books of Traditional Chinese Medicine, cannot be said to be proven according to the strict criteria of evidence-based medicine. For the indications of proven efficacy the reader is referred to the scientific evidence and in particular to the conclusions of the cited National Institutes of Health Consensus Conference.

Clinical research on acupuncture poses unique methodologic challenges. In recent reviews (Mayer, 2000, Kaptchuk, 2002) the evidence for the efficacy of acupuncture is examined and the conclusion reached is that acupuncture is indisputably valid for the treatment of postoperative and post-chemotherapy nausea and vomiting, and is probably also useful for headache, low back pain, alcoholism. It reduces postoperative pain, the analgesic requirement, and opioid-related side effects after both upper and lower abdominal surgery (Kotani et. al., 2001). Acupuncture analgesia also reduces the activation of the sympathoadrenal system that normally accompanies surgery. There are some reports, but not convincing evidence, of the efficacy of acupuncture in treating asthma (Martin et al, 2002) and to improve motor recovery after stroke (Sze et al, 2002). There is no clear evidence that acupuncture, acupressure, laser therapy or electrostimulation are effective for smoking cessation (White *et al.*, 2002). Properly performed acupuncture seems to be a safe procedure (Kaptchuk, 2002).

The field is still wide open to clinical and experimental research. Basic-science research provides evidence that begins to offer plausible mechanisms for the presumed physiologic effects of acupuncture. The neurophysiological correlates of acupuncture (beta-endorphins, reflexes, postsynaptic block) are beginning to provide convincing explanations for the therapeutic effects of acupuncture, though they are still only very partial hypotheses limited to the area of pain therapy. Multiple research approaches have shown that acupuncture activates endogenous opioid mechanisms. Recent data, obtained by using functional magnetic resonance imaging, suggest that

acupuncture has regionally specific, quantifiable effects on relevant brain structures (Zhang *et al.*, 2003).

One final note of caution is in order regarding herbal drugs of Chinese origin, for which the recommendations to be made for western phytotherapy hold good, all the more so in view of the risk inherent in the fact that the raw materials of these products are subject to less thorough control as regards the presence of toxic or contaminating substances. Undeclared conventional western drugs such as the non-steroidal anti-inflammatory and antihistamine drugs, steroids and oral hypoglycaemic agents are frequently added to Chinese herbal medicines (Kam and Liew, 2002). The constituents of the herbal products can cause adverse effects.

At the time of writing (sept 2003), the PubMed database of the National Library of Medicine reviews 8488 papers on Chinese medicine and 8564 papers on acupuncture.

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AYURVEDIC MEDICINE

Scientific evidence

Scientific research on Ayurveda has developed only in the past few decades. There are a number of good specialist scientific journals on the subject and occasionally articles are published in prestigious journals such as *JAMA* or *The Lancet*. Most of the studies are conducted in India, but there is no lack of western researchers, including top level ones, who in recent years have shown an interest in the study of Indian plants and the remedies prepared with them.

Broadly speaking, we can say that the main lines of research in the field are the following:

- research on the fundamental principles of Ayurveda in order to verify their scientific basis;
- research on the plants used in Ayurveda and on Ayurvedic preparations in order to verify their therapeutic efficacy in specific disorders;
- research on the antioxidising and anti-aging effects of a number of special Ayurvedic compounds, mentioned above, called *Rasayana*. This line of research has been developed most notably outside India, and is of particular interest on account of its value in preventive medicine;
- research on the non-pharmacological therapies of Ayurveda. There are, for instance, hundreds of scientific studies on transcendental meditation, conducted mainly in the United States, which document its usefulness as an adjuvant antistress method in the treatment of nervous and cardiovascular disorders, such as arterial hypertension.

Scientific research into Ayurveda, however, finds itself faced with a by no means indifferent set of problems. As regards the first of these main lines of research, it should be borne in mind that the Ayurvedic system is based on a model of thought which is very different from the dominant model today (Mishra *et al.*, 2001; Chopra and Doiphode, 2002). Vedic civilisation, with its values, language, philosophy and science is light years away from our modern world. To study Ayurveda and conduct research into it one has to approach that other world, enter into its mentality and understand its technical language. As regards clinical research on Ayurvedic

preparations, however, one serious problem consists in the fact that the Ayurvedic remedies are often very complex formulae, sometimes comprising dozens of ingredients and it is therefore difficult to isolate the individual active components. The western researcher, who is accustomed to testing the efficacy of single molecules, is inevitably disoriented when faced with a formula containing 20 to 30 different ingredients. Even when he has proved its efficacy, he will find it very hard to establish what the active components of the compound actually are.

Clearly, then, if we want to conduct serious research into Ayurveda, our study criteria must be geared to the Ayurvedic method, in the sense that they must necessarily take into account the very special nature of the subject under investigation.

Discussion and critical evaluation

The general principles enunciated by Ayurveda, such as the need for a treatment that takes into consideration all the relevant aspects (psychological, physical and environmental) of the person and the strong emphasis laid upon prevention, meaning prevention not only in terns of an early diagnosis, but also in terms of the balance between man and his environment, are principles that can be shared by all physicians and that should be an integral part of any therapeutic approach. It should also be acknowledged that, in medical practices of oriental origin, the methodologies deriving from these principles are coherent with them, whereas in the West they have often been set aside precisely on account of the emergence of apparently curative methods and instruments, irrespective of any reference to such ideal principles. The fact that Ayurveda teaches you to live better, eat better, respect the proper timing of activity and rest, and engage in the right amount of physical exercise bears witness, in no uncertain terms, to the merits of this method and of the physicians who practice it.

In eastern schools of medicine, and particularly in Ayurveda, one sees that the aim of finding methods, medicines and therapeutic practices that ensure the preservation of health is pursued by means of the elaboration of complex theories and equally complex pharmacopoeias and/or physiotherapy and rehabilitation practices. It should also be noted that, as is the case with other forms of complementary and alternative

medicine, in Ayurveda, too, different schools have developed, variously conforming to the original doctrine. The latter is currently interpreted by Maharishi Ayurveda.

The Ayurvedic theory of the three *Doshas* and the five *Mahabhutas* is based on an empirical-analogical-philosophical approach and not on observation, verifiable hypotheses or calculation. A further element that the western medical mindset finds it hard to accept consists in the fact that many assessments of the physiopathological condition of the individual, in addition to being based on theories for which there are no western equivalents, use a qualitative and not a quantitative touchstone. “Qualities” may be hard to assess by those who are not endowed with particular observation skills, which in turn require a long period of basic training within the framework of the corresponding medical discipline. To understand the diagnostic methods used in Ayurveda thoroughly one needs to make an effort to enter into the logic of the system.

The purpose of these considerations is not to confute the Ayurvedic doctrine but to present the objective difficulties encountered in learning it. What astonishes the external observer is that a system of medicine dating back over two thousand years and, moreover, one which is an intrinsically difficult, “closed” system, in the sense that it is characterised by a high degree of self-referencing, should have met with approval in the West and that it should be establishing itself amongst both the public at large and amongst prescribing medical practitioners. The recent revival of this system, both in India and in Europe and the United States, indicates that it meets a perceived need which otherwise has not been satisfied by modern scientific medicine. This does not in any way constitute proof of the efficacy and appropriateness of the treatments, but merely provides a framework that accounts for its wide-scale popularity.

It is for this reason that we should view favourably those attempts to furnish a scientific and not merely a metaphorical explanation for the alleged medicinal effects of the Ayurvedic formulations (such as, for instance, the positive effects of mixtures of antioxidants contained in high concentrations in Ayurvedic phytotherapeutic preparations) (Scartezzini and Speroni, 2000) and the attempts to provide objective evidence of the benefit of practices such as meditation (Edwards, 2003; Canter, 2003).

Most authors rightly emphasise both the fact that scientific research is highly desirable and useful and that, with the “modern” approach, there is a risk of

neglecting a number of more subjective, but also more characterising traditional aspects of the method. Here, too, one is faced with a dilemma, which bedevils many non-conventional forms of medical practice from other cultures and consists in striking a balance between, on the one hand, integrating Ayurveda and modern medicine, with an inevitable watering-down of the original inspiration, and, on the other, the desire to conserve a strong measure of identity, which would tend to accentuate the “alternative” character of the Ayurvedic medical system. In view of the fact that it is so hard to reconcile the oriental concepts of disease, diagnosis and therapy with those prevalent in the west, it would appear to be of the utmost importance to consider the Ayurvedic approach as a complementary one and not as a substitute for western therapies that have quite clearly proved effective.

The principle underlying the use of very large numbers of phytotherapy preparations has not been illustrated here for reasons of space. As regards Ayurvedic phytotherapy, the same precautions need to be taken as already mentioned in relation to similar western and Chinese preparations, bearing in mind that, in this case, too, there is no lack of reports of adverse effects associated with misuse, wrong dosing, or the presence of contaminants such as heavy metals (Ernst, 2002). This serious problem is properly addressed in this chapter. In the case of Ayurvedic herbal therapeutic agents, as with other plant derivatives, there is also the recently emerging problem of possible interactions with conventional drugs. A review of this topic was recently published in *The Lancet* (Fugh-Berman, 2000). There is an urgent need for the practitioners of the allopathic and non-allopathic systems to work together to optimise the risk-benefit profile of these medicines (Gogtay *et al.*, 2002). The PubMed database of the National Library of Medicine currently reviews 914 publications on Ayurvedic medicine and 410 publications on the therapeutic effects of transcendental meditation.

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NON-CONVENTIONAL BIOELECTRONIC DIAGNOSTIC TECHNIQUES

Scientific evidence

During the last few decades, many unconventional bioelectronic diagnostic procedures have been proposed (Voll, 1975; Tsuei *et al.*, 1984; Krop,*et al.*, 1985; Ionescu-Tirgoviste and Pruna, 1990; Fuller-Royal *et al.*, 1991; Fox, 1991, 1993; Schimmel and Penzer, 1996). A variety of electrodermal devices (i.e. Dermatron®, DRIA®, Vega® devices) are commercialised and used. Those procedures, based on electrical skin responses, are probably the most commonly unconventional tests used to diagnose allergies. However, scientifically based research to support the efficacy of these procedures still lacks.

Electrodermal tests are based on the hypothesis that the disease states are associated with measurable variations of the cutaneous electric potential at specific acupuncture points. Altered skin potentials at acupuncture points would indicate an "electromagnetic perturbation" transferred by untolerated substances (even in sealed vials) to the patient.

There is no strong scientific evidence regarding these electrodermal bioelectronic techniques: most of publications in this field have appeared in journals that are not officially indexed and reviewed or books. Research studies on allergies and food intolerance have compared the results obtained with bioelectronic techniques with those obtainable with the Cyto test (another method not validated by official science), with trigger-test and with the Prick-test. Double-blind studies have given either positive (van Wijk and Wiegant, 1994; Krop *et al.*, 1997) or negative (Lewith *et al.*, 2001; Semizzi *et al.*, 2002) results, as regards the reliability of these tests in diagnosing allergies.

Discussion and critical evaluation

The bioelectronic techniques of the type presented in this chapter are the expression of the fusion, at a very preliminary stage, of concepts deriving from

Chinese acupuncture, homeopathy and homotoxicology, on the one hand, and scientific and technical knowledge of bio-electromagnetism, on the other. For this reason, they constitute a system whose use calls for extreme caution and which must never be regarded as an alternative to conventional diagnostics. Electrodermal testing (ED testing) is an acupuncture-based approach and was developed to refine homeopathic prescriptions. It is currently being used to advise patients about their "allergies". The evidence for its use in "allergy testing" is limited and often misrepresented (Lewith, 2003). The medical applications of appliances such as those described here are viewed by official medicine, at best, as something belonging to the sphere of science fiction and, at worst, as a form of quackery (a hasty but very common judgement).

In any case, there is every reason to regard as plausible some of the “claims” made for bioelectronic medicine as developed in the complementary and alternative medicine field. The assumption on which the functioning of bioelectronic appliances is based is that the state of disease is detectable as a pathological bioelectric reaction to perturbations induced by contact with chemicals or with electromagnetic fields (exogenous or endogenous). Owing to their low intensity and non-localisation, these signals are thought to come into play at very extensive, global levels of electromagnetic homeostasis systems and thus permit assessment of the bioelectric dynamics of the body in a global or holistic manner. It is in the context of these issues that we should place the attempts being made to develop sensitive, versatile bioelectronic methodologies, capable of helping the doctor to identify functional imbalances associated with the various diseases.

There have been a number of preliminary studies on the diagnostic and therapeutic applications of various appliances of this type, though little research has been done on the levels of specificity and sensitivity of these tests. This is a field of study in which there is undoubtedly a great deal to discover on a frontier linking areas such as complexity, molecular biology and electromagnetism to other areas recently brought to light by immunology, neurobiology and biophysics. Therefore, if the field of use of such appliances were to be defined with a greater measure of certainty, they would probably offer the prospect of providing a further diagnostic aid for the general practitioner and the clinician.

Despite the positive results reported by various authors, many aspects of the methodology of electro-acupuncture according to Voll (EAV) and its related

techniques are still uncertain, as is its electrophysiological and biophysical basis, with the result that the possible diagnostic applications must still be regarded as experimental and hypothetical.

The main problem with the use of these appliances lies in the interpretation of the results in diagnostic terms, in that bioelectronic investigation of the human body has been developed to date substantially with regard to individual segments (heart, brain, muscle, etc.), but has yet to be codified in terms of electrical conduction according to the parameters measured with these check-up appliances. Therefore, the aim of current research is to compare the results furnished by these tests with clinical data obtained with conventional procedures in order to establish the reliability of the diagnostic response.

The most controversial issue has to do with the role of the operator performing the test: the question is whether he or she is only an observer or whether he or she may participate in some way in the procedure as a whole (e.g. by altering the patient's electric field or by taking measurements with different pressure on the electrodes according to expectations or other subconscious factors).

Bioelectronic procedures such as those described here should in no way be regarded as substitutes for other consolidated diagnostic methods, but should be viewed rather as means of offering the chance of a functional, dynamic assessment of the bioelectrical phenomena related to the exogenous and endogenous perturbations of the body as a whole and in all its complexity. In other words, they should be used with a great deal of caution: on all occasions the diagnostic "response" should be compared with other monitoring parameters and, above all, these procedures should be used in conformity with a rigorous clinical rationale.

Much of the literature in this field consists of books or publications in non-indexed journals. The PubMed database of the National Library of Medicine currently reviews only 10 papers on electro-acupuncture according to Voll, 6 papers on the Ryodoraku method, and 1 papers on the VEGA test. There are many studies on electro-acupuncture but these refer to therapy and not to diagnosis.

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CHIROPRACTIC

Scientific evidence

The aim of most of the scientific research on chiropractic or vertebral manipulation is to assess improvement, if any, in terms of pain symptoms after a course of manipulative therapy. This has involved the use of questionnaires, the basic purpose of which is to define the nature of the disability and/or pain before and after the manipulative therapy. Clearly, then, statistical objectivity in such research is much more complex and harder to achieve. Moreover, it is important to recall that almost all the studies conducted in an attempt to assess the efficacy of chiropractic have considered this discipline not in its entirety as a complex of aids to diagnosis and therapy, but have identified it solely with the act of manipulation as an end in itself.

Efficacy

Most of the research studies reported in the literature and regarded as being of a certain importance have to do with low back pain (LBP) in its acute and chronic forms. As regards the studies on the acute forms (less than 3 weeks), several of them have demonstrated excellent resolution with the use of manipulation, but these same studies have been promptly criticised in the most authoritative meta-analyses, due to the fact that acute low back pain is associated with a high rate of spontaneous resolution. It should be remembered, however, that there are no studies of substance assessing the difference between 5- or 10-year recurrence rates in patients whose lower back pain has been left to resolve spontaneously, or at most with the prescription of analgesic drugs, and those who have undergone manipulation as a curative and preventive therapeutic approach. The area in which the literature presents the most relevant data is that of subacute-to-chronic spinal pain (over 6 weeks) which is associated with a low spontaneous resolution rate.

Among the thousands of studies published in various international journals we will mention here only a few of the most critical, objective and generally accepted ones. Abenhaim examined 21 randomised trials with acute and subacute back pain by electromyography (EMG) and assessment of the degree of movement as well as the extent of the pain. On average, a positive short-term effect was observed, whereas

the long-term effects still need to be defined (Abenhaim and Bergeron, 1992). Aker reviewed 24 trials on manipulative treatment of neck pain and reached the conclusion that the efficacy of such therapy for neck pain can be confirmed (Aker, 1996). Anderson, in a review of 23 trials with more than 3000 cases of LBP, concluded that it was possible to assess variations in the range of movement, as well as pain scores and return to work; manipulation appeared to be more effective than the comparator treatments (Anderson *et al.*, 1992). Koes *et al.* (1996) performed a systematic review of randomized clinical trials to assess the efficacy of spinal manipulation for patients with low back pain. Thirty-six randomized clinical trials comparing spinal manipulation with other treatments were identified, most of them were of low methodological quality. Nineteen studies (53%) showed favorable results for chiropractic manipulation. In addition, five studies (14%) reported positive results in one or more subgroups only. Among the five best studies, three were positive, and two were positive only for a subgroup of the study population. There certainly are indications that manipulation might be effective in some subgroups of patients with low back pain.

Important guidelines for the treatment of low back pain were presented by the Royal College of General Practitioners in the U.K. in 1996 (Weddel *et al.,* 1996). They report a fair amount of interesting data: vertebral manipulation, compared with physiotherapy, rest, medical therapy, orthopaedic corsets, and corrective exercises, appears to be much more effective in the first 6 weeks after onset of LBP. The guidelines, which are distributed to general practitioners throughout the U.K., therefore also suggest the use of vertebral manipulation as a therapeutic approach for spinal pain. The study also shows that the risk of complications is very low, if the manipulation is done by qualified chiropractors. The same study describes as ineffective or harmful the use of lumbar traction, opiates and steroids, bed-rest, manipulation under general anaesthetic, plaster casts, ionophoresis and ultrasound treatment.

Often regarded as one of the most important and authoritative trials (in that it is the one with the largest number of patients, in conjunction with a rigorous methodology and statistical analysis, and the only one to have investigated not only manipulation, but also chiropractic as a whole) is the study published by the *British Medical Journal* comparing chiropractic with hospital physiotherapy in 741 patients over a 3-year period (Meade *et al.*, 1990; Koes *et al.*, 1992). It concludes with statistically

significant evidence in favour of chiropractic in terms of pain scales at 6, 12 and 24 months ($P < 0.01$). At 6 weeks, a substantial improvement in Lasegue test scores was noted as compared to the control group ($P < 0.05$) and time off work was 21% in the chiropractic group as against 35% in the group treated with hospital physiotherapy.

Risks

Another area in which the literature data are illuminating is in the assessment of the risks of chiropractic. The risks most commonly analysed are those relating to circulatory complications (above all with regard to the cervical spine) and joint and bone injuries.

The total number of documented cases of *circulatory deficits* due to vertebro-basilar insufficiency as a result of manipulation over the period from 1947 to 1993 was 165. Of these, only 92 (55%) were the result of manipulations performed by chiropractors; in the other 73 cases the manipulations were done by doctors, osteopaths, physiotherapists, barbers, etc. (Assendelft *et al.*, 1996).

The risk of vascular accidents has been estimated, in the various analyses, as being of the order of one case in a million cervical manipulations (Assendelft *et al.*, 1996); thus, as confirmed by Calman in the *British Medical Journal*, the risk may be regarded as negligible (Calman, 1996). Moreover, it is now accepted practice, in medicine, that greater weight is attached to the relative risk, and thus, in this case, the risk of manipulation compared to that of the other therapies used. For example, a realistic comparison would be one between manipulative therapy and drug therapy. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in musculoskeletal disorders has been estimated as possibly leading to complications defined as serious (haemorrhage and/or gastric perforation) in approximately 1000 patients per million (Langman *et al.*, 1994). On comparing manipulation with spinal surgery, it goes without saying that the sum of the risks of the anaesthesia and the surgery itself leads to a relative risk substantially higher than 1 case in a million (Coulter *et al.*, 1996).

The other potential risks of manipulation considered in the literature are those of *articular or periarticular injuries*. The cases reported world-wide in the literature from 1925 to 1993 amount to 56, only 6 of which occurring in the last 20 years of that

period. Of the total of 56 cases, only 14 had received manipulative treatment at the hands of chiropractors (Terrett, 1995; Assendelft *et al.*, 1996).

As regards *accidents affecting the intervertebral discs,* no data on this topic have yet been published in the literature. We know, however, that, on account of its characteristic morphological features, a healthy lumbar intervertebral disc withstands up to 22° rotation-torsion before any signs of yielding of the annular structural fibres are detectable. A degenerate disc (i.e. a disc characterised by herniation, protrusion, dehydration, or degenerative disc disease) is capable of withstanding 14° rotation-torsion. Owing to the particular conformation of the articular (e.g. lumbar) facets, the maximum segmental rotation permitted during manipulation is 2-3° beyond that at which the anatomical bone barrier intervenes, which therefore can never be exceeded (Farfan *et al.*, 1967; Cassidy *et al.*, 1993).

Clearly, then, any such corrective manoeuvres should be performed with a wide safety margin and all due concern for tissue integrity. In addition, no post-manipulative accidents have ever been reported which could be attributed to a more or less accentuated degree of spondyloarthrosis or osteoporosis. We can therefore conclude that such conditions of the spinal column are not absolute contraindications to vertebral manipulation. It is, however, important to bear in mind that the type of manipulation is decided on the basis of the experience and sensitivity of the therapist, who, of course, must be able to differentiate clearly between one case and another, selecting the most appropriate intervention technique and carefully assessing all the elements available.

Cost:benefit ratio

Several studies have focused on an analysis of the cost:benefit ratio of chiropractic therapy (Carey *et al.*, 1995; Dagenais and Haldeman, 2002). These have constituted one of the basic criteria in the process of the recognition and regulation of chiropractic in numerous states. The role and position of chiropractic care in the health care system must be transformed from being alternative and separate to alternative and mainstream. This transformation requires that chiropractic services become integrated in the many health care delivery organizations that collectively constitute the health care system.

Elements basically in favour of chiropractic in terms of a reduction in health costs are:

- a more rapid return to work after convalescence;
- a saving in drug costs;
- a drastic reduction in the use of various forms of physiotherapy;
- a distinct reduction in recurrences.

It is therefore worth citing here one of the main research studies in this connection: the most complete study assessing efficacy in relation to cost is the one conducted by Manga, a Canadian expert in medical economics, who examined cost elements and evidence in this sector in various states such as Great Britain, the United States and Canada and came to the conclusion that: *"If the treatment of low back pain were to be transferred from the sphere of traditional medicine to that of the chiropractic approach, there would be a significant reduction in costs. Indeed, the cost data suggest a potential saving of hundreds of billions per year. We should recall that spinal pain is the second most common cause of time off work, second only to 'flu-related bronchitis"* (Manga *et al.,* 1993). Many of the conclusion's of this study were taken on board by the Royal College of General Practitioners in the U.K., who, after a thorough analysis of the literature, came out openly in support of the use of chiropractic.

Discussion and critical evaluation

Chiropractic is now more than a century old, and it is licensed throughout the United States and Canada and recognized in more than 60 countries worldwide. Doctors of Chiropractic receive training that is focused on the treatment through manual and physical procedures, such as manipulation, massage, exercise, and nutrition. Most patients present to chiropractors with low back pain, neck pain, whiplash, and headaches. Many original clinical trials and several review papers have come to the conclusion that manipulation is safe and effective for the treatment of these conditions and particularly for low back pain. (Cooperstein *et al.*, 2001; Dagenais and Haldeman, 2002).

This method makes use of a detailed knowledge of normal and pathological anatomy of the locomotor system and has its own semeiology based on traditional principles; the basis on which it rests is strictly mechanistic. The use of manipulative techniques, moreover, may have the effect of reducing the use of pharmacological compounds and thus in some way represents a revival of natural medicine, which

can be viewed positively if we consider the numerous side effects of anti-inflammatory and analgesic drugs.

There is clinical evidence from randomised trials regarding the beneficial effects of spinal manipulation on neck and back pain, though some of these studies have been criticised as being methodologically “unsound”. A blind study comparing routine therapy, placebo, traditional physiotherapy, and manipulative therapy has demonstrated the short-term superiority of the two latter treatments compared to placebo and routine therapy, and the long-term superiority of manipulative therapy over physiotherapy. The scientific evidence, however, is very poor in other musculoskeletal pathological conditions and entirely lacking with regard to the benefits of chiropractic in visceral conditions (Vickers and Zollman, 1999). A recent trial showed that in patients with chronic spinal pain, manipulation, if not contraindicated, results in greater short-term improvement than acupuncture or medication (Giles and Muller, 2003). However, the data do not strongly support the use of only manipulation, only acupuncture, or only nonsteroidal antiinflammatory drugs for the treatment of chronic spinal pain.

Studies reporting beneficial effects of chiropractic often fail to report the by no means negligible contraindications, consisting in acute infectious and inflammatory disease, vertebro-basilar insufficiency, acute trauma, myelopathy, osteoporosis, anticoagulant therapy and haemorrhagic diathesis.

Chiropractic is very widely practised in northern European and particularly in English-speaking countries; in the USA it is the commonest form of complementary medicine. There is solid and impressive economic and related justification for the desired integration (Manga, 2000). Chiropractic care is a cost-effective alternative to the management of neuromusculoskeletal conditions by other professions.

The PubMed database of the National Library of Medicine currently reviews 2831 scientific publications on chiropractic. A number of journals specifically devoted to the subject (such as the *Journal of Manipulative and Physiological Therapeutics*) are published and there are numerous official schools of chiropractic in the above-mentioned countries.

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HOMEOPATHY

Scientific evidence

Apart from a limited number of recent experiences, knowledge in the field of homeopathy has developed autonomously with its own publications, its own journals, congress proceedings, etc., in almost all cases unbeknown to the world of conventional medicine. Compared to conventional medicine, there have been very few scientific studies to date, despite the fact that in recent years we have been witnessing a steady increase in publications. Thus, almost all the knowledge we have of the procedures and results of homeopathic medicine is that possessed by the homeopathic practitioners themselves and not documented in official scientific journals. In reply, then, to the question “On what evidence is homeopathy based?”, we must consult not so much the indexed medical journals, but rather the homeopathy journals and organised groups of homeopaths (Consensus Conferences).

On the other hand, one of the disciplines that most concerns itself with the level of evidence substantiating medical knowledge is evidence-based medicine, and we should stress that evidence-based medicine stems from the integration of the physician’s experience and the best evidence available in the literature (Sackett *et al.,* 1996). While homeopaths have good clinical experience (and this may help explain the growing popularity of homeopathy amongst patients), the demonstration of their clinical results in the scientific literature is undoubtedly still in its infancy.

Most of the scientific literature in medicine consists of clinical trials. A clinical trial, like any other form of experimentation, should reflect the clinical reality being studied, otherwise its very definition as an experiment fails to stand up. One frequent methodological error, the result of which is to prevent a trial reflecting the reality the investigators intend to study, is to apply assessment criteria, when designing the trial and particularly its objectives (end-points), which differ from those of the type of medicine one claims to be studying. If, then, one simply applies to homeopathy *en bloc* the procedures, aims and criteria typical of conventional medicine, the results obtained will not be valid. For example, one of the end-points of homeopathic therapy is the elimination of *all* the patient’s symptoms and not just the symptoms of the

disease he or she may present at that particular time, as is the case with conventional medicine. Unfortunately, most of the homeopathy trials published today in scientific journals apply only procedures typical of conventional medicine. The results of such trials (whether positive or negative) therefore fail to reflect standard homeopathic clinical practice and consequently no valid conclusions can be drawn from them in therapeutic terms. It has been demonstrated, for instance, (Reilly *et al.,* 1986) that a mixture of homeopathically prepared pollens is active compared to placebo in the allergic reaction to pollens (pollinosis), but since homeopaths usually prescribe other homeopathic medicines in pollinosis, according to prescribing rules which are different from the standardisation used here, the study cannot provide a valid reply to the question: "Is homeopathy effective in patients suffering from pollinosis?". The *efficacy assessment* of a homeopathic therapy should therefore be done in ways that differ from the efficacy assessments of conventional medicine, and vice versa. Moreover, this point is also stressed in several scientific journals: *"We think that different experimental models are needed in order to reply to different questions"* (Dean, 1998).

Since homeopathy is a holistic form of medicine, a model more closely reflecting homeopathic practice should take into consideration the evolution of the symptoms and the patient's general situation, according to the parameters of Hering's Law of Cure. To date we know of no valid experimental model for measuring the clinical course of symptoms according to this reference principle. As can be seen, then, there are still several problems that need to be solved in constructing appropriate experimental models; the fact, however, that people are beginning to devise new models, closer to the reality of homeopathic practice, and that the application of such models is tending initially to yield positive results would suggest that these problems may be solved in the near future.

Despite the problems and shortcomings outlined here, we already have a sufficient amount of data from controlled clinical trials to be able to answer a number of general questions.

Is homeopathy effective?

In this connection, an important review was carried out by Kleijnen and co-workers in 1991 (Kleijnen *et al.,* 1991). The aim of this review was to "…*establish whether there was any evidence of efficacy of homeopathy stemming from clinical trials".* A total of 107 trials were analysed and the results were interpreted according

to the methodological correctness of the studies. Positive results were achieved in 81 trials. The conclusions were: *"As things stand at present, the evidence from clinical trials is positive but not sufficient for us to draw any definitive conclusions, since the methodology of most of the trials is of poor quality. This indicates that new studies are warranted for further evaluation of homeopathy, which should be done on the basis of well conducted trials",*

Is the clinical action of homeopathy due to the placebo effect?

This aspect was reviewed by Linde and co-workers in 1997 (Linde *et al.,* 1997). The results of 89 double-blind and/or randomised controlled trials were pooled and examined by meta-analysis. The conclusions of the study were: *"The results of our meta-analysis are not consistent with the hypothesis that the clinical effects of homeopathy are entirely due to a placebo".*

A further meta-analysis of homeopathic trials (Cucherat *et al.*, 2000) stated that "*there is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials*."

What is the impact of homeopathy on health?

To design studies capable of answering this question, it is interesting to note the observations made by Linde and co-workers (Linde *et al.,* 1997). The suggested to separate the line of research addressing the issue of whether or not homeopathy is a placebo (the academic issue that usually dominates the debate) more clearly from the line of research that seeks to understand whether or not homeopathy is a useful tool in the management of health (the more important issue for the patients and health operatives). To answer this latter question, the article goes on to say that we need new study models more closely reflecting homeopathic clinical practice. This type of detailed clinical information can be obtained with prospective observational studies, capable of permitting the rational design of randomised trials that actually reflect homeopathic practice and that have scientific and clinical implications.

To answer the more important question for patients and health workers alike ("What is the impact of homeopathy on health?", we therefore need to:

- design research studies conducted by independent groups. In 1998 a study appeared in the *British Medical Journal* reporting evidence showing that the results of most of the studies published in scientific journals are influenced by

the funding of the studies by pharmaceutical companies (Smith, 1998). It has often been said that the opposition to homeopathy is due amongst other things to pressure brought to bear by the pharmaceutical companies manufacturing synthetic drugs. By the same token, studies financed by the manufacturers of homeopathic remedies may present a similar sort of bias, though, obviously of an opposite nature;

- conduct research that takes homeopathic clinical practice as its starting point. These studies must therefore necessarily reflect the experience of practising homeopaths;
- conduct research that proposes new study models closely reflecting the specific nature of homeopathic medicine (this point has been discussed earlier). Among such studies, those of an observational type would appear to be particularly interesting and appropriate. A tangible example of such new models for the study of homeopathy that match up to the three indications outlined above is the observational study conducted by a group of homeopaths under the aegis of the Venice Association of Medical Practitioners (Muscari Tomaioli *et al.,* 2001). Other studies are in progress (Niederle, 1999; Riley *et al.*, 2001; Thompson and Reillly, 2002).

Risks of homeopathy

Since homeopathic medicines are hyperdiluted, it follows that they cannot be endowed with any intrinsic toxicity. One of the indications of choice for homeopathy therefore consists in those situations in which conventional drugs are risky or contraindicated on account of their toxicity. One should not believe, however, as is often the case, that homeopathy “is absolutely incapable of doing harm”; we should never forget, in fact, that whenever a homeopathic medicine is prescribed, in practice the physician is “prescribing symptoms”. Consequently, there may be a brief initial phase when the patient has two sets of symptoms, those belonging to the disease itself (“natural disease”) and those induced by the medicine (“artificial disease”). The patient may therefore experience an initial worsening of his or her condition (“homeopathic aggravation”). In almost all cases this worsening is mild and temporary, and also it does not always occur. An expert homeopath is capable of managing the homeopathic aggravation and is often able to avoid it by careful adjustment of the posology.

Discussion and critical evaluation

Homeopathy has now been practised for some 200 years or so, and today, after a long period in which it was consigned to oblivion (corresponding to the first part of the 20th century and coinciding with the development of scientific medicine and, particularly, of conventional pharmacology), is experiencing a strong revival throughout the western countries. This boom would appear to be due more to the "popularity" it enjoys in certain quarters of the population than to the results of clinical and experimental studies of such a probative nature as to justify the use of homeopathic medicines according to the criteria adopted today for conventional medicines. One by no means negligible element in favour of homeopathy lies in the fact that the medicines are usually given at such low doses as to rule out any possible risk of direct toxicity, though it is true to say, as is rightly reported here, that errors of diagnosis and prescription are also made in homeopathic practice.

Scientific research on the action of homeopathic remedies has developed over the past 10 to 15 years, though it still addresses only a small proportion of the problems posed by this therapeutic method and has so far failed to come up with firm, conclusive evidence on any of the fundamental points. There are some one hundred or so published reports on clinical research conducted with conventional methods (double-blind, control group, randomisation) and about the same number of basic research studies (laboratory and animal studies).

The randomised controlled clinical trials on homeopathy have to do mainly with the following nosological categories: allergies, diseases of the vascular apparatus and of coagulation, diseases of the gastrointestinal tract, diseases of the musculoskeletal apparatus (including rheumatological conditions), respiratory diseases and influenza syndromes, surgery and anaesthesiology, and dermatological, neurological and obstetrical and gynaecological diseases. On the whole, in approximately half the studies, the therapeutic result in the patient group treated with the homeopathic remedy proved superior to that in the control group (mainly consisting of patients treated with placebo). In a quarter of the studies the homeopathic treatment tended to be positive, though doubts have been voiced as to the statistical validity of the results. In the remaining quarter, no therapeutic effects of the homeopathic treatment were registered.

A definitive answer as to the clinical efficacy of homeopathy in given clinical conditions is therefore still not possible, both on account of the poor quality of some of the published studies and because of lack of repetition of such studies by independent groups, and also because of the uncertainty as to what the most suitable methodology is for investigating this therapeutic method. The main problem, in this connection, lies in the fact that the therapeutic action of homeopathy is aimed at restoring the overall balance of the patient and not merely at curing a specific diagnosed disease; thus, for any given homeopathic remedy, there is no such thing as a specific therapeutic indication for its use in this or that disease. According to the report of a commission set up by the European Community (HMRG, Homeopathic Medicine Research Group), entitled “Overview of data from homeopathic medicine trials” and drawn up in 1997, the cumulative results of reviews of the best homeopathic clinical trials rule out the possibility that the effects claimed for homeopathy may be due solely to a generalised “placebo effect”. The HMRG report adds that this does not mean that homeopathy is unquestionably effective in all the trials considered, but that the number of significant results cannot be due solely to chance. On the whole, the report is to be regarded as positive and as an invitation to proceed in the direction of further studies, providing these are conducted with appropriate methods.

As regards the possible pathophysiological, biophysical and pharmacological explanations of the action of homeopathic remedies, a number of models exist that tend to regard the law of similars as a general expression of the action-reaction principle, viewed in the context of the dynamics of complex systems. In other words, the claim that homeopathic remedies stimulate the reactions of the body, restoring its balance in the presence of various levels of pathophysiological imbalance, would appear to be increasingly plausible. Clarification of the more controversial aspects relating to the “high dilutions” and “dynamisations”, must necessarily await the promising developments of the physics of condensed matter and of biophysics.

There is evidence from randomized, controlled trials that homeopathy may be effective for the treatment of influenza, allergies, postoperative ileus, and childhood diarrhea. Evidence suggests that homeopathy is ineffective for migraine, delayed-onset muscle soreness, and influenza prevention. There is a lack of conclusive evidence on the effectiveness of homeopathy for most conditions (Jonas *et al.*, 2003).

Apart from the unsoundness of the scientific evidence, which today is progressively improving (*see also* Taylor *et al.*, 2000; Bellavite and Signorini, 2002; Bellavite *et al.*, 2003), it is important to stress the fact that the most characteristic objective of homeopathic medicine is the management of the sick person considered as a whole embracing both body and mind. This objective cannot be dissociated from the classic Hahnemann methodology, according to which the homeopathic physician investigates not only the disease itself, but also all the patient's physiological, pathological and temperamental aspects, as well as the particular ways in which the patient expresses his or her state of distress. The expert homeopath devotes extraordinary care to eliciting the patient's recent and remote medical history, and the first visit may take as long as a couple of hours. This is necessary not only in order to establish a good doctor-patient relationship (something which should be mandatory in any branch of medicine), but, above all, in order to choose the *simillimum* remedy, i.e. the one capable of producing a state most similar to that encountered in the patient among the many hundreds of possible medicines available.

As also emerges in the text presented here, homeopathy is by no means a simple method to master perfectly. Very considerable training is necessary:

- in the ability to discover the important symptoms and the constitutional characteristics of a patient through appropriate investigation and analysis of the case;
- in knowledge of the "pathogenesis" of the remedies (the symptoms caused in healthy subjects) and the methods used for identifying them;
- in the ability to assess the effect of the remedies prescribed.

In conclusion, in view of the difficulties of the method and the uncertainty as to the clinical efficacy of homeopathy in a number of conditions, this approach calls for skill and all due caution. It should not be used as an alternative to treatments of proven efficacy. In this connection, it is worth recalling the official definition proposed by the American Institute of Homeopathy, which is the official homeopathic organisation in the United States: *"The homeopathic doctor is one that adds his special knowledge of homeopathy to his knowledge of general medicine"* (Boyd, 1936).

The PubMed database of the National Library of Medicine currently reviews 2061 papers in which reference is made to homeopathy. Not all of these, but a significant proportion of them, refer to clinical studies or to experimental research, while the

others discuss general topics regarding the scientificity or applicability of homeopathic therapies.

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PHYTOTHERAPY

Scientific evidence

From a survey of the literature it emerges that the choices made in phytotherapy (or herbal medicine) are mainly based on empirical knowledge which has never been abandoned over the years on account of its essential practical validity. In recent decades, however, there has been a perceived need to provide well documented evidence, on the basis of scientific criteria, for many of the notions that have come down to us over centuries of history of the practice of medicine.

Among the many studies presented in the international literature, we will cite here, by way of examples, only a few of those reporting clinical results obtained with the use of scientific criteria.

In double-blind, randomised, placebo-controlled, multicentre studies, it was found that an extract of *Ginkgo biloba*, one of the most ancient living plants on earth (already present at the end of the primary era), which is now cultivated in Korea, Japan and the south-east of France, is safe and capable of improving cognitive performance and social functioning of dementia patients for 6 to 12 months (Le Bars *et al.*, 1997) and in patients suffering from cerebral circulatory insufficiency (Vorberg, 1985) and intermittent claudication (Drabael *et al.*, 1996). A recent randomized, double-blinded cross-over design using oral treatment with *G. biloba* extract versus placebo showed that active treatment is able to dilate forearm blood vessels causing increments in regional blood flow without changing blood pressure levels in healthy subjects (Mehlsen *et al.*, 2002). The effect of *Ginkgo* in elderly dementia patients and age-associated memory impairment is still controversial according to more recent trials (Curtis-Prior *et al.*, 1999; van Dongen *et al.*, 2003).

In a double-blind, randomised, placebo-controlled study conducted in 58 patients with anxiety syndrome not caused by psychotic disorders, an extract of kava (*Piper methysticum,* a plant extensively used by South Pacific islanders who obtain an intoxicating beverage from it) induced no adverse reactions, and the HAMA (Hamilton Anxiety Scale) scores for anxiety symptoms showed a significant reduction in the group receiving the active drug as early as one week after the start of treatment (Kinzler *et al.*, 1991). In another double-blind study with an extract of kava roots vs. oxazepam, recognition memory task performance was compared using lists of words presented for the first time and then repeated. The *kava* root extract was

found to induce a slight increase in word recognition ability and a greater capacity to differentiate between new and repeated words as compared to control subjects (Munte *et al.*, 1993).

Numerous studies have been conducted on the immunomodulatory activity of mistletoe (*Viscum album*) and on its possible mechanisms (Hajto *et al.,* 1997; Samtleben *et al.,* 1999). Randomised double-blind studies in healthy subjects have revealed that injections of agglutinin extracted from mistletoe bring about an immunomodulatory action (Kleijenen *et al.*, 1994) and, despite the fact that the clinical evidence regarding its anticancer action is still a matter of debate, it has been reported that mistletoe-based treatment can improve the quality of life in cancer sufferers by inducing the release of beta-endorphins (Heiny *et al.*, 1994).

Extracts of the fruits of the saw palmetto (*Serenoa repens),* a dwarf palm growing along the sandy, southern, subtropical coasts of the United States, have been analysed biochemically and pharmacologically, with experiments in animals and clinical trials in human subjects. These studies, conducted in Italy, France, Germany and the United Kingdom, have shown that *Serenoa* is capable of appreciably reducing the discomfort caused by benign prostatic hypertrophy. According to Cochrane database, a number of randomised, double-blind, placebo-controlled studies have recently confirmed that this plant remedy is superior to placebo, causing a significant regression of the functional disorders related to benign prostatic adenoma as well as reducing the frequency of impotence induced by finasteride used in the control subjects (Wilt *et al.*, 2002).

Hypericum or St. John's wort (*Hypericum perforatum),* a plant spontaneously growing in vast areas of Europe, Africa and Asia and used since ancient times for the treatment of many somatic and mental disorders, has recently achieved media notoriety on account of its efficacy as an antidepressant. A randomised, double-blind study versus imipramine in mild-to-moderate depression has furnished evidence of better tolerance of hypericum due to its less severe side effects (Woelk, 2000). Similar studies versus other antidepressants have shown that hypericum, and particularly extracts rich in hyperphorin, have a better therapeutic index (Laakmann *et al.,* 1998; review by Linde and Mulrow, 2000). The *British Medical Journal* published a meta-analysis of 23 randomised clinical trials, 15 comparing hypericum extract with placebo and 8 comparing it with other antidepressants. In the former group of trials, approximately 2% of patients responded positively to the placebo as

against 51% responding positively to hypericum. In the studies comparing hypericum with an active control substance, approximately 59% of the patients responded positively to the standard treatment and 64% to hypericum. The meta-analysis concludes that, despite methodological limitations, there is good evidence to show that hypericum is more effective than placebo (Linde *et al.*, 1996).

A plant used both for culinary and pharmacological purposes is garlic (*Allium sativum*), for which a substantial body of scientific evidence has been obtained. Among the numerous types of activity of this traditional phytotherapeutic agent, those most extensively documented are its serum lipid lowering and antiatherogenic effects, its antihypertensive effects, its anti-platelet-aggregation activity and its antithrombotic activity (Kiesewetter *et al.*, 1991; Warshafsky *et al.,* 1993; Silagy *et al.,* 1994).

Discussion and critical evaluation

As compared to the topics addressed in other fields of complementary and alternative medicine, phytotherapy unquestionably shows a closer affinity to conventional medicine both as regards its theoretical principles and its therapeutic modalities. Modern pharmacology has its roots in herbal medicine and many of the active ingredients of traditional drugs are of plant origin, even though they may be produced in the laboratory. Essentially, modern medicines uses those active ingredients contained in plants which, after being isolated and purified, have been shown to exert pharmacological activity and clinical efficacy in given diseases. In some conditions, the use of plant extracts has also eventually become part and parcel of official medicine, on the basis of their proven advantages in terms of efficacy, tolerability or cost compared to other available therapies.

An important issue is the different and more complex approach of the phytotherapist, according to which the efficacy of medicinal plants is never wholly attributable to its isolated active ingredients but is believed to stem from the entire set of compounds (both active and inert) that make up the phytocomplex.

Encouraging data support the efficacy of some popular herbal medicinal products, and the potential for doing good seems greater than that for doing harm. The published evidence (reviewed by Ernst, 2002) suggests that *Ginkgo* is of questionable use for memory loss and tinnitus but has some effect on dementia and

intermittent claudication. St. John's wort (*Hypericum perforatum*) is efficacious for mild to moderate depression, but serious concerns exist about its interactions with several conventional drugs. Well-conducted clinical trials do not support the efficacy of Ginseng to treat any condition. *Echinacea* may be helpful in the treatment or prevention of upper respiratory tract infections, but trial data are not fully convincing. Saw palmetto (*Serenoa repens*) has been shown in short-term trials to be efficacious in reducing the symptoms of benign prostatic hyperplasia. *Kava* is an efficacious short-term treatment for anxiety. None of these herbal medicines is free of adverse effects.

Serenoa repens extracts, according to a recent systematic review (Cochrane Library Issue 1, 2000), is a valid alternative to finasteride in benign prostatic hypertrophy, in that it is endowed with comparable efficacy and is associated with a lower impotence rate (1.5% of patients as against 3% of those treated with finasteride). Another example of a plant which has been the subject of many studies, corroborated by meta-analyses, is *Hypericum perforatum,* containing active ingredients with well documented antidepressive effects.

Ginseng has been used medicinally in the Far East for several millennia and is currently one of the most widely taken herbal products throughout the world. It has been attributed with a plethora of physiological effects that could potentially benefit cognitive performance or mood. Studies involving animals show that ginseng and its constituent ginsenosides can modulate indices of stress, fatigue, and learning. However, there is a lack of adequately controlled research showing behavioural effects following chronic administration to humans (Kennedy and Scholey, 2003).

Extracts and preparations from the tree parasitic plant mistletoe (*Viscum album L*.) have been used in the treatment of cancer for decades. Numerous preclinical and in vitro studies have reported immunostimulatory, cytotoxic, and proapoptotic effects. Translation of these effects into clinical response continues to pose a problem. While a number of clinical studies have found improvement in quality of life (QOL), data on the efficacy of mistletoe to prolong survival are conflicting and of variable quality (Mansky, 2002).

In a recent systematic review of clinical trials on the lipid-lowering effect of garlic (Alder *et al.*, 2003), six of ten studies were found to show a real efficacy of this plant. The average drop in total cholesterol was 24.8 mg/dL (9.9%), LDL 15.3 mg/dL (11.4%), and triglycerides 38 mg/dL (9.9%). However, major shortcomings of many of

the trials, like lack of control of diet as a confounding variable, make it difficult to draw definite conclusion and to recommend garlic as an evidence-based antihyperlipidemic agent (Brace, 2002). Various preparations of garlic, mainly aged garlic extract, have been shown to have promising antioxidant potential, but the standardization of these products and their effects is difficult (Banerjee *et al.*, 2003).

A major problem and one which is difficult to solve is the lack of standardisation of herb-based preparations due to the lack of good manufacturing practices, which may partly explain the contrasting results of a number of studies. For example, 4 out of 26 controlled clinical trials on *Echinacea*-based preparations are based on the use of a fresh extract of the whole *E. purpurea* plant, 1 on the use of the root tincture, and 1 on that of the root extract of *E. pallida,* while the other 20 have to do with combinations with root extracts of other plants, mother tinctures and homeopathic compounds. It should be noted that the compositions of the roots of the various *Echinacea* species are different and the use of the plant as a whole as compared to the roots leads to changes in the amounts of the individual active ingredients. It is clear that, in these conditions, it is impossible to compare the various studies and, in more general terms, getting the results of phytotherapy trials into a proper scientific perspective would appear to be no easy task.

Another aspect which is increasingly being addressed in the scientific literature is the toxicity of medicinal plants and their potential interactions with drugs. Although, in many cases, phytotherapy is characterised by a blander action and thus by less toxicity than drug therapy, any pharmacologically active substance involves risks for the body, and the often uncontrolled expansion of the use of herbs calls for awareness and attention on the part of all physicians and pharmacists. Many articles and case reports have described toxic and even fatal effects and pharmacological interactions related both to the active compounds from certain plants and to contamination of plant-based preparations, which are often taken by the patient without the physician knowing anything about it. Even those doctors who do not practice phytotherapy should be aware of these problems, both in order to be able to advise patients who may make use of them as self-medication and to interpret the prescriptions of colleagues who are phytotherapists.

Single medicinal herbs and combination preparations are associated with hepatotoxic events. Clinically, the spectrum ranges from transient elevations of liver enzyme levels to fulminant liver failure and death. In most instances hepatotoxic

herbal constituents are believed to be the cause, while others may be due to herb-drug interactions, contamination and/or adulteration (Pittler and Ernst, 2003). Aflatoxins, toxic metals such as arsenic and lead, corticosteroids and anti-inflammatory agents have been found in plant-based preparations from Asian countries. Also the risk of anaphylactic reactions, especially when phytocompounds are injected, should not be underestimated.

On the database of the World Heath Organisation center in Uppsala, which collects reports from 57 countries, there are currently some 9000 adverse reactions to plants, including a number of serious ones (hepatitis, thrombocytopaenia, circulatory failure), and the WHO centre has set up a project aimed at achieving global standardisation of medicinal plants in terms both of terminology and of indications (which vary from one country to another), The WHO has also published an initial volume containing the monographs of 28 medicinal plants complete with complete with pharmacological data (experimental and clinical) and toxicological data (contraindications, precautions for use, and adverse reactions). Recently some countries have implemented specific pharmacovigilance systems. In the United Kingdom since 1996 the reporting of adverse reactions has been extended to plants, and guidelines as to what and how this reporting should be done are regularly issued to medical practitioners.

The PubMed database of the National Library of Medicine currently reviews 8080 papers on phytotherapy and 1490 papers on *herbal medicine,* while, if one runs a search for the key word “plant extracts”, the number of hits is an extraordinary 41,172. The substantial number of publications having to do with phytotherapy confirms that research is ongoing and ranges from studies on the molecular action mechanisms of components of medicinal plants to randomised clinical trials evaluating the efficacy of complete extracts. In synthesis, recent years have also witnessed the growth of meta-analyses and of systematic reviews demonstrating the superiority of a number of plants over placebo and their substantial equivalence to the other available therapies in a number of clinical conditions. On the whole, however, the results of the various clinical trials are to some extent contradictory and the quality of the methodology poor.

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